Nos. 14-1418, 14-1453, 14-1505, 15-35, 15-105, 15-119 & 15-191

IN THE

# Supreme Court of the United States

DAVID A. ZUBIK, ET AL., Petitioners,

v.

SYLVIA BURWELL, ET AL., *Respondents.* 

[CAPTIONS CONTINUED ON INSIDE COVER]

On Writs of Certiorari to the United States Courts of Appeals for the Third, Fifth, Tenth, and D.C. Circuits

APPENDIX VOL. II OF II OF AMICI CURIAE THE OVARIAN CANCER RESEARCH FUND ALLIANCE AND ITS PARTNER MEMBERS AND SCIENTIFIC ADVISORS' BRIEF IN SUPPORT OF RESPONDENTS

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ROMAN CATHOLIC ARCHBISHOP OF WASHINGTON, ET AL., *Petitioners*,

v. Sylvia Burwell, et al., *Respondents.* 

EAST TEXAS BAPTIST UNIVERSITY, ET AL., Petitioners,

v.

SYLVIA BURWELL, ET AL., Respondents.

LITTLE SISTERS OF THE POOR HOME FOR THE AGED, DENVER, COLORADO, ET AL., *Petitioners*,

> v. SYLVIA BURWELL, ET AL., *Respondents.*

SOUTHERN NAZARENE UNIVERSITY, ET AL., Petitioners,

> v. Sylvia Burwell, et al., *Respondents.*

> GENEVA COLLEGE, *Petitioner,* v. Sylvia Burwell, et al., *Respondents.*

### **APPENDIX N**

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#### ORAL CONTRACEPTIVE USE AND BREAST OR OVARIAN CANCER RISK IN BRCA1/2 CARRIERS: A META-ANALYSIS

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#### Abstract

*Background*: Women with BRCA1 or BRCA2 mutations are at increased risk of breast and ovarian cancer. Oral contraceptives (OC) use has been associated with a reduction in ovarian cancer risk and with a moderately increased breast cancer risk, which tends to level off in the few years after stopping. The association between oral contraceptive and BRCA1 or BRCA2 gene mutations carriers is unclear.

*Methods*: We performed a comprehensive literature search updated to March 2010 of studies on the associations between OC users and breast or ovarian cancer for ascertained BRCA1/2 carriers. We obtained summary risk

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estimated for ever OC users, for duration of use and time since stopping.

Results: A total of 2855 breast cancer cases and 1503 ovarian cancer cases, carrying an ascertained BRCA1/2 mutation, were included in our meta-analyses, based on overall 18 studies. Use of OC was associated with a significant reduced risk of ovarian cancer for BRCA1/2 carriers (summary relative risk (SRR) = 0.50; 95% confidence interval (CI), 0.33- 0.75). We also observed a significant 36% risk reduction for each additional 10 years of OC use (SRR: 0.64; 95% CI, 0.53–0.78; P trend < 0.01). We found no evidence of a significant association between OC and breast cancer risk in carriers (SRR: 1.13; 95% CI, 0.88-1.45) and with duration of use. OC formulations used before 1975 were associated with a significant increased risk of breast cancer (SRR: 1.47; 95% 1.06, 2.04), but no evidence of a significant association was found with use of more recent formulations (SRR: 1.17; 95% 0.74, 1.86).

*Conclusions*: OC users carrying an ascertained BRCA1/2 mutation have a reduced risk of ovarian cancer, proportional to the duration of use. There is no evidence that recent OC formulations increase breast cancer risk in carriers.

#### 1. Background

There is clear evidence that germ line mutation in BRCA1 (MIM #113705) or BRCA2 (MIM #600185) account for a large proportion of familial breast/ovarian cancer and confer very high lifetime risks for both cancer sites.<sup>1</sup> Approximately 5–10% of all epithelial ovarian carcinomas result from genetic predisposition<sup>2</sup> and the great majority of these are associated with BRCA genes, as opposed to 25% of all hereditary breast cancers.<sup>3,4</sup> The lifetime risk of breast or ovarian cancer for women who inherited a BRCA mutation is highly variable and depends on the specific mutation, on the population studied and are extremely higher than the lifetime risk in the general population.<sup>5–10</sup> In addition, there is evidence that cancer patients with BRCA1 and BRCA2

mutation are characterised by different pathological and clinical features, some of which have prognostic value.<sup>11</sup> Some studies demonstrated that breast cancers in BRCA1 carriers more likely do not express oestrogen and progesterone receptors or Her-2/neu (triple-negative breast cancer), while breast cancers in BRCA2 carriers seem to share the same pathologic characteristics as non-carriers.<sup>12</sup> Moreover, oral contraceptives (OC) use was associated with an increased risk of cancer among triple-negative breast cancer, but not among non-triple-negative breast cancer.<sup>13</sup>

In the general population long-term exposure to oestrogen may increase a woman's chance of developing breast and ovarian cancer. The level of estrogens is associated with the repair capacity of breast and ovarian epithelial cells that may result in tumour formations, instead of apoptosis.<sup>14,15</sup> Oestrogen levels are high in ovulating women and any factor that limit the period of ovulation (pregnancy, late onset of menstruation or early onset of menopause) decreases the lifetime exposure to oestrogen and thus the risk for both types of cancer.

The measures for ovarian cancer prevention and early detection are limited as symptoms are frequently non-specific, patients are often diagnosed with advanced disease and family history of early-onset breast/ovarian cancer remains the single most important factor in determining individual ovarian cancer risk.<sup>17–20</sup>

Some studies suggest that non-genetic risk factors may differ in women with hereditary breast and ovarian cancer caused by alterations in the BRCA1/2 genes. Breast cancer typically occurs in these women at a much younger age, but the risk is not influenced by the age at menarche and it is also unclear whether the relationship between parity, age at menopause and breast cancer risk holds true in women who have BRCA mutations.<sup>1,21</sup>

OC use has been associated with a moderately increased breast cancer risk, which tends to decline progressively after

termination of use and with a reduction in ovarian cancer risk for women unselected for predisposing genetic mutations.<sup>22,23</sup>

The use of OC for mutation carriers could be controversial because of the increasing breast cancer risk, especially earlyonset, and the contemporary protective effects for ovarian cancer.

The present meta-analysis was conducted to examine and clarify whether exogenous hormone in the form of OC might modify the risk of breast or ovarian cancer in BRCA mutation carriers. Furthermore we investigated the association between specific mutation (BRCA1 or BRCA2) and OC use for breast or ovarian cancers.

# 2. Materials and methods

# 2.1. Search strategy, inclusion criteria and data abstraction

We conducted a literature search updated to March 2010 using validated search strategies<sup>23–25</sup> on the following databases: PUBMED, EMBASE, Ovid MEDLINE<sup>®</sup>, using combinations of the following MeSH terms and keywords: 'oral contraceptives', 'cancer', 'ovarian' or 'breast', 'BRCA1' or 'BRCA2'. We also identified the most cited articles on the topic using ISI Web of Knowledge<sup>®</sup> Science Citation Index Expanded<sup>TM</sup> (Journal Citation Report). In addition we reviewed the references of all articles of interest and preceding reviews on the topic to identify additional relevant studies. The search was limited to human studies and no language or time restrictions were applied.

# 2.2. Meta-analysis on the impact of OC use on cancer risk in mutation carriers

Our aim was to study the association between OC use and the risk of breast/ovarian cancer in women carrying a BRCA1/2 mutation.

Published reports fulfilling the following inclusion criteria were included in the meta-analysis:

(1) Studies containing the minimum information to obtain an estimate of the relative risk (RR), with its uncertainty, of:

(a) breast and/or ovarian cancer associated with OC use in BRCA1/2 mutation carriers ascertained by a genetic test;

(b) ascertained BRCA1/2 mutation, in association with OC use, in patients with breast and/or ovarian cancer.

(2) Case–control, cohort studies and nested case–control studies, published as original articles.

(3) Independent studies. In case of multiple reports on the same population or sub-population, we considered the estimates from the most recent or most informative report.

(4) Study populations that were as homogeneous as possible. We excluded study performed on subjects all submitted to a surgical procedure (bilateral salphingo-oophorectomy), which could have modified the association between OC and cancer risk for affected.

(5) Case–controls studies with controls not directly tested for the mutation were excluded by the analyses evaluating cancer risk in BRCA1/2 carriers.

The exposure of interest was ever OC use, defined as any duration of OC use lifetimes. In Tables 1 and 2 we detailed definitions of the exposures as reported originally by authors.

#### Table 1

Features of the studies included in the meta-analysis on the impact of OC use on cancer risk in mutation carriers

\* \* \*

#### Table 2

Features of the studies included in the meta-analysis on association between of OC use and mutation status in cancer patients Presence of heterogeneous exposures was investigated in a sensitivity analysis. We also explored duration of OC use, time since last use and age at start use.

When available we used fully adjusted estimates. Articles were reviewed and data were extracted and crosschecked independently by two investigators (S.I. and S.G). Any disagreement was resolved by consensus among them.

The following information were extracted and coded from the original articles: adjusted risk estimates or crude data, year of publication, type of study, country of the study, features of populations, definition of the exposure, cancer site, mutation status, adjustments and matching variables used in the analysis and study design. When dose–response estimates on duration of OC use and time since last OC use were provided, we retrieved the study-specific dose response risk estimates and frequencies for each level of exposure.

Results from unpublished data obtained in our Institute were also added in the meta-analysis and evaluated in a sensitivity analysis.

# 2.3. Association between BRCA1/2 carrier status and OC use for breast or ovarian cancer patients

We also studied the magnitude of the association between BRCA1/2 mutation and OC use in patients with breast/ovarian cancer in a case–case approach.

# Fig. 1 Flow chart of selection of studies

\* \* \*

#### 3. Statistical methods

When available, we retained estimates adjusted for the maximum number of confounders.

We always presented random effects models to evaluate summary relative risk (SRRs) obtained with maximum likelihood estimates, in order to be more conservative.<sup>42</sup> Homogeneity of effects across studies was assessed using the Chi-square statistic (which we considered statistically significant when the P-value was 60.10)<sup>43</sup> and quantified by  $I^2$ , which represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance.<sup>44</sup> When more than a single risk estimate was present in a study (i.e. separate estimates for BRCA1 and BRCA2), we adjusted the pooled estimates for intra-study variation. When possible we performed separate analyses for type of mutation by using a bivariate approach. Sub-group and metaregression analyses were carried out to investigate potential sources of between-study heterogeneity.<sup>45</sup> Many studies reported estimates for first use of OC in or after 1975, when dose of oestrogen in OC formulation was reduced substantially. We performed meta-regression by year at start OC, assuming that women who started their OC after 1975 have used low-dose OC.

In the dose–response analysis, we considered duration of OC use and time since last use as explanatory variables. In pooling dose–response data, we took into account correlation between RRs categories within the same study, using Greenland and Longnecker method.<sup>46</sup>

We also studied the magnitude of the association between BRCA1/2 mutation and OC use in patients with breast/ovarian cancer with a case–case comparison. Following this approach, cancer patients with the mutation formed the 'pseudo-cases' and patients without the genotype formed the 'pseudo-controls' group. The two groups were then compared with respect to the prevalence of each exposure. The SRRs obtained reflects the association between the exposure (OC use) and the genotype (BRCA1/2 mutation), assuming the independence of genotype and exposure in the source population.

Sensitivity analysis was carried out in order to evaluate whether overall results were influenced by a single or a group

of studies.<sup>47</sup> Publication bias was evaluated by funnel plots and quantified by the Egger's test.<sup>48,49</sup> All analyses were performed with SAS Software using PROC MIXED (SAS, 8.02 for Windows, Cary, NC).<sup>50</sup>

#### Table 3

# Summary risk estimates of the association between OC use and cancer risk in mutation carriers

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#### 4. **Results**

Details on the search strategy and the data extrapolation are described in Fig. 1. The main characteristics of the studies included in the analyses are shown in Table 1.

#### 4.1. OC-associated breast cancer risk

The analysis was based on five studies (2855 breast cancer cases, 2954 healthy carriers). Breast cancer risk estimates for various categories of OC use are described in Table 3.

For BRCA1/2 carriers, we found that breast cancer risk was not significantly increased by OC use (SRR = 1.13; 95% confidence interval (CI): 0.88–1.45). Similarly, no significant association was found when we limited the analysis to BRCA1 or BRCA2 carriers (Fig. 2 left).

There was no evidence of a dose–response relationship with duration of OC use (P = 0.20).

The association between time since stopping OC use and breast cancer was assessed basing on three studies and overall 2109 cases. Compared to never users, BRCA1/2 carriers who stopped OC at least 10 years before diagnosis were at significant increased risk of breast cancer (SRR = 1.46; 95% CI, 1.07– 2.07). By contrast, no significant association was observed for women who stopped OC use within the last 10 years. Difference between the two estimates was statistically significant (P = 0.03).

We also found that OC formulations used before 1975 were associated with increased risk of breast cancer (SRR = 1.47;

95% CI, 1.06–2.04). On the contrary no evidence of an association was found with use of recent formulations (SRR = 1.17; 95% CI, 0.74–1.86).

# Fig. 2 Association between oral contraceptive (OC) use and breast or ovarian cancer in BRCA1/2 carriers

\* \* \*

#### 4.2. OC-associated ovarian cancer risk

Overall the meta-analysis was based on five studies (1503 ovarian cancer cases, 6315 healthy carriers).

In Table 3, we present risk estimates for ovarian cancer associated with different exposures to OC. We found a significant protective association between OC use and the risk of ovarian cancer (SRR = 0.50; 95% CI, 0.33-0.75).

When we performed separate analyses by type of mutation, OC use was associated with a significant reduced risk of cancer for both BRCA1 (SRR = 0.51; 95% CI, 0.40–0.65) and BRCA2 mutations carriers (SRR = 0.50; 95% CI, 0.29–0.89) (Fig. 2 right).

We found a significant linear decrease in risk for carriers with increasing duration of OC use: each additional 10 years of OC use the risk decreased by 36% (95% CI, 22–47%, P < 0.01 for trend).

# 5. Sensitivity analysis, meta-regression and publication bias

In this meta-analysis, the term 'ever OC use' was referred to any use of OC reported during lifetime. This is a general definition, which includes all meanings considered by the authors: Haile<sup>29</sup> included in that definition OC users for at least 1 month, Heimdal<sup>28</sup> for at least 3 months, while Whittemore<sup>33</sup> evaluated OC users for at least 1 year. The influence of these different definitions of exposure was evaluated in sensitivity analyses with no substantial differences for breast/ ovarian cancers risk.

Among the studies included in the analysis on breast cancer, one study<sup>27</sup> has a very large weight. Similarly, McLaugh-lin<sup>34</sup> could drive the analysis on ovarian cancer and it is also the only study with no histological confirmation of cancer diagnosis. Testing whether the exclusion of these studies may have potentially biased the estimates, we did not observe any change in the overall results.

In order to prevent from inclusion of prevalent cases, two studies<sup>31,34</sup> reported separate estimates limiting the cohort to subjects with a diagnosis within 5 and 3 years since diagnosis, respectively, in order to prevent from survival bias. We investigated the possible effect of inclusion of prevalent cases performing the analysis including the estimates form the cohorts restricted to incidence cases, where the survival bias is likely to be smaller, without marked change in breast (SRR = 1.10; 95% CI: 0.93–1.29) or ovarian cancer estimates (SRR = 0.49; 95% CI: 0.32–0.75).

The core of our meta-analysis included case–controls, both hospital and population based, and cohort studies. However, we performed in a sensitivity analysis a separate analysis for case–controls and cohort studies, without any difference in the estimates. Our main analysis on the effect of OC on cancer for mutation carriers comprised only one cohort<sup>31</sup> for breast cancer. Excluding the latter from the analysis the summary estimate remains similar (SRR = 1.04; 95% CI: 0.79–1.38).

Some studies included patients who had undergone salphingo-oophorectomy. Most of them presented estimates adjusted for this effect or used it as a matching variable. We performed separate analysis for studies taking into account this risk modifier, with lower estimates for studies taking into account this factor, but no differences in the estimates for both breast and ovarian cancer (P = 0.19 and P = 0.19; respectively).

No indication of publication bias was found when assessing OC effect on both cancer sites: P-values from weighted Egger's test for funnel plot were 0.90 for breast cancer and 0.73 for ovarian cancer.

Since our analysis includes studies based on familial cancer cases, we evaluated in breast cancer analyses whether there was any difference between estimates adjusted or not for family history. No difference was found between them through meta-regression (P = 0.41). The estimates used for ovarian cancer analysis were not adjusted for this factor.

# 6. Association between OC use and mutation status in cancer patients

Features of the studies included in the analysis are detailed in Table 2. We evaluated estimates from case–case approaches to study whether mutation carriers were more likely than non-carriers to use OC.

The estimates were based on a total of 241 breast cancer cases and 371 ovarian cancer cases with a BRCA1/2 mutation. We found no significant associations between BRCA1/2 mutation status and use of OC for breast/ovarian cancer, even separately investigating the cancer sites and mutations (Fig. 3).

#### 7. Discussion

Our meta-analysis was based on 2855 breast and 1503 ovarian cancer cases with a BRCA1/2 mutation. We found no evidence of a significant increased breast cancer risk in OC users overall, for recent formulation of OC and in the first 10 years after cessation.

#### Fig. 3

# Association between BRCA1 and BRCA2 combined carrier status and oral contraceptives (OC) use in cancer patients

\* \* \*

Our outcomes differ from results obtained in a previous pooled-analysis, based on 54 studies. The authors investigated the association between OC use and breast cancer risk in the general population, showing a significant association between OC use and breast cancer. However, the estimate in this pooled analysis was slightly above the unit  $(RR = 1.07; SD = 0.02)^{22}$  and the risk progressively declines, disappearing during the 5 years after stopping. Our study on mutation carriers was based on ever OC users, and it suggests evidence of an increased risk of breast cancer of 46% only for women who ceased OC use more than 10 years before diagnosis. This increasing risk could be explained by the effect of age as women who ceased in more distant time are supposed to be older than recent guitters. To some extent these results could also be explained by differences in OC formulations: most women who stopped OC use 10 or more years before diagnosis tend to have used higher dose preparation. In fact, in our analyses OC formulations used before 1975 (when drugs were likely to contain high doses of hormones) were associated with a 46% increased risk of breast cancer, on the contrary no association was found with use of recent formulations.

We also confirmed that carriers who use OC are at a significant reduced risk of ovarian cancer. The reduction is associated with ovarian cancer in a dose–response relationship: risk is greater the longer women used OC.

The reduction in ovarian cancer risk of 50% for BRCA1/2 carriers ever OC users was consistent with, and higher than, the reduction observed in the general population: in a pooled meta-analysis, based on 45 epidemiological studies, the reduction observed for ever OC users was 27%. Similarly, in our results the overall risk decreased by a 20% for mutation carriers for each five years of use, consistent with the 20% reduction observed in the general population.<sup>23</sup>

We carried out a separate analysis by type of mutation, based on the rationale that cancer patients with BRCA1 and BRCA2 mutation are characterised by different cancer subtypes in terms of oestrogen, progesterone or Herb2 status. In fact we could suppose that the risk for triple negative breast cancer, which is more frequent in BRCA1, due to hormonal risk factors, such as OC use, could be higher.<sup>12,13</sup> However, we did not find significant differences between BRCA1 and BRCA2 mutation carriers.

We also conducted a separate meta-analysis to determine whether OC use differs in breast/ovarian cancer cases with or without a mutation. Oral contraceptive use was not significantly more common for carriers compared with cases without any mutation.

Relative risk estimates of case–case approach are based on the assumption of independence between presence of a mutation and OC. This seems to be reasonable in all studies we included in the analyses, even if there may be a possibility of a violation of this assumption. If there were a positive association between genotype and exposure in the underline population, this could lead to some bias in the estimates, when compared to the ratio of the relative risk that the authors are attempting to estimate. Only analyses on case–controls and cohort studies would address this limitation. Therefore, we based our conclusions mainly on the latter results.

Studies included in the analyses are based on different study designs and analyses, different types of mutations and baseline cancer risk. We investigated how these aspects could have influenced the estimates through subgroup analyses and meta-regressions.

The studies that formed the basis of our meta-analysis included case–controls, both hospital and population based, and cohort studies. We found no difference in the estimates obtained from separate analyses on case–controls and cohort studies.

Some studies included patients who had undergone salphingo-oophorectomy, a cancer prevention strategy that could have an impact on the magnitude of the protection afforded by oral contraceptives use. Most of these studies presented adjusted estimates for this effect or used it as a matching variable. We evaluated whether this could have overestimated the protective association, performing separate analysis for studies taking into account this risk modifier, with no differences in the estimates for both cancer sites.

One possible source of bias is that the studies we included in the analyses reported different definitions of exposure. In fact, the majority of the authors defined ever OC users as women with any duration of use. We investigated differences in the estimates by types of definitions reported by the authors and we found no substantial variations.

Another possible limitation of the present analysis could arise from the inclusion of prevalent cases which may result in survival bias. If OC use is associated with a higher mortality in women with breast or ovarian cancer, the selection of prevalence cases might operate to reduce the risk. However, the investigation of heterogeneity and sensitivity analyses did not show any substantial effect of this factor, suggesting that survival bias was limited.

Most of the published evidence related to BRCA1/2 was based on large families with many individuals affected by breast/ovarian cancer. Because family members share heritable and probably environmental factors, it is possible that an amount of cancer cases diagnosed in these families may be partly due to other genetic or environmental factors.

Moreover, the inclusion of studies conducted on members of families with multiple cases of cancer may bias the risk estimates as oral contraceptives use in these carriers may not pertain to the general population of carriers. However, the study with the highest weight, used for breast cancer analysis,<sup>27</sup> selected participants from previous trials and research protocols; therefore, cohort selection from clinical genetic centres should not be the main issue of this analysis.

There has been a change in the formulation of OC over the past several decades. In the recent formulations there is a

substantial reduction in the oestrogen content. Typical oestrogen doses in the 1960s were more than double the typical doses in the 1980s and later, so that recent formulations may be considered less hazardous than the older. Calendar year (before or after 1975) is used in many studies as an indicator of the average oestrogen dose of the preparations. We found that OC formulations used before 1975 were associated with increased risk of breast cancer. On the contrary no association was found with use of recent formulations.

This is the first meta-analysis addressing breast or ovarian cancer risk for OC users for BRCA1/2 carriers. The study involved overall 5809 and 7818 mutation carriers in the analysis on breast and ovarian cancer, respectively. The main strength of our meta-analysis is the large number of cases included, with a known mutation in one of the BRCA1 or BRCA2 genes, and the possibility to investigate the association with duration of use, age at start, time since quitting and calendar time.

Even if the ideal would be to present all the estimates of risk by types of mutation, we could not carry out all our analyses by BRCA status because many authors presented only estimates for BRCA carriers combined, presumably due to limited statistical power.

Another possible limitation of this meta-analysis is the lack of published prospective studies. In fact all but two retrospective cohort studies were case–controls, and even if we try to investigate the effect of study design, we were not able to completely address the issue of potential presence of recall bias. However, in the pooled analysis on observational studies, there was no difference in the association of OC use with breast cancer between prospective cohort studies and case– controls studies.

Our investigation of the potential effect of different study designs and adjusting factors did not show any impact on the

summary estimates, however, possible sources of unexplained bias could remain and influence our results.

Our meta-analysis provides evidence that OC reduces ovarian cancer risk and no evidence that recent formulation of OC increases breast cancer risk for women with a germ line mutation in BRCA1 or BRCA2.

Further prospective studies on carriers may have to confirm our results and could also evaluate the additive effect of posthormone use or types of OC that we could not deeply investigate in this setting.

#### **Conflict of interest statement**

None declared.

#### REFERENCES

- 1. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003;72:1117–30.
- 2. Pal T, Permuth-Wey J, Betts JA, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. *Cancer* 2005;104:2807–16.
- 3. Boyd J. BRCA: the breast, ovarian, and other cancer genes. *Gynecol Oncol* 2001;80:337–40.
- Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in BRCA1-mutation carriers. Breast cancer linkage consortium. *Lancet* 1994;343:692–5.
- 5. Narod S, Ford D, Devilee P, et al. Genetic heterogeneity of breast-ovarian cancer revisited. Breast cancer linkage consortium. *Am J Hum Genet* 1995;57:957–8.
- 6. Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast

cancer linkage consortium. Am J Hum Genet 1995;56:265–71.

- Easton DF, Steele L, Fields P, et al. Cancer risks in two large breast cancer families linked to BRCA2 on chromosome 13q12–13. Am J Hum Genet 1997;61:120–8.
- 8. Moslehi R, Chu W, Karlan B, et al. BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. *Am J Hum Genet* 2000;66:1259–72.
- 9. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* 1997;336:1401–8.
- 10. Parkin DM, Whelan SL, Ferlay J, Storm H. Cancer Incidence in Five Continents. Lyon; 2005.
- 11. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature* 2000;406:747–52.
- 12. Atchley DP, Albarracin CT, Lopez A, et al. Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. *J Clin Oncol* 2008;26:4282–8.
- Dolle JM, Daling JR, White E, et al. Risk factors for triple-negative breast cancer in women under the age of 45 years. *Cancer Epidemiol Biomarkers Prev* 2009 Apr;18(4):1157–66.
- 14. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. *Lancet Oncol* 2001;2:133–40.
- 15. Horner MJ, Ries LAG, Krapcho M, Neyman N, Aminou R, Howlader N, et al., editors. SEER cancer statistics review, 1975–2006. Bethesda, MD: National Cancer Institute; 2009.

- 17. Quinn JE, Carser JE, James CR, Kennedy RD, Harkin DP. BRCA1 and implications for response to chemotherapy in ovarian cancer. *Gynecol Oncol* 2009;113:134–42.
- 18. Riman T, Persson I, Nilsson S. Hormonal aspects of epithelial ovarian cancer: review of epidemiological evidence. *Clin Endocrinol (Oxf)* 1998;49:695–707.
- 19. McGuire V, Felberg A, Mills M, et al. Relation of contraceptive and reproductive history to ovarian cancer risk in carriers and noncarriers of BRCA1 gene mutations. *Am J Epidemiol* 2004;160:613–8.
- 20. Whittemore AS, Harris R, Itnyre JCollaborative Ovarian Cancer Group. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case–control studies. II. Invasive epithelial ovarian cancers in white women. *Am J Epidemiol* 1992;136:1184–203.
- 21. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science* 2003;302:643–6.
- 22. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. Lancet 1996;347:1713–27.
- 23. Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet* 2008;371:303–14.
- Haynes RB, Wilczynski N, McKibbon KA, Walker CJ, Sinclair JC. Developing optimal search strategies for detecting clinically sound studies in MEDLINE. J Am Med Inform Assoc 1994;1:447–58.

- 25. Shojania KG, Bero LA. Taking advantage of the explosion of systematic reviews: an efficient MEDLINE search strategy. *Eff Clin Pract* 2001;4:157–62.
- 27. Narod SA, Dube MP, Klijn J, et al. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst* 2002;94:1773–9.
- 28. Heimdal K, Skovlund E, Moller P. Oral contraceptives and risk of familial breast cancer. *Cancer Detect Prev* 2002;26:23–7.
- 29. Haile RW, Thomas DC, McGuire V, et al. BRCA1 and BRCA2 mutation carriers, oral contraceptive use, and breast cancer before age 50. *Cancer Epidemiol Biomarkers Prev* 2006;15:1863–70.
- 30. Gronwald J, Byrski T, Huzarski T, et al. Influence of selected lifestyle factors on breast and ovarian cancer risk in BRCA1 mutation carriers from Poland. *Breast Cancer Res Treat* 2006;95:105–9.
- 31. Brohet RM, Goldgar DE, Easton DF, et al. Oral contraceptives and breast cancer risk in the international BRCA1/2 carrier cohort study: a report from EMBRACE, GENEPSO, GEO-HEBON, and the IBCCS collaborating group. *J Clin Oncol* 2007;25:3831–6.
- 32. Runnebaum IB, Wang-Gohrke S, Vesprini D, et al. Progesterone receptor variant increases ovarian cancer risk in BRCA1 and BRCA2 mutation carriers who were never exposed to oral contraceptives. *Pharmacogenetics* 2001;11:635–8.
- 33. Whittemore AS, Balise RR, Pharoah PD, et al. Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations. *Br J Cancer* 2004;91:1911–5.

- 34. McLaughlin JR, Risch HA, Lubinski J, et al. Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case–control study. *Lancet Oncol* 2007;8:26–34.
- 35. Antoniou AC, Rookus M, Andrieu N, et al. Reproductive and hormonal factors, and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers: results from the international BRCA1/2 carrier cohort study. *Cancer Epidemiol Biomarkers Prev* 2009;18:601–10.
- 36. Ursin G, Henderson BE, Haile RW, et al. Does oral contraceptive use increase the risk of breast cancer in women with BRCA1/BRCA2 mutations more than in other women? *Cancer Res* 1997;57:3678–81.
- 37. Jernstrom H, Loman N, Johannsson OT, Borg A, Olsson H. Impact of teenage oral contraceptive use in a population-based series of early-onset breast cancer cases who have undergone BRCA mutation testing. *Eur J Cancer* 2005;41:2312–20.
- 38. Sade RB, Chetrit A, Figer A, et al. Hormone replacement therapy is more prevalent among Jewish BRCA1/2 mutation carriers. *Eur J Cancer* 2006;42:650–5.
- Lee E, Ma H, McKean-Cowdin R, et al. Effect of reproductive factors and oral contraceptives on breast cancer risk in BRCA1/2 mutation carriers and noncarriers: results from a population-based study. *Cancer Epidemiol Biomarkers Prev* 2008;17:3170–8.
- 40. Modan B, Hartge P, Hirsh-Yechezkel G, et al. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. *N Engl J Med* 2001;345:235–40.
- 41. Modugno F, Moslehi R, Ness RB, et al. Reproductive factors and ovarian cancer risk in Jewish BRCA1 and BRCA2 mutation carriers (United States). *Cancer Causes Control* 2003;14:439–46.

- 42. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
- 43. Sterne JA, Juni P, Schulz KF, Altman DG, Bartlett C, Egger M. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. *Stat Med* 2002;21:1513–24.
- 44. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
- 45. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med* 1999;18:2693–708.
- 46. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose–response data, with applications to meta-analysis. *Am J Epidemiol* 1992;135:1301–9.
- 47. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med JID 8215016 2002;21:589–624.
- 48. Copas JB, Shi JQ. A sensitivity analysis for publication bias in systematic reviews. *Stat Methods Med Res* 2001;10:251–65.
- Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. Stat Med JID – 8215016 2001;20:641–54.
- 50. SAS Institute Inc. SAS windows version. (8.02). Cary, NC: 1999.

### **APPENDIX O**

#### **HHS PUBLIC ACCESS**

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### FALLOPIAN TUBE LIGATION OR SALPINGECTOMY AS MEANS FOR REDUCING RISK OF OVARIAN CANCER

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#### The Problem of Ovarian Cancer

Ovarian cancer remains the most lethal gynecologic malignancy in the United States, both in rate of fatality (64 percent of patients ultimately die of their disease [1]) and in overall deaths (14,270 in 2014 [2]). Although 50–75 percent of patients treated with chemotherapy initially respond to the medications, most will have recurrences of the disease [1]. The driving force behind the poor survival rates is the stage at diagnosis. Approximately 65 percent of patients present with widespread (stages III or IV) disease, at which point

cure is uncommon [2]. For patients with stage I disease, on the other hand, five-year survival rates exceed 90 percent [2].

One reason that most patients are diagnosed at late stages is that the clinical symptoms of ovarian cancer usually do not become apparent until the disease has disseminated throughout the peritoneal cavity. Although multiple attempts have been made to develop screening programs aimed at detecting early-stage disease, current screening methods are fraught with low sensitivity and specificity, high falsepositive rates, and an unfavorable balance between the risks of early intervention and the benefits of cancer risk reduction [2-4].

#### **Attempts at Ovarian Cancer Screening**

Because the clinical symptoms of ovarian cancer are vague and often appear late in the course of disease, numerous attempts have been made to initiate screening programs to identify preclinical disease in asymptomatic women [3]. Some methods for screening include pelvic examination, ultrasound, and blood testing. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial found that screening did more harm than good with respect to ovarian cancer [3]. Specifically, study subjects underwent unnecessary surgeries that did not diagnose ovarian cancer and were associated with intraoperative and postoperative complications. The United Kingdom Collaborative Trial of Ovarian Cancer Screening, published in 2015, found that serial testing of the cancer antigen (CA) 125 protein, interpreted according to the Risk of Ovarian Cancer Algorithm (ROCA), and ultrasound were better at detecting ovarian cancer than a single threshold CA 125 test [5]. Ultimately, screening for ovarian cancer is not ready for application outside of clinical trials because the results have not been validated in independent cohorts. Clinicians must maintain a high index of suspicion, i.e., consider ovarian cancer a likely possibility, to clinically diagnose it.

Due to the absence of an effective screening algorithm for assessing risk or clinical symptoms that develop with earlystage disease, primary prevention strategies are crucial for reducing ovarian cancer-related deaths.

# **Experience from Hereditary Breast and Ovarian Cancer** Syndromes

Identifying patients at increased risk for ovarian cancer is key to prevention, early detection, and, ultimately, improving survival. Those with BRCA1 mutations have a 39-46 percent lifetime risk of ovarian cancer, those with BRCA2 mutations have a 10–27 percent risk, and up to 24 percent of those with Lynch syndrome will develop ovarian cancer [6]. At this time, the best tools that clinicians have for ovarian cancer prevention are a thorough family history and testing appropriate patients for genetic susceptibility [7]. The Society of Gynecologic Oncologists (SGO) policy statement on genetic counseling says unaffected individuals with increased risk-i.e., relatives with ovarian cancer; a family history suggestive of Lynch syndrome based on Amsterdam Criteria or Bethesda Guidelines; known mutations in the family or a family member diagnosed with breast cancer before age 45; multiple breast cancers, male breast cancer, pancreatic cancer, or aggressive prostate cancer (with a Gleason score of 7 or above)-should be referred for genetic counseling and, potentially, testing for germline mutations in BRCA [7]. If BRCA mutations or Lynch syndrome are identified, the National Comprehensive Cancer Network (NCCN) recommends removal of both fallopian tubes and ovaries between the ages of 35 and 40, based on the particular mutation carried. CA 125 tests and pelvic ultrasound have been considered, but there is not sufficient evidence that these tests are sensitive or specific enough to obviate the need for surgery [8].

#### Fallopian Origin and Prevention of Ovarian Cancer

A proposed model for ovarian carcinogenesis arising in the fallopian tube has emerged over the last decade [9, 10]. This

tubal-origin hypothesis has gained traction with identification of pre-invasive lesions in the fallopian tubes of high-risk patients undergoing risk-reducing surgery [10]. Thus, bilateral salpingectomy with ovarian conservation was proposed as a "middle-ground" method of primary prevention, with the benefit of removing potential tissue of origin and without the risks of surgical menopause. This method has been proposed for clinical trials in high-risk patients, but results are not currently available [11]. The SGO clinical in 2013 published a practice statement recommending that a bilateral salpingectomy should be considered "at the time of abdominal or pelvic surgery, hysterectomy, or in lieu of tubal ligation" [12]. The American College of Obstetricians and Gynecologists (ACOG) had a more tempered statement, saying that salpingectomy should be considered for population-risk patients, i.e., those without increased risk based on personal or family history, but they were clear that the approach to pelvic surgery, hysterectomy, or sterilization should not change simply to increase the chances of completing bilateral salpingectomy [13]. Both of these statements were more conservative than the proposed plan of the British Columbia Ovarian Cancer Research Group program, instituted in 2010, which involved performing opportunistic salpingectomy with benign hysterectomy or in lieu of bilateral tubal ligation for permanent contraception. These authors suggested that this approach would yield a 20-40 percent population risk reduction for ovarian cancer over the next 20 years [14].

The estimated risk reduction for any individual person undergoing opportunistic salpingectomy is up to 50 percent [14]. Although this is an appreciable benefit, it must be tempered with a reminder that women at population risk of ovarian cancer have only a 1:70 or 1.4 percent lifetime risk [14]. The significant benefits of opportunistic salpingectomy, besides the risk reduction, are the ease and speed of the procedure, the rarity of complications, the convenience of removing the specimen, and the fact that surgical removal is theoretically the only way to permanently reduce the risk of ovarian cancer [15] (although bilateral tubal ligation without salpingectomy has also been associated with decreased risk [16]). Whether salpingectomy is more beneficial than tubal ligation has not been established.

#### **Unresolved Questions**

Despite the popularity of salpingo-oophorectomy as a method of reducing risk of ovarian cancer, data from the Nurses' Health Study suggest that oophorectomy before age 47.5 years may be associated with increased risk of death from other causes, such as cardiovascular disease [4], and that the actual permanent risk reduction with salpingectomy, as opposed to the theoretical 50 percent reduction [14], is not entirely clear.

Numerous questions remain regarding the optimal timing of salpingectomy, as the timespan during which the ovaries are susceptible to induction of cancer from the fallopian tubes is certainly not infinitely large. A bilateral salpingectomy at age 30 is logically more effective at risk reduction than the same surgery at age 60. Unfortunately, the relationship between time and risk reduction has not been not characterized, and prospective studies of the effect of age at salpingectomy on risk reduction would require prohibitively large cohort sizes and long follow-up periods. Similarly, there are other commonly accepted interventions associated with risk reduction, including oral contraceptive pill use and breastfeeding [2, 15, 16]. It is not known how salpingectomy and oral contraceptive pill use interact with one another, although presumably women with a history of bilateral salpingectomy will use birth control pills less frequently, given that the prevention of unintended pregnancy is no longer a concern.

Another unresolved question is whether salpingectomy should be used instead of tubal ligation for a "two birds with one stone" approach to sterilization and risk reduction. Caution should be exercised when choosing salpingectomy over tubal ligation for sterilization, not because of the inability to reverse salpingectomy-tubal ligation also should not be performed on women who may desire future childbearing, and in vitro fertilization is a viable method of achieving pregnancy after salpingectomy or tubal ligation [17]-but because "low-risk" surgery does not equal "no risk." We should be cautioned by prior experience with opportunistic appendectomy at the time of cesarean section or hysterectomy [18]: with opportunistic appendectomy, stump leaks, bleeding, and infection were all possible. Furthermore, salpingectomy increases the length of the operation, and length of surgery has consistently been identified as an independent risk factor for postoperative morbidity [19–23], so even an opportunistic salpingectomy can increase some risks.

Another issue is that payers may be reluctant to authorize the charges for risk-reducing procedures, given the number needed to prevent a single case of ovarian cancer. The theoretical number needed reported by Kwon and colleagues in 2015 was 273 for salpingectomy at the time of hysterectomy and 366 for salpingectomy in lieu of other tubal occlusion methods for sterilization [14]. Although these numbers are on the same order of magnitude as the number needed to vaccinate with the human papilloma virus vaccine in the United States [14], the costs associated with vaccination are less than the costs of salpingectomy.

#### Conclusions

Ultimately, we think ACOG's recommendation of a discussion about risks and benefits of removing both fallopian tubes at the time of hysterectomy is reasonable. However, we cannot place enough importance on the statement, "the approach to hysterectomy or sterilization should not be influenced by the theoretical benefit of salpingectomy" [13]. In the absence of results from prospective studies, which will not be available for decades,

fallopian tubes should be removed when a convenient opportunity arises, but extensive surgery should not be attempted just for that purpose.

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#### References

- 1. Sopik V, Igbal J, Rosen B, Narod SA. Why have ovarian cancer mortality rates declined? Part II. Case-fatality. Gynecol Oncol. published online ahead of print June 14, 2015. 10.1016/j.ygyno. 2015.06.016
- Sopik V, Igbal J, Rosen B, Narod SA. Why have ovarian cancer mortality rates declined? Part I. Incidence. Gynecol Oncol. published online ahead of print June 14, 2015. 10.1016/j.ygyno. 2015.06.017
- Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA. 2011; 305(22):2295–2303. [PubMed: 21642681]
- 4. Parker WH, Feskanich D, Broder MS, et al. Long-term mortality associated with oophorectomy compared with ovarian conservation in the nurses' health study. Obstet Gynecol. 2013; 121(4):709–716. [PubMed: 23635669]
- Menon U, Ryan A, Kalsi J, et al. Risk algorithm using serial biomarker measurements doubles the number of screen-detected cancers compared with a singlethreshold rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. J Clin Oncol. 2015; 33(18):2062–2071. [PubMed: 25964255]
- Lancaster JM, Powell CB, Chen LM, Richardson DL. SGO Clinical Practice Committee. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions.

Gynecol Oncol. 2015; 136(1):3–7. [PubMed: 25238946]

- 7. American College of Obstetricians and Gynecologists Committee on Gynecologic Practice. Committee Opinion No. 477: the role of the obstetriciangynecologist in the early detection of epithelial ovarian cancer. Obstet Gynecol. 2011; 117(3):742–746. [PubMed: 21343791]
- 8. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: genetic/ familial high-risk assessment: breast and ovarian version 1.2015.
- Kurman RJ, Shih IeM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol. 2010; 34(3):433–443. [PubMed: 20154587]
- Kindelberger DW, Lee Y, Miron A, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: evidence for a causal relationship. Am J Surg Pathol. 2007; 31(2):161–169. [PubMed: 17255760]
- Greene MH, Mai PL, Schwartz PE. Does bilateral salpingectomy with ovarian retention warrant consideration as a temporary bridge to risk-reducing bilateral oophorectomy in BRCA1/2 mutation carriers? Am J Obstet Gynecol. 2011; 204(1):19e1–19.e6. [PubMed: 20619389]
- 12. Society of Gynecologic Oncology (SGO). [Accessed July 27, 2015] SGO clinical practice statement: salpingectomy for ovarian cancer prevention. Nov. 2013 https://www.sgo.org/clinicalpractice/guidelines/sgo-clinical-practice-statementsalpingectomy-for-ovarian-cancer-prevention/
- 13. American Congress of Obstetricians and Gynecologists Committee on Gynecologic Practice. Committee opinion no. 620: salpingectomy for ovarian cancer

prevention. Obstet Gynecol. 2015; 125(1):279–281. [PubMed: 25560145]

- Kwon JS, McAlpine JN, Hanley GE, et al. Costs and benefits of opportunistic salpingectomy as an ovarian cancer prevention strategy. Obstet Gynecol. 2015; 125(2):338–345. [PubMed: 25568991]
- Cibula D, Widschwendter M, Májek O, Dusek L. Tubal ligation and the risk of ovarian cancer: review and meta-analysis. Hum Reprod Update. 2011; 17(1):55– 67. [PubMed: 20634209]
- Cibula D, Widschwendter M, Zikan M, Dusek L. Underlying mechanisms of ovarian cancer risk reduction after tubal ligation. Acta Obstet Gynecol Scand. 2011; 90(6):559–563. [PubMed: 21355863]
- Lin YJ, Ou YC, Huang FJ, Lin PY, Kung FT, Lan KC. Ovarian response to gonadotropins in patients with tubal factor infertility: salpingectomy versus nonsalpingectomy. J Minim Invasive Gynecol. 2013; 20(5):637–641. [PubMed: 23706676]
- ACOG Committee on Gynecologic Practice. ACOG Committee Opinion #323: elective coincidental appendectomy. Obstet Gynecol. 2005; 106(5 pt 1):1141–1142. [PubMed: 16260547]
- Matulewicz RS, Sharma V, McGuire BB, Oberlin DT, Perry KT, Nadler RB. The effect of surgical duration of transurethral resection of bladder tumors on postoperative complications: an analysis of ACS NSQIP data. Urol Oncol. 2015; 33(8):338 e19–338.e24. [PubMed: 26072111]
- Catanzarite T, Saha S, Pilecki MA, Kim JY, Milad MP. Longer operative time during benign laparoscopic and robotic hysterectomy is associated with increased 30day perioperative complications. J Minim Invasive Gynecol. published online ahead of print June 9, 2015. 10.1016/j.jmig.2015.05.022

- Qin C, de Oliveira G, Hackett N, Kim JY. Surgical duration and risk of urinary tract infection: an analysis of 1,452,369 patients using the National Surgical Quality Improvement Program (NSQIP). Int J Surg. 2015; 20:107–112. [PubMed: 26054658]
- Tan TW, Kalish JA, Hamburg NM, et al. Shorter duration of femoral-popliteal bypass is associated with decreased surgical site infection and shorter hospital length of stay. J Am Coll Surg. 2012; 215(4):512–518. [PubMed: 22819641]
- Reames BN, Bacal D, Krell RW, Birkmeyer JD, Birkmeyer NJ, Finks JF. Influence of median surgeon operative duration on adverse outcomes in bariatric surgery. Surg Obes Relat Dis. 2015; 11(1):207–213. [PubMed: 25066438]

# **APPENDIX P**

# WHY HAVE OVARIAN CANCER MORTALITY RATES DECLINED? PART I. INCIDENCE

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### ABSTRACT

The age-adjusted mortality rate from ovarian cancer in the United States has declined over the past several decades. The decline in mortality might be the consequence of a reduced number of cases (incidence) or a reduction in the proportion of patients who die from their cancer (case-fatality). In part I of this three-part series, we examine rates of ovarian cancer incidence and mortality from the Surveillance Epidemiology and

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End Results (SEER) registry database and we explore to what extent the observed decline in mortality can be explained by a downward shift in the stage distribution of ovarian cancer (i.e. due to early detection) or by fewer cases of ovarian cancer (i.e. due to a change in risk factors). The proportion of localized ovarian cancers did not increase, suggesting that a stage-shift did not contribute to the decline in mortality. The observed decline in mortality paralleled a decline in incidence. The trends in ovarian cancer incidence coincided with temporal changes in the exposure of women from different birth cohorts to various reproductive risk factors, in particular, to changes in the use of the oral contraceptive pill and to declining parity. Based on recent changes in risk factor propensity, we predict that the trend of the declining age-adjusted incidence rate of ovarian cancer in the United States will reverse and rates will increase in coming years.

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#### I. Introduction

Ovarian cancer accounts for 3% of all cancers in women, but is overrepresented in terms of cancer deaths (5%). In 2014, in the United States, 21,980 women were diagnosed with ovarian cancer and 14,270 women died of it [1]. Ovarian cancer is primarily a disease of postmenopausal women; approximately 70% of cases and 85% of ovarian cancer deaths occur after age 55 [2]. A woman who is diagnosed with breast cancer at age 70 is likely to die of another cause [3] — in contrast, if a woman is diagnosed with ovarian cancer at age 70, there is an 80% chance that the cancer will cause her death [4]. This is because the fatality rate is high (70%) and because 80% of deaths occur within five years of diagnosis [4]. As the American population ages and expands [5], the annual number of ovarian cancer cases is expected to rise. In order to reduce the burden of ovarian cancer in the population, it is necessary to prevent deaths across the age spectrum, and in particular, deaths in older women.

The modern era of ovarian cancer therapy began in 1977 with the introduction of cis-platinum. Nowadays, over 60% of women with invasive ovarian cancer are treated with debulking surgery and with a combination of a platinum agent and a taxane [6]. Since 1975, the mortality rate for ovarian cancer in the USA has declined by 23% [7]; it is tempting to conclude that the decline was the consequence of chemotherapy, but before doing so, it is prudent to explore alternative explanations. In the first two parts of the three-part series, we examine SEER rates of ovarian cancer incidence, case-fatality and mortality, with reference to calendar year, age and tumour stage, and we consider possible reasons for the observed decline in mortality. In Part I, we consider if the decline was
due to a reduced number of cases (through changing trends in elective oophorectomy and/or in reproductive risk factors) or

elective oophorectomy and/or in reproductive risk factors) or was due to a downward stage shift at presentation (through screening or better awareness). In part II, we consider if the decline in mortality was due to new and better treatments [8]. In part III, we discuss potential approaches for reducing ovarian cancer mortality in the future, through prevention, early detection and treatment [9].

Mortality rates describe the number of deaths from ovarian cancer in a given year, relative to the size of the population. A decline in mortality may reflect a reduction in the number of women diagnosed with ovarian cancer (incidence) or a reduction in the proportion of ovarian cancer patients who die from their disease (case-fatality). After a decline in incidence or in case-fatality, there will be a corresponding decline in mortality following a lag period of several years.

The Surveillance, Epidemiology, and End Results (SEER) registry has reported incidence, case-fatality and mortality data for 26% of the United States population since 1975 [7]. The use of standardized (versus crude) rates removes the effect of any changes in the age distribution of the underlying population in order to facilitate comparisons over time. All age-adjusted incidence and mortality rates are standardized to the 2000 United States population (the standard population) and are expressed in terms of cases per 100,000 women per year. We complement the SEER data analysis by cross-referencing other data sources which compile information on reproductive risk factors and oophorec-tomies. Information on the use of oral contraceptives, parity, breast-feeding and tubal ligations was abstracted from questionnaires that were completed by 2000 North American women without ovarian cancer who attended a clinic appointment for BRCA genetic testing at our research laboratory and were found to be negative for mutations in Oophorectomy data were obtained from the BRCA1/2. National Health Discharge Survey database maintained by the

Centers for Disease Control and the National Center for Health Statistics.

### 2. Trends in mortality

From 1975 to 2011, in the United States, the age-adjusted mortality rate from ovarian cancer declined by 23%, from 9.8 per 100,000 per year to 7.5 per 100,000 per year. The rate declined by 8% from 1975 to 2001 and by 17% from 2002 to 2011 (Fig. 1).

The 23% decline in the age-adjusted mortality rate is an indication that progress has been made; however, it does not reflect the actual burden of the disease in the United States. The total number of ovarian cancer deaths in a given year is influenced by the age-specific mortality rates, as well as by the age-distribution and the size of the population at risk The unadjusted (i.e. crude) mortality rate is calculated by dividing the total number of ovarian cancer deaths in a given year by the total number of women in the population. From 1975 to 2011, the crude mortality rate fell by only 2% (from 93 per 100,000 per year to 9.1 per 100,000 per year) (Fig. S1). That is, the aging of the female population between 1975 and 2011 has offset the decline in age-specific mortality rates. From 1975 to 2011, the total number of ovarian cancer deaths in the United States increased by 38%, from 10,367 deaths to 14,323 deaths, despite the 23% reduction in the age-adjusted mortality rate.

The trends in age-adjusted mortality differed for women in different age groups (Fig. S2). From 1975 to 2011, for women from ages 50 to 64, the mortality rate declined continuously (by 44.7%). For women between ages 65 to 74, the mortality rate first increased (by 9.2% from 1975 to 1991) and then declined (by 22.8% from 1991 to 2011). For women ages 75 and older, the rate increased by 43% from 1975 to 2002 and then declined (by 123% from 2002 to 2011).

Trends in age-specific rates may be attributable to period and/or cohort effects. A period effect results from the introduction of a change that affects the risk of an entire population simultaneously, irrespective of age. A cohort effect compares the lifetime experiences of individuals grouped by year of birth. For example, women who were 50 years of age in 1975, 65 years of age in 1990 and 75 years of age in 2000 all belong to the same birth cohort — the first women exposed to the oral contraceptive pill, which was introduced in 1960 [10].

## 3. Trends in incidence

Incidence rates describe the number of women who are diagnosed with ovarian cancer in a given year, relative to the size of the population. Incidence rates are calculated by dividing the number of cases by the population at risk. Only people with ovaries are at risk for developing ovarian cancer (i.e. males are not included in the denominator of ovarian cancer rate calculations). Women who have had their ovaries removed are also, by definition, not at risk for ovarian cancer, but these women are not excluded from the population at risk in SEER incidence and mortality rates. Changes in the proportion of women in the population with intact ovaries may therefore influence trends in ovarian cancer incidence and mortality. Incidence rates differ from mortality rates because not all women who are diagnosed with ovarian cancer will die from it. If a particular factor affects the incidence of ovarian cancer, the impact on the number of ovarian cancer deaths will not be seen until several years later. The lag period between a change in incidence and a change in mortality reflects the survival times of the patients (i.e. from diagnosis to death).

The observed trends in ovarian cancer incidence parallel the trends in ovarian cancer mortality. From 1975 to 2011, the age-adjusted ovarian cancer incidence rate fell by 26%, from 163 per 100,000 women per year to 12.1 per 100,000 women per year (Fig. 2). Ovarian cancer incidence declined by 3.4% from 1975 to 1991 and by a further 23% from 1991 to 2011. The decline, which began in 1991, was followed by a decline in mortality about 10 years later.

The trends in incidence varied for women from different age groups (Fig. S3). From 1975 to 2011, ovarian cancer incidence

in women ages 50 to 64 years fell by 13.5 per 100,000 per year (a relative decline of 36%). Incidence in women ages 65 to 74 rose by 8.6 per 100,000 per year from 1975 to 1985 (a relative increase of 17%), and then fell by 18.4 per 100,000 per year from 1985 to 2011 (a relative decline of 31%). Incidence in women ages 75 and older rose by 14.8 per 100,000 per year from 1975 to 1993 (a relative increase of 31%) and 133 per 100,000 per year from 1993 to 2011 (a relative decline of 21%). The decline in incidence in women ages 65 and older suggests that the reduction in ovarian cancer deaths is the result of a reduction in cases of ovarian cancer (surprisingly, in 1984 and 1985, the age-specific incidence rates were higher in women ages 65 to 74 than in women ages 75 and older. This is unexpected, given that incidence rates for ovarian cancer typically increase monotonically with age (Fig. 3). This transient reversal in 1984 and 1985 may be an artifact of sampling error or small sample size rather than a true increase in incidence. It might also reflect changing constellations in risk factor propensity for ovarian cancer).

# Fig. 1 Ovarian cancer mortality rates, United States, 1975 to 2011 (age-adjusted).

\* \* \*

In 2011, the incidence rate of ovarian cancer in the United States peaked among women ages 80 and older (Fig. 3), whereas the incidence count of ovarian cancer (i.e. the actual number of new ovarian cancer diagnoses) peaked among women ages 60 to 64, and then declined (Fig. S4). Women who were 60 to 64 years old in 2011 were born between 1946 and 1950, and represent the first born of the baby boom generation. After age 80, women tend to die of other causes and the at risk population becomes smaller.

## 4. Early detection

If the decline in ovarian cancer mortality were attributable to improvements in early detection (i.e. through screening or better

awareness) we would expect to see a stage-shift in disease at presentation. Ovarian cancer may be diagnosed because of symptoms (e.g. abdominal pain) or signs of disease (e.g. distended abdomen), or as a consequence of a positive screening test in an asymptomatic woman (i.e. abnormal pelvic examination, serum CA125 concentration or trans-vaginal ultrasound). The definitive diagnosis of ovarian cancer requires histological confirmation; the conventional date of diagnosis is the date of surgery.

## Fig. 2 Ovarian cancer incidence and mortality rates (age-adjusted).

\* \* \*

# Fig. 3 Age-specific ovarian cancer incidence rates, by age, 2011.

#### \* \* \*

In the SEER database, between 1975 and 2011, ovarian cancers were classified as either localized, regional or distant, based on the extent of cancer present at the time of surgery (i.e. stage at diagnosis). Localized disease (stage I) refers to ovarian cancer that is confined to the ovary, regional (stage II) refers to ovarian cancer that is confined to the pelvic tissues (uterus, fallopian tubes, ovaries or other intra-peritoneal tissues), and distant (stage III/IV) refers to ovarian cancer that has spread beyond the pelvic tissues (i.e. retroperitoneal lymph nodes, peritoneal cavity, liver, spleen or pleural effusion). The goals of staging are to aggregate patients into groups who have a similar prognosis and who require a similar approach to treatment, and to facilitate comparisons over time.

Statistical cure is defined as the point in time following diagnosis when the mortality rate from ovarian cancer is the same as the mortality rate of women in the general population. Ovarian cancer patients who survive for 12 years may be considered cured [11]. In the following pages, the term "cure rate" refers to the proportion of patients who are alive 12 years after diagnosis. The cure rate for patients with localized ovarian cancer is 88%; however, most patients (65%) present with distant-stage ovarian cancer, and for them the cure rate is 18% (SEER database).

It is hoped that the proportion of women who are diagnosed with early-stage ovarian cancer (and who are ultimately cured) might be increased through screening (i.e. by identifying presymptomatic ovarian cancer), through increased awareness (i.e. by reducing the time from first symptoms to doctor visit) or through better diagnostic methods (i.e. by reducing the time from first doctor visit to pathologic confirmation of ovarian cancer). If ovarian cancer screening has contributed to the observed decline in mortality, we would expect to see an increase in the incidence of localized ovarian cancer and a decrease in the incidence of distant ovarian cancer (i.e. a stageshift). From 1975 to 2011, the incidence of localized ovarian cancer fell by 1.5 per 100,000 per year (a relative decline of 35%), the incidence of regional ovarian cancer fell by 0.1 per 100,000 per year (a relative decline of 8%), and the incidence of distant ovarian cancer fell by 2.1 per 100,000 per year (a relative decline of 22%) (Fig. 4). The incidence of ovarian cancer has declined at all stages; therefore it is unlikely that screening has had a significant impact on ovarian cancer rates.

An increase in the incidence of early-stage ovarian cancer without a proportionate decline in late-stage ovarian cancers is an indicator of overdiagnosis, i.e. the detection of low-risk cancers that might never become clinically apparent in the absence of screening (and rarely lead to death). For ovarian cancer, the detection of borderline tumours through screening may be considered examples of overdiagnosis; in general, these cancers do not progress into high-grade or advanced-stage tumours [12]. The absence of a significant increase in the incidence of localized ovarian cancer through screening precludes overdiagnosis. Further, there is no evidence that invasive ovarian cancers, however small, regress spontaneously.

Several randomized control trials have shown that screening asymptomatic women using trans-vaginal ultrasound and CA125 can detect a significant proportion of ovarian cancers in pre-clinical and early stages [11,12]; however, no screening protocol has yet been shown to reduce the number of advanced stage diagnoses or the number of ovarian cancer deaths [13]. Other approaches to ovarian cancer screening that are being evaluated include the use of serial CA125 measurements (e.g. the Risk of Ovarian Cancer Algorithm) [14] and the addition of other bio-markers (e.g. Human Epididymis Protein 4) in combination with CA125 [15]. The United States Preventive Services Task Force currently recommends against screening for ovarian cancer in asymptomatic women at average risk [16].

The symptoms of ovarian cancer are non-specific (e.g. bloating, pelvic pain or bowel irregularities) and patients and doctors may overlook their potential significance. Retrospective studies have reported delays of four to six months from symptom onset to a diagnosis of ovarian cancer [17-19]. Delays attributable to the patient and the doctor are roughly equal; about 70% of patients present with symptoms to their doctor within two months of first symptom onset, and about 65% of patients are diagnosed with ovarian cancer within two months after presenting with symptoms to their doctor. There has recently been an impetus to increase awareness of ovarian cancer symptoms in an attempt to reduce the time from first symptoms to diagnosis with the hope of improving ovarian cancer survival rates [20].

If formal efforts to increase awareness are successful, there should be an increase in the proportion of cancers diagnosed at an early stage. However, from 1975 to 2011, the proportion of patients with localized ovarian cancer declined from 29% to 25% (Fig. S5). This indicates that early diagnosis through

better awareness has not contributed to the observed decline in mortality.

## Fig. 4

# Ovarian cancer incidence rates, by stage at diagnosis, 1975 to 2011 (age-adjusted).

\* \* \*

It has recently been proposed that early detection of ovarian cancer should strive towards the diagnosis of low-volume advanced stage ovarian cancer, rather than the identification of early-stage (stages I and II) ovarian cancer [21]. The best predictor of long-term survival from advanced stage ovarian cancer is primary surgical resection to no residual disease (i.e. no visible tumour remaining in the abdomen) [22], and the lower the volume of tumour at presentation, the greater the probability that surgery will result in no residual disease [23]. Better awareness of ovarian cancer symptoms might result in an improvement in survival rates among patients with advanced stage ovarian cancer, rather than a stage shift per se. The premise for earlier diagnosis of ovarian cancer in symptomatic women is currently being investigated by the Diagnosing Ovarian Cancer Early (DOvE) study in Canada. In the preliminary report, prompt screening of symptomatic women with CA125 and trans-vaginal ultrasound identified a greater proportion of early-stage ovarian cancers compared with patients diagnosed through usual assessment (36% versus 23%) and a greater proportion of low-volume advanced stage ovarian cancers (35% versus 21% in clinic patients) [21]. Importantly, 73% of patients diagnosed through prompt screening based on symptoms had no residual disease after debulking surgery (versus 44% of clinic patients). In comparison, between 30% and 40% of women with advanced stage ovarian cancer in the United States currently achieve a status of no residual disease through primary debulking surgery [24]. This is discussed in greater detail in part II.

#### 5. Ovarian cancer histology

Approximately 90% of all ovarian cancers arise from ovarian or fallopian tube epithelial cells. Ovarian carcinomas are of four main histologic types: serous (68%), endometrioid (20%), clear cell (8%) and mu-cinous (6%). The 12-year survival rates (all stages) of patients with endometrioid (57%), clear cell (64%) or mucinous carcinoma (58%) are superior to that of patients with serous ovarian carcinoma (27%) (Table S1). A shift in the histological distribution of ovarian carcinomas over time may therefore impact on mortality rates.

It has recently been proposed that the category of serous carcinomas be subdivided into two subcategories, which are distinguishable from each other (primarily) by grade. The largest category, high-grade serous carcinomas, comprises 90% of the total. It is proposed that the majority of high-grade serous carcinomas arise from the epithelium of the fallopian tube [25].

SEER does not distinguish between high-grade and lowgrade serous carcinomas. The distinction has important implications for treatment; the smaller group (low-grade serous carcinomas) does not respond to chemotherapy. The distinction is also potentially important for screening and prevention. In principal, the greatest impact of any prevention program will be realized by reducing the number of highgrade serous cancers (discussed in part III). Also, screening must go beyond detecting non-serous and low-grade serous carcinomas if it is to be used to reduce ovarian cancer mortality.

#### 6. Ethnic group

The incidence of ovarian cancer is higher in white women than in women from other racial or ethnic groups (Table S2). Ovarian cancer survival rates at 12 years are superior in white women (38%) compared with African-American women (32%) but they are inferior compared with Hispanic women (43%) and Asian women (52%). If the relative frequencies of the various racial and ethnic groups in the United States population change appreciably over time, this might impact on ovarian cancer incidence and mortality rates. From 1970 to 2011, the proportion of females that were white dropped from 87% to 80% [26]. At the same time, the proportion of Asian women increased from 1% to 5%. From 1992 to 2011, ovarian cancer incidence fell by 19% in white women, by 8% in African-American and by 8% in Asian women.

## 7. Bilateral oophorectomy

Bilateral oophorectomy refers to the surgical removal of the ovaries. Elective bilateral oophorectomy may be undertaken for the prevention of ovarian cancer or for the treatment of benign conditions such as pelvic pain, ovarian cysts or Approximately 90% of all elective endometriosis [27]. oophorectomies in the United States are performed as an adjunct operation in women who undergo hysterectomy for a benign condition [28]. At the time of hysterectomy, about 45% of pre-menopausal women and 75% of post-menopausal women undergo a concomitant bilateral (salpingo-) oophorectomy [29]. Women who have had their ovaries (and tubes) removed have a 95% reduction in their risk of developing ovarian cancer [30,31]. The probability that a woman will have both ovaries intact (i.e. have not undergone an elective bilateral oophorectomy) at a given age can be calculated based on the age-specific rates of bilateral oophorectomy for each year since birth.

Between 1965 and 2005, the rates of elective bilateral oophorectomy fluctuated between 1.5 and 3.0 per 1000 women per year [32,33]. Following the Women's Health Initiative report on the adverse health effects associated with the use of hormone replacement therapy in 2002 [34], rates of oophorectomy in premenopausal women began to decline [35]. In 2008, the American Congress of Obstetricians and Gynecologists released a statement recommending against prophylactic bilateral oo-phorectomy in women below age 45 [36].

From 1975 to 2005, there was a steady decline in the proportion of women in the population without ovaries. Women from recent birth cohorts (i.e. born after 1950) have had fewer oophorectomies than older women (Fig. S6). In 2005, an estimated 19% of women ages 70 and older have previously undergone an elective bilateral oophorectomy (Fig. S7). We estimate that, in the absence of these oophorectomies, there might have been 25,155 cases of ovarian cancer in 2005 versus 21,557 observed (i.e. about 14% of ovarian cancers were prevented in 2005 as a result of elective bilateral oophorectomies).

#### 8. Risk factors for ovarian cancer

The principal risk factors for ovarian cancer are oral contraceptives, pregnancy, breast-feeding and tubal ligation [37]. These factors are of particular importance as they are protective, ubiquitous, and they have significant and long-lasting effects. Temporal changes in exposure to these four risk factors are expected to impact upon ovarian cancer incidence and mortality rates. Few risk factors that increase the risk of ovarian cancer have been confirmed; these include hormone replacement therapy [38], talcum powder [39], high body mass index [40] and endometriosis [41] and are not considered here. The role of genetic predisposition in ovarian cancer is discussed in part III [9].

#### Fig. 5

# Proportion of women in 2014 who have ever taken an oral contraceptive, by age.

\* \* \*

We plotted the age-specific incidence rates for ovarian cancer by birth cohort (Fig. S8). The cumulative risk of ovarian cancer to age 70 was 1.1% for women born in 1920 and was 0.98% for women born in 1940 (a relative decline of 10.9%). The cumulative risk to age 50 was 0.29% for women born in 1940 and was 0.25% for women born in 1960 (a relative decline of 13.8%). (Because age-specific incidence data are only available beginning in 1975,

cumulative risk estimates for earlier birth cohorts are partially based on incidence rates from later birth cohorts, and will underestimate any difference in risk between birth cohorts.)

Using data abstracted from questionnaires that were completed by 2000 women from North America, we estimated the probability that women born in various birth cohorts (from 1920 to 1969) were exposed to each risk factor at some time (Table S3), and based on the estimates for each risk factor we generated relative risks for developing ovarian cancer at or above age 60 compared with a theoretical reference group with no exposure (Fig. 5).

#### 8.1. Oral contraceptives

Oral contraceptives were introduced in the United States in 1960 by G.D. Searle and Company [10]. Women of reproductive age in 1960 (ages 15 to 44) were born between 1920 and 1945. The proportion of women who have ever taken an oral contraceptive increased from 18% for women born in 1920 to 84% for women born in 1945, and has remained stable at 83% to 86% thereafter (Table S3).

On average, women who have ever used oral contraceptives have a 25% reduced risk of ovarian cancer compared with women that have never used oral contraceptives [42]. The level of protection increases with the duration of use and attenuates with time since last use. Thirty years after discontinuation of an oral contraceptive, the relative risk for ovarian cancer is approximately 0.8 for less than five years of use, 0.7 for five to ten years of use and 0.6 for more than 10 years of use. Because most women with ovarian cancer are diagnosed after age 60, the full impact of exposure to oral contraceptives on ovarian cancer incidence and mortality has only recently been observed.

In the United States population in 2014, about 85% of women below age 70 have previously taken an oral contraceptive, whereas only 18% of women age 90 to 95 have previously taken an oral contraceptive (Fig. 5). This indicates that between 1990 and 2015, the proportion of 70-year old women who had ever taken an oral contraceptive increased from about 20% to 85%.

## 82. Parity

On a population basis, parity is the second most important risk factor for ovarian cancer. The relative risk for ovarian cancer is estimated to be approximately 0.81 per child born (for practical purposes, we limit the protective effect of parity at five births, which corresponds to a 65% reduction in risk, compared with nulliparous women) [37]. In the United States, the average number of children per woman (mean parity) peaked at 3.8 children between 1946 and 1964 (during the post-World War II baby boom), and declined thereafter [43]. The mean parity of women born between 1920 and 1935 fell from 3.9 to 3.0 children (Table S3). This declined further to 1.8 children for women born in 1945 and to 1.5 children for women born in 1965.

#### 8.3. Breast-feeding

Women who breast-feed their infants have a lower risk of ovarian cancer, compared with mothers who do not breast-The relative risk for ovarian cancer among parous feed. women that have ever breast-fed is approximately 0.85 The extent of protection (independent of parity) [44]. increases with duration of breast-feeding (i.e. the total number of months). 51% of mothers born between 1920 and 1924 breast-fed at some point. This fraction dropped to 44% of mothers born between 1935 and 1939, because of increasing numbers of women entering the workforce and because of the introduction and promotion of infant formula around 1970 [45]. In 1975, the proportion of mothers who breast-fed began to increase, stabilizing at 70% to 75% of mothers born in 1960 or later. The resurgence of breast-feeding has been attributed to increased knowledge about the benefits of breastfeeding and successful efforts to increase breast-feeding awareness, initiation and duration [45].

Breast-feeding is unique among risk factors in that the prevalence of ever-exposure is currently increasing (Table S3). However, the extent of protection is dependent on the total duration of breast-feeding (number of months), which in turn, depends on the number of children born (parity). Although the proportion of mothers who breast-feed their infants have increased in the United States, the mean parity of women in the population has decreased; in consequence, the average number of months of breast-feeding in the population has declined.

#### 8.4. Tubal ligation

Tubal ligation is associated with a 15% to 25% reduction in the risk of ovarian cancer [46]. The magnitude of risk reduction is greater for endometrioid and clear cell carcinomas (50%) than for mucinous (30%) and serous carcinomas (20%). The protective effect appears to persist for 20 or more years; however, long-term studies are required to confirm the duration of protection. From 1975 to 1990, there was a shift in contraceptive use among women ages 30 to 44 from the oral contraceptive pill to tubal ligation [47]. The prevalence of tubal ligation increased from 4% of women born in 1920 to about 35% of women born between 1940 and 1949, and has declined thereafter (Table S3).

# 8.5. Relative risk of ovarian cancer from exposure to the four risk factors

Compared with a theoretical cohort of women who have never taken an oral contraceptive, the estimated proportion of cases prevented by the use of oral contraceptives was 3% for women born between 1920 and 1924 and increased to 25% for women born between 1945 and later (Fig. 6). Compared with nulliparous women, parity conferred a 56% reduction in ovarian cancer risk for women born between 1920 and 1924, after which the extent of protection from parity began to decline, with a 32% reduced risk for women born between 1945 and 1949, and a 27% reduced risk for women born between 1965 and 1969. Women born between 1920 and 1945 experienced a 22% reduction in ovarian cancer risk due to oral contraceptives, and a 24% increase in ovarian cancer risk due to declining parity.

The impacts of breast-feeding and tubal ligation on ovarian cancer incidence rates in the United States are modest in comparison with the effects of oral contraceptives and parity. Compared with women who have never breast-fed, the percent of ovarian cancers prevented by breast-feeding is estimated to be 7% for women born in 1920, decreasing to 6% for women born between 1945 and 1954, and then increasing to 9% for women born in 1960 or later (Fig. 6). Compared with women who have not had a tubal ligation, the greatest protection against ovarian cancer from tubal ligations was for women born between 1940 and 1949 (5% risk reduction).

#### 8.6. Cumulative effects

The probability that a woman will develop ovarian cancer in her lifetime depends to a large extent on her cumulative exposure to all risk factors. In the absence of any exposure to the protective factors described above, the lifetime risk of ovarian cancer is estimated to be approximately 2.7% (as opposed to the observed population risk of 1.4%). Fig. S9 shows the overall propensity for women in different birth cohorts to develop ovarian cancer, as a result of exposure to all risk factors. Compared with a theoretical cohort of women with exposure to none of the four risk factors, the percentage of ovarian cancers prevented rises from 66% for women born between 1920 and 1924 to 71% for women born between 1940 and 1944 (a 5% reduction in ovarian cancer risk), and subsequently declines to 63% for women born between 1965 and 1969 (an 8% increase in ovarian cancer risk).

Examination of the trends in reproductive risk factors can be used to predict future ovarian cancer incidence rates. Women born between 1920 and 1945 were below age 65 between 1975 and 2010, corresponding to the continuous decline in ovarian cancer incidence in the 20 to 49 and 50 to 64 age groups since 1975 (Fig. S3). Women born between 1920 and

1945 were between the ages of 65 to 74 years beginning in 1985 (and ending in 2019), coinciding with the decline in incidence in women ages 65 to 74 that also began in 1985. Women born between 1920 and 1945 were 75 years of age and older beginning in 1995. In 2025, these women will be 75 to 100 years of age, at which point the decline in incidence due to risk factors is expected to reverse. (We assume that the relative risk for ever-exposure to a given risk factor is constant with time. We did not account for differences in the duration of exposure or recency of risk factor exposure between birth cohorts. We assume that the relative risks attributable to each factor are independent and cumulative.)

#### 9. Synopsis

From 1975 to 2011, ovarian cancer mortality fell by 23%. The greatest period of decline (18%) was between 2001 and 2011, when mortality fell from 9.0 per 100,000 per year to 7.5 per 100,000 per year. The decline in ovarian cancer mortality is a consequence of a decline in ovarian cancer incidence. The decline in incidence is largely due to the introduction of oral contraceptives in 1960, and the subsequent expansion in their use (from 0% to 85%) from 1960 to 1990. The introduction of oral contraceptives has previously been implicated in declining incidence and mortality rates among women younger than age 60 [48,49], but the impact in older women and on overall mortality is only now being captured.

The SEER database is a very useful resource due to its large size and long period of record; however, there are some intrinsic limitations of using SEER data which should be acknowledged. SEER does not have a centralized review. There may be some misclassification of the ovarian cancer diagnoses in terms of both primary site and histology. The staging classification of ovarian cancer has changed over time. We do not have information on stage for all women and it is possible that some women were classified incorrectly. Our risk factor analysis is based on prevalence data from 2000 North American women

and this may not be representative of the entire United States female population.

## Fig 6

# Relative risk of ovarian cancer from exposure to a given risk factor, by year of birth, compared with a theoretical cohort of women with no exposure to the risk factor. OCP - oral contraceptive pill.

\* \* \*

#### 10. Future trends

In 2025, it is estimated that 85% of women younger than age 80 will have taken an oral contraceptive at some time, and the mean parity will fall below two. The total duration of breast-feeding in the population and the proportion of women with a tubal ligation are also declining. As a result, after 2025 age-standardized ovarian cancer incidence rates will increase. Due to the aging of the baby boom generation (i.e. women born between 1946 and 1965), the mean age of the United States population is increasing. The population is also expanding in size. As a result, we estimate that from 2010 to 2030 the annual number of ovarian cancer cases diagnosed in the USA will increase by 37%, from 20,921 cases to 28,591 The number of cases will increase by 18% (3698 cases. cases) due to a shift in the age-distribution and by 19% (3972 cases) due to population growth. Based on changing risk factor propensity and changing population demographics, we expect to see an increase in the number of ovarian cancer cases over the next 15 to 30 years.

In part II, we examine SEER rates of ovarian cancer casefatality, and we explore to what extent advances in ovarian cancer treatment contribute to the decline in ovarian cancer mortality [8]. In part III, we discuss future prospects for reducing ovarian cancer mortality, which incorporate genetic testing, preventive surgery, screening and treatment [9].

## **Conflict of interest**

The authors have nothing to disclose.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/jygyno.2015.06.017.

#### References

- [1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2015, CA Cancer J. Clin. 65 (1) (2015) 5-29.
- [2] U.S. Cancer Statistics Working Group, United States Cancer Statistics: 1999-2011 incidence and mortality webbased report U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute Atlanta, GA., 2014.
- [3] S.G. Diab, R.M. Elledge, G.M. Clark, Tumor characteristics and clinical outcome of elderly women with breast cancer, J. Natl. Cancer Inst 92 (7) (2000) 550-556.
- [4] N. Howlader, NA, M. Krapcho, J. Garshell, D. Miller, S.F. Altekruse, CL Kosary, M. Yu, J. Ruhl, Z Tatalovich, A. Mariotto, D.R. Lewis, H.S. CHen, E.J. Feuer, KA. Cronin, SEER Cancer Statistics Review, 1975-2011, National Cancer Institute Bethesda, MD., 2014.
- [5] J.M. Ortman, VA, H. Hogan, An Aging Nation: The Older Population in the United States, in: US.C. Bureau (Ed.), 2014 (Washington, DC).
- [6] R.E. Bristow, et al., Adherence to treatment guidelines for ovarian cancer as a measure of quality care, Obstet Gynecol. 121 (6) (2013) 1226-1234.
- [7] Surveillance, Epidemiology, and End Results (SEER) Program research data (1973-2011), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, 2014 released April 2014, based on the November 2013 submission http://www.ser.cancer.gov.

#### 318a

- [8] V. Sopik, et al., Why have ovarian cancer mortality rates declined? Part II. Case-fatality, Gynecol. Oncol. (2015).
- [9] V. Sopik, et al., Why have ovarian cancer mortality rates declined? Part III. Prospects for the future, Gynecol. Oncol. (2015).
- [10] S.W. Junod, L. Marks, Women's trials: the approval of the first oral contraceptive pill in the United States and Great Britain, J. Hist Med. Allied Sd. 57 (2) (2002) 117-160.
- [11] J.R. McLaughlin, et al., Long-term ovarian cancer survival associated with mutation in BRCA1 or BRCA2, J. Natl. Cancer Inst. 105 (2) (2013) 141-148.
- [12] J.D. Seidman, R.J. Kunsan, Ovarian serous borderline tumors: a critical review of the literature with emphasis on prognostic indicators, Hum. Pathol. 31 (5) (2000) 539-557.
- [13] SS. Buys, et al., Effect of screening on ovarian cancer mortality: the prostate, lung, colorectal and ovarian (PLCO) cancer screening randomized controlled trial, JAMA 305 (22) (2011) 2295-2303.
- [14] U. Menon, et al., Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCIDCS), Lancet Oncol. 10 (4) (2009) 327-340.
- [15] B.Y. Karlan, et al., Use of CA125 and HE4 serum markers to predict ovarian cancer in elevated-risk women, Cancer Epidemiol. Biomarkers Prey. 23 (7) (2014) 1383-1393.
- [16] V.A. Moyer, Screening for ovarian cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement, Ann. Intern. Med. 157 (12) (2012) 900-904.

- [17] BA. Goff, et al., Ovarian carcinoma diagnosis, Cancer 89 (10) (2000) 2068-2075.
- [18] C.M. Nagle, et al., Reducing time to diagnosis does not improve outcomes for women with symptomatic ovarian cancer: a report from the Australian Ovarian Cancer Study Group, J. Clin. Oncol. 29 (16) (2011) 2253-2258.
- [19] C. Wikbom, F. Pettersson, P.J. Moberg, Delay in diagnosis of epithelial ovarian cancer, Int J. Gynaecol. Obstet 52 (3) (1996) 263-267.
- [20] Committee Opinion No. 477: the role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer, Obstet Gyneco1.117 (3) (2011) 742-746.
- [21] L. Gilbert, et al., Assessment of symptomatic women for early diagnosis of ovarian cancer: results from the prospective DOvE pilot project, Lancet Oncol. 13 (3) (2012) 285-291.
- [22] A. du Bois, et al., Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO), Cancer 115 (6) (2009) 1234-1244.
- [23] G.D. Aletti, et al., Ovarian cancer surgical resectability: relative impact of disease, patient status, and surgeon, Gynecol. Onco1.100 (1) (2006) 33-37.
- [24] S.J. Chang, R.E. Bristow, Evolution of surgical treatment paradigms for advanced-stage ovarian cancer: redefining 'optimal' residual disease, Gynecol. Oncol. 125 (2) (2012) 483-492.

- [25] S. Salvador, et al., The fallopian tube: primary site of most pelvic high-grade serous carcinomas, Int J. Gynecol. Cancer 19 (1) (2009) 58-64.
- [26] C.J. Gibson, K., Historical census statistics on population totals by race, 1790 to 1990, for the United States, regions, divisions, and states, Working Paper, No. 56, P.D. U.S. Bureau of the Census, 2002 (Editor 2002).
- [27] V.L. Jacoby, et al., Factors associated with undergoing bilateral salpingo-oophorectomy at the time of hysterectomy for benign conditions, Obstet Gynecol. 113 (6) (2009) 1259-1267.
- [28] L.J. Melton III, et al., Bilateral oophorectomy trends in Olmsted County, Minnesota, 1950-1987, Epidemiology 2 (2) (1991) 149-152.
- [29] J.L. Lowder, et al., Prophylactic bilateral oophorectomy or removal of remaining ovary at the time of hysterectomy in the United States, 1979-2004, Am. J. Obstet Gynecol. 202 (6) (2010) 538 el-9.
- [30] J.K. Chan, et al, Ovarian cancer rates after hysterectomy with and without salpingo-oophorectomy, Obstet Gyneco1. 123 (1) (2014) 65-72.
- [31] H. Falconer, et al., Ovarian cancer risk after salpingectomy: a nationwide population-based study, J. Natl. Cancer Inst 107 (2) (2015).
- [32] R. Pokras, H.V., Hysterectomies in the United States, 1965-84, in: V.a.H. Statistics (Ed.) US. Government Printing Office, Washington, 1987.
- [33] Prevention, C.f.D.C.a., CDC surveillance summaries: surveillance for reproductive health, in: USD.o.H.aH. Services (Ed.),MMWR, 1997 (Atlanta, GA).
- [34] J.E. Rossouw, et al., Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal

results: from the Women's Health Initiative randomized controlled trial, JAMA 288 (3) (2002) 321-333.

- [35] A.P. Novetsky, L.R Boyd, J.P. Curtin, Trends in bilateral oophorectomy at the time of hysterectomy for benign disease, Obstet Gynecol. 118 (6) (2011) 1280-1286.
- [36] ACOG Practice Bulletin No. 89. Elective and riskreducing salpingo-oophorectomy, Obstet Gyneco1.111 (1) (2008) 231-241.
- [37] AS. Whittemore, R. Harris, J. Itnyre, Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group, Am. J. Epidemiol. 136 (10) (1992) 1184-1203.
- [38] B. Zhou, et al., Hormone replacement therapy and ovarian cancer risk: a meta-analysis, Gynecol. Oncol. 108 (3) (2008) 641-651.
- [39] K.L. Terry, et al., Genital powder use and risk of ovarian cancer: a pooled analysis of 8525 cases and 9859 controls, Cancer Prey. Res. (Phila.) 6 (8) (2013) 811-821.
- [40] Ovarian cancer and body size: individual participant meta-analysis including 25,157 women with ovarian cancer from 47 epidemiological studies, PLoS Med. 9 (4) (2012) e1001200.
- [41] P.S. Munksgaard, J. Blaakaer, The association between endometriosis and ovarian cancer: a review of histological, genetic and molecular alterations, Gynecol. Oncol. 124 (1) (2012) 164-169.
- [42] V. Beral, et al., Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls, Lancet 371 (9609) (2008) 303-314.

- [43] B.E. Hamilton, CM. Cosgrove, Cumulative Birth Rates, by live-birth Order, Exact Age, and Race of Women in Each Cohort from 1911 Through 1991: United States, 1961-2006. Table 2, National Center for Health Statistics, Hyattsville, MD, 2010.
- [44] N.N. Luan, et al., Breastfeeding and ovarian cancer risk: a meta-analysis of epidemiologic studies, Am. J. Clin. Nutr. 98 (4) (2013) 1020-1031.
- [45] K.W. Eckhardt, G.E. Hendershot, Analysis of the reversal in breast feeding trends in the early 1970s, Public Health Rep. 99 (4) (1984) 410-415.
- [46] W. Sieh, et al., Tubal ligation and risk of ovarian cancer subtypes: a pooled analysis of case-control studies, Int J. Epidemiol. 42 (2) (2013) 579-589.
- [47] A. Chandra, Surgical sterilization in the United States: prevalence and characteristics, 1965-95, Vital Health Stat 23 (20) (1998) 1-33.
- [48] KA. Oriel, E.M. Hartenbach, P.L. Remington, Trends in United States ovarian cancer mortality, 1979-1995, Obstet Gynecol. 93 (1) (1999) 30-33.
- [49] S. Gnagy, et al., Declining ovarian cancer rates in U.S. women in relation to parity and oral contraceptive use, Epidemiology 11 (2) (2000) 102-105.

## **APPENDIX Q**

# ENDOMETRIAL CANCER AND ORAL CONTRACEPTIVES: AN INDIVIDUAL PARTICIPANT META-ANALYSIS OF 27276 WOMEN WITH ENDOMETRIAL CANCER FROM 36 EPIDEMIOLOGICAL STUDIES

Collaborative Group on Epidemiological Studies on Endometrial Cancer\*

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See Online for appendix

## Summary

**Background** Oral contraceptives are known to reduce the incidence rate of endometrial cancer, but it is uncertain how long this effect lasts after use ceases, or whether it is modified by other factors.

**Methods** Individual participant datasets were sought from principal investigators and provided centrally for 27 276 women with endometrial cancer (cases) and 115 743 without endometrial cancer (controls) from 36 epidemiological studies. The relative risks (RRs) of endometrial cancer associated with oral contraceptive use were estimated using logistic regression, stratified by study, age, parity, body-mass index, smoking, and use of menopausal hormone therapy.

Findings The median age of cases was 63 years (IQR 57-68) and the median year of cancer diagnosis was 2001 (IQR 1994-2005). 9459 (35%) of 27 276 cases and 45 625 (39%) of 115 743 controls had ever used oral contraceptives, for median durations of 3.0 years (IQR 1-7) and 4.4 years (IQR 2-9), respectively. The longer that women had used oral contraceptives, the greater the reduction in risk of endometrial cancer; every 5 years of use was associated with a risk ratio of 0.76 (95% CI 0.73-0.78; p<0.0001). This reduction in risk persisted for more than 30 years after oral contraceptive use had ceased, with no apparent decrease between the RRs for use during the 1960s, 1970s, and 1980s, despite higher oestrogen doses in pills used in the early years. However, the reduction in risk associated with ever having used oral contraceptives differed by tumour type, being stronger for carcinomas (RR 0.69, 95% CI 0.66-0.71) than sarcomas (0.83, 0.67-1.04; case-case comparison: p=0.02). In high-income countries, 10 years use of oral contraceptives was estimated to reduce the absolute risk of endometrial cancer arising before age 75 years from 2.3 to 1.3 per 100 women.

**Interpretation** Use of oral contraceptives confers longterm protection against endometrial cancer. These results suggest that, in developed countries, about 400 000 cases of endometrial cancer before the age of 75 years have been prevented over the past 50 years (1965-2014) by oral contraceptives, including 200 000 in the past decade (2005-14).

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#### Introduction

Use of oral contraceptives is known to reduce the incidence of endometrial cancer.' Because endometrial cancer is uncommon in young women but its incidence increases sharply with age, the public health effects of this inverse association depend mainly on the extent to which the reduced risk of endometrial cancer persists long after use ceases. To

investigate the association between use of oral contraceptives and the subsequent risk of endometrial cancer, individual participant data from 36 epidemiological studies of endometrial cancer have been brought together and analysed centrally.

#### Methods

### Identification of studies and collection of data

This collaboration was established in 2005. Since 2012, epidemiological studies were eligible for indusion if they collected individual data about use of hormonal contraceptives and reproductive history from at least 400 women with endometrial cancer in retrospective studies, and at least 200 women in prospective studies. Before 2012, retrospective studies with fewer than 400 cases of endometrial cancer had been eligible, so some studies with fewer cases are included in this analysis. Eligible studies were identified from review articles, computer-aided literature searches in PubMed and Medline (up to Jan 31, 2012), using combinations of the search terms "endometrial cancer risk", "endo-metrium cancer risk", "hormon\*", "oral contraceptive", and "OC", plus the additional terms "cohort", "prospective", "women", and "cancer risk", and from discussions with colleagues. Efforts were made to identify all studies that induded relevant information, irrespective of whether or not results about oral contraceptives had been published, and principal investigators from each eligible study were invited to participate.

Cases were defined as women with invasive cancer of any histological type of the body of the uterus who were without previous cancer (except non-melanoma skin cancer); controls were women without previous cancer who had an intact uterus. Prospective studies were incorporated by a nested case-control design, in which up to four controls were selected at random from cohort members, matched for exact year of birth, date of recruitment (within 6 months), duration of follow-up (at disease onset), and, when appropriate, other matching criteria used by the principal investigators (eg, geographical region). Individual participant data on sociodemographic and reproductive factors, use of contraceptives, use of hormonal therapies for the menopause, reproductive history, height, weight, consumption of alcohol and tobacco, and family history of breast and endometrial cancer were sought from the principal investigators of every study. For prospective studies, reported information on the use of oral contraceptives was taken from the last record before disease onset, to calculate duration of use and time since last use (assuming no further use). Information about the use of menopausal hormonal therapy and hysterectomy was also that most recently recorded. Datasets provided by investigators were collated centrally and recoded using as far as possible. Apparent similar definitions, inconsistencies in the data were discussed with the study investigators and if they could not be rectified, decisions were made about which values to incorporate into the pooled dataset. After the records had been checked and corrected. investigators were sent summary analyses of the variables to be used for final confirmation that their data had been interpreted correctly.

44 eligible studies were identified<sup>2-45</sup> of which 36 are included in the current analysis.<sup>2-37</sup> Four groups of researchers declined to participate in this collaboration<sup>38-41</sup> and a further four groups agreed in principle to provide data at a future date.<sup>42-45</sup>

Principal investigators provided individual information about whether or not women had ever used hormonal contraceptives (as defined by each study) and most also provided information about the total duration of use and age or calendar year at first and last use. Only 13 studies collected information on the type of hormonal contraceptives;<sup>7,17,19,21,25-30,33,35,36</sup> women from the remaining 23 studies were assumed to be using combined oral contraceptives (ie, those containing both oestrogen and progestin) because more than 95% of hormonal contraceptive users included in studies with such information reported using combined preparations. There were too few women with endometrial cancer who had used exclusively progestinonly oral contraceptives (56 cases), progestin-only injectable hormonal contraceptives (19 cases), combined injectable hormonal contraceptives (three cases) or sequential oral contraceptives (41 cases) for reliable analysis.

#### **Statistical analysis**

Statistical analyses were done with Stata version 13.0. Conditional logistic regression was used to calculate relative risks (RRs) of endometrial cancer in relation to the use of oral contraceptives and their corresponding 95% CIs. Where only two groups were compared, conventional CIs were used. When several groups were compared, with one taken as the reference group with an RR of 1, the variance of the log risk in the reference group and in each of the other groups was calculated from the variances and covariances of the log RRs in those other groups.<sup>47</sup> These group-specific variances yield the group-specific CIs for each group (including the reference group) that are plotted in the figures.

All analyses were stratified by study, centre (for multicentre studies), age group (16-19, 20-24 years, and so on up to 75-79, 80-84, and 85-89 years), parity (0, 1, 2, 3, 4,  $\geq$ 5, or not known), body-mass index (BMI <25, 25-30, z30 kg/m<sup>2</sup>, or not known), smoking (never, ever, or unknown) and type of menopausal hormone therapy used (never, oestrogen-only exclusively, combined exclusively, both oestrogen-only and combined, other types, or unknown use). The effect on the main findings of further stratification by ethnic origin, education, age at first birth, age at last birth, age at menarche, age at menopause, menopausal status, and family history of endometrial cancer was examined by comparing results before and after stratification for each variable separately. Women with missing information for any of these adjustment factors were assigned to a separate stratum for the relevant

variable to conserve total numbers analysed; sensitivity analyses excluded these women.

The RR of endometrial cancer per 5-year duration of oral contraceptive use was estimated by fitting a log-linear trend across categories of duration (never, <1, 1—<5, 5—<10, 10—<15, and  $\geq$ 15 years), using the median value within each category.

The association of endometrial cancer risk and duration of oral contraceptive use was cross-classified by time since last use and by mid-calendar-year of use (grouped as 1960-69, 1970-79, and 1980-89) to assess the independent effect, if any, of these factors on risk. Although the composition of oral contraceptive pills has varied substantially over time, a strong association exists between calendar year of use and oestrogen dose in the oral contraceptives typically used.<sup>48-50</sup> In the USA and UK, for example, the oral contraceptives prescribed before 1970 were typically high-dose preparations, often containing 100 pg or more of oestrogen; between 1970 and 1980 prescriptions were typically for medium-dose preparations containing about 50 µg of oestrogen; and by 1980 most prescriptions were for low-dose preparations, containing 35 pg or less of oestrogen.<sup>49,50</sup> Thus, in these analyses, decade of use was taken as a correlate of oestrogen dose of oral contraceptives.

The classification system adopted in each study was used centrally to categorise tumours into three broad histological subtypes: type I (endometrioid carcinomas); type II (nonendometrioid carcinomas); and uterine sarcomas. Type I tumours, which were much the most common type, induded endometrioid tumours (International Classification of Diseases for Oncology [ICD]-0-3 morphology codes: 8380, 8381, 8382, and 8383), adeno-carcinoma tubular (8210 and 8211), papillary adenocarcinoma (8260, 8262, and 8263), adenocarcinoma with squamous metaplasia (8570), mutinous adeno-carcinoma (8480 and 8481), and adenocarcinoma not otherwise specified (8140). Type II tumours included serous

(8441), papillary serous (8460 and 8461), squamous cell (8050, 8070, 8071, and 8072), adenosquamous (8560), small-cell carcinoma (8041), mixed-cell adenocarcinoma (8323), and dear cell carcinoma (8310), as described elsewhere.<sup>51</sup>

# Table 1Details of studies and women included

\* \* \*

#### Figure 1

# Relative risk\* of endometrial cancer by use of oral contraceptives in each of the contributing studies

\* \* \*

Information about duration of use was available for 8873 cases and 43 783 controls across all studies combined. BCDDP=Breast Cancer Detection Demonstration Project. NHS=Nurses' Health Study. CNBSS=Canadian National Breast Screening Study. IWHS=lowa Women's Health Study. MEC=Multiethnic Cohort Study. NIH-AARP=NIH-AARP Diet and Health Study. EPIC=European Prospective Investigation into Cancer and Nutrition. PLCO=Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. MISS=Melanoma Sweden in Southern Cohort. CASH=Cancer and Steroid Hormone Study. ANECS=Australian National Endometrial Cancer Study. \*Stratified by study (centre), age, parity, body-mass index, smoking, and type of menopausal hormone therapy used.

Uterine sarcomas were defined as sarcoma, not otherwise specified (8800-8806), fibrosarcoma (8810-8833), liposarcoma (8850-8858), myosarcoma (8890-8896), rhabdomyosarcoma (8900-8902, 8910-8912), endometrial stromal sarcoma (8930-8931), or cancer coded as sarcoma by study investigators. Significance tests for heterogeneity of the relative risks for oral contraceptive use by tumour subtype compared cases only (case-case comparisons), because controls provide no additional information. Analyses by histological subtype were based on smaller numbers than those for all endometrial cancers. Hence, although they were still stratified by study (centre) and age, to retain sufficient statistical information within each stratum they were adjusted rather than stratified for parity, BMI, smoking, and type of menopausal hormone therapy used.

When results are presented in the form of plots, RRs are represented by squares and their corresponding CIs or groupspecific CIs by horizontal lines. The position of the square indicates the point estimate of the RR, and the area of the square is inversely proportional to the variance of the logarithm of the RR (or, for multigroup analyses, log risk), thus providing an indication of the amount of statistical information available for that particular estimate. Where summary RRs have been calculated, these are shown as open diamonds. Because of the large number of RR estimates presented, 99% CIs are generally used in the figures; however, throughout the text 95% CIs are quoted.

Cumulative incidence rates of endometrial cancer (up to the age of 75 years) associated with different durations of use of oral contraceptives were estimated by application of RR estimates for endometrial cancer from the present analyses to age-specific incidence rates for women in 21 high-income countries in western Europe, North America, and Australasia (appendix p 8)." Absolute numbers of cancers prevented were estimated from birth cohort-specific prevalences of oral contraceptive use.<sup>53</sup>

#### Figure 2

Relative risk of endometrial cancer in users of oral contraceptives compared with never-users, by (A) duration of use, and (B) duration of use and time since last use of oral contraceptives.

\* \* \*

## **Role of the funding source**

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. The writing committee had full access to all the data, could request any analyses, and had final responsibility for the decision to submit for publication.

## Results

Table 1 presents the details of the 36 participating studies. The studies are listed by their design and, within each type of design, by the median year when the endometrial cancers were diagnosed in each study. Most studies were done in Europe or North America, with three from Asia, one from Australia, one from South Africa, and one multinational study. Together, the analyses induded 27 276 women with endometrial cancer (cases) and 115 743 women without endometrial cancer (controls). The median year of cancer diagnosis was 2001 (IQR 1994-2005) and the median age at diagnosis was 63 years (IQR 57-68), with 847 (3%) of women diagnosed before 45 years of age, 3743 (14%) at 45-54 years, 11 287 (41%) at 55-64 years, and 11 399 (42%) at 65 years or older.

Overall, 9459 (35%) of 27 276 women with endometrial cancer and 45 625 (39%) of 115 743 controls had ever used oral contraceptives, with a median duration of use of 3.0 years (IQR 1-7) and 4.4 years (2-9), respectively. The prevalence of ever having used oral contraceptives was substantially lower in controls from Asia (899/11180; 8%) than in controls from Europe and North America (39 050/86 293; 45%).

Figure 1 shows the study-specific and combined relative risks of endometrial cancer in ever-users compared with never-users of oral contraceptives and, in the ever-users, the RR per 5 years of use. Results are presented according to study design. Studies with a low information content (defined as 1/var[ln RR] <20) are induded in the "other" category for each relevant study design. Overall, the risk of endometrial cancer was significantly lower in women who had ever used oral contraceptives than in women who had

never used them (RR 0.69, 95% CI 0 .67-0 .72), with no significant heterogeneity between the three types of study design (heterogeneity test; p=0.15).

The longer women had used oral contraceptives for, the lower their risk of endometrial cancer was, with each 5 years of use associated with an RR of 0.76 (95% CI 0.73-0.78, p<0.0001), based on 8873 cases and 43 783 controls who were ever-users (figure 1). In women who had used oral contraceptives for a duration of 10-15 years (median 11.8 years) the relative risk of endometrial cancer was 0.52 (95% CI 0 .48-0 .57; figure 2A). These analyses were stratified by study (centre), age, parity, BMI, smoking, and type of any menopausal hormone replacement therapy used. Similar results were obtained when the analyses were stratified by age and study alone (RR per 5 years use of oral contraceptives 0.75 [95% CI 0.73-0.77]), and further stratification for each of ethnic origin, education, age at first birth, age at last birth, age at menarche, age at menopause, menopausal status, or family history of endometrial cancer likewise changed the RR per 5 years of use by 0.01 or less The proportional reduction in risk of (appendix p 4). endometrial cancer per 5 years of oral contraceptive use varied slightly by age at diagnosis (heterogeneity test; p=0.004), with RR 0.71 (95% CI 0.67-0.75) for women diagnosed before 60 years of age and RR 0.79 (0.75-0.82) for women diagnosed at 60 years of age or older. The association did not vary by BMI, parity, use of menopausal hormone therapy, menopausal status, smoking status, age at menarche, ethnic origin, or alcohol use (figure 3). The exdusion of women with missing values for any of these stratification variables also made a negligible difference to the risk estimates (making the fully stratified RR per 5 years use of oral contraceptives 0.75, 95% CI 0.72-0.77).

#### Figure 3

### Relative risk of endometrial cancer per 5 years use of

# oral contraceptives, by various lifestyle and reproductive characteristics.

\* \* \*

Most women with endometrial cancer had stopped using oral contraceptives many years before their cancer diagnosis (median time since last use 29 years [IQR 22-34]). Women who had used oral contraceptives more recently had also, on average, used them for a longer duration (eg, women who had used oral contraceptives less than 15 years previously had a median duration of use of 4.7 years [IQR 1.3-9.9], whereas women who had last used oral contraceptives 30 years or more previously had a median duration of use of 3.0 years [1.0-5.3]). For a given duration of use, the reduction in risk was slightly greater in women with more recent use, although a significant protective effect remained more than 30 years after use had ceased (figure 2B and appendix p 5).

In 7452 women with endometrial cancer for whom information about the timing of their oral contraceptive use was available, 3235 (43%) had a mid-year of oral contraceptive use in the 1960s and 371 (5%) had a midyear of use in the 1980s (appendix p 6). The RRs per 5 years duration of use of oral contraceptives in the 1960s, 1970s, and 1980s did not vary significantly (heterogeneity test; p=0.15, appendix p 6). There was also no significant heterogeneity in the RR per 5 years of use by age at first use or age at last use (appendix p 7).

However, there was some evidence that the RR depended on the histological subtype of endometrial cancer (table 2). Compared with women who had never used oral contraceptives, ever-users had an RR of 0.69 (95% CI 0.66-0.71) for carcinomas, based on 26 877 cases, which was similar for type I and type II carcinomas. Based on relatively few cases, ever-use of oral contraceptives was not significantly associated with the risk of uterine sarcoma (RR 0.83 [95% CI 0.67-1.04], based on 399 cases; heterogeneity, from direct case-case comparison of sarcomas vs carcinomas p=0.02). Analyses were also done in women with information about duration of oral contraceptive use. For carcinoma, the RR per 5 years use of oral contraceptives was 0.75 (95% CI 0.73-0.77, based on 8701 cases); for uterine sarcoma, the corresponding RR was 0.88 (95% CI 0.74-1.03, based on 172 cases; heterogeneity, from direct case-case comparison of sarcomas vs carcinoma p=0.24).

Based on the RRs presented in figure 2 and age-specific rates of endometrial cancer for women in high-income countries, cumulative incidence rates of endometrial cancer were estimated for never-users of oral contraceptives and for women who had used them for different durations, beginning at 20 years of age. For women who never used oral contraceptives, an estimated 2.3 in every 100 would be diagnosed with endometrial cancer before the age of 75 vears. The corresponding cumulative incidence rate for women who had used oral contraceptives for 5, 10, and 15 years was estimated to be 1.7, 1.3, and 1.0 per 100 users, respectively (figure 4). The annual incidence of endometrial cancer is low in women still young enough to be using oral contraceptives, but it is much higher in those aged 60-70 years. In this age range, the number of women who were ever-users of oral contraceptives has grown steeply over the past 50 years, from essentially zero in the 1960s to about three-quarters in high-income countries today.<sup>53</sup> Hence, the annual number of endometrial cancers prevented by ever-use of oral contraceptives has also increased steeply over the past 50 years. Using birth cohort-specific prevalences of oral contraceptive use in western developed countries,<sup>53</sup> we estimate that over the past 50 years (1965-2014) in 21 countries in western Europe, North America, and Australasia, oral contraceptive use has prevented a total of about 400 000 endometrial cancers, including 200 000 in the past 10 years (2005-14), at ages 30-74 years (appendix p 8). Because these results are based on population incidence rates, they

automatically allow for the different rates of hysterectomy in those populations.

## Figure 4

Absolute risk of endometrial cancer incidence per 100 women up to 75 years of age in high-income countries by duration of oral contraceptive use (population-weighted rates, 2003-07, for 21 countries in Western Europe, North America, and Australasia)

\* \* \*

## Discussion

This international collaboration has brought together and re-analysed almost all of the available epidemiological evidence on the reduction in endometrial cancer incidence associated with oral contraceptive use, and indudes data from 27 000 women with endometrial cancer from 36 studies. Overall, the longer women had used oral contraceptives, the greater the reduction in the risk of endometrial cancer. On average, every 5 years of oral contraceptive use was associated with a relative risk of 0.76, so about 10-15 years of use halves the risk. A protective effect persists for at least 30 years after use ceases, and does not seem to depend much on the dose of oestrogen in the contraceptive formulations or on personal characteristics such as parity, adiposity, or menopausal status.

Combining results from many studies has the obvious advantage of yielding a large sample size, which reduces random errors, and it also avoids the biases that could be produced by undue emphasis on particular studies with extreme results. Only a third of the eligible studies have published on oral contraceptives and endometrial cancer, <sup>4,7,8,10,17,18,21,24,29-31,33,35</sup> so a review based solely on these studies could be affected by publication bias. Despite extensive efforts to identify all studies with unpublished results, it is impossible to guarantee that others do not exist; furthermore, it is not possible to have completely up-to-date
information from the continuing prospective studies. However, the eight eligible studies that were identified but did not contribute data to this collaboration together contain only about 12% as many women with endometrial cancer as the included studies. Hence, failure to indude these studies probably had no material effect on the main findings. Only one of these eight studies has published results on oral contraceptives and endometrial cancer, and its reported findings are broadly similar to ours." The 36 induded studies were of varied design and were done in different settings, with wide variation in the duration of use and time since last use of oral contraceptives. However, the effects of a given duration of use did not vary significantly between women with different characteristics or between studies with different designs.

The main analyses were stratified simultaneously by study, centre within study, age at diagnosis, parity, BMI, smoking, and use of menopausal hormone therapy. This fine stratification was feasible because of the large sample size. It meant that the analyses of the association between oral contraceptive use and risk of endometrial cancer are based on comparisons between women in the same study who were of the same age and who had a similar history of other risk factors for endometrial cancer.

Although few studies provided information about hormonal constituents of the preparations used, the oral contraceptives of the 1960s would generally have contained much higher doses of oestrogen than those of the 1980s. Overall, however, there was no apparent decrease between use in the 1960s and 1980s in the relative risk associated with a given duration of use. These results show that the amount of oestrogen in the lower-dose pills is still sufficient to reduce the incidence of endometrial cancer, which is consistent with findings from two studies that have assessed individual dosages of the hormonal constituents.<sup>41,54</sup> The numbers of women who reported using anything other than combined

oral contraceptives (eg, sequential oral or progestin-only oral contraceptives and/or injectable hormonal contraceptives) were too small for reliable analysis.

The decline in endometrial cancer risk with increasing duration of use does not seem to vary substantially with parity, BMI, use of menopausal hormone therapy, menopausal status, smoking status, age at menarche, ethnic origin, or alcohol intake. The reduction in risk associated with 5 years use of oral contraceptives was slightly greater in women diagnosed before 60 years of age than in women diagnosed at an older age, but given the number of significance tests done, this could be due to chance. The reduction in endometrial cancer risk with increasing duration of use does not seem to vary much with factors related to the timing of use, such as age of first or last use, time since last use, or calendar period of use.

The effect of oral contraceptives does, however, seem to vary by histological subtype, with ever-use strongly associated with a reduced risk of type I and probably of type II endometrial carcinoma, but somewhat less strongly associated with a reduced risk of uterine sarcoma—a much rarer type of cancer. Another pooled analysis that included 15 studies, most of which contributed to the current analysis, also reported a similar reduction in risk of both type I and type II endometrial carcinoma for ever use of oral contraceptives<sup>51</sup> but no significant association with uterine sarcoma.<sup>55</sup>

Taken together, it is reasonable to infer that the associations recorded here are causal (ie, that current or past oral contraceptive use reduces the incidence of endometrial cancer in otherwise similar women). Almost all of the hormonal contraceptive use in these studies is likely to involve combined oral contraceptives, which contain oestrogen plus progestin. These contraceptives might protect against endometrial cancer by minimising exposure to unopposed oestrogen during the follicular phase of the menstrual cyde, thereby inhibiting oestrogen-induced cell proliferation;<sup>56,57</sup> moreover, the addition of a progestin to menopausal hormone therapy has been shown to reduce the adverse effects of oestrogen on the risk of endometrial cancer in postmenopausal women.<sup>53,58-60</sup> However, the exact mechanisms by which oral contraceptives cause substantial protection against endometrial cancer many years after cessation of use are still unclear.

Since the introduction of oral contraception in the early 1960s, about 400 million women have used it in high-income countries alone,<sup>61</sup> often for prolonged periods during early adulthood.<sup>53</sup> Medium-to-long-term use of oral contraceptives (eg, for 5 years or longer) results in a substantial proportional reduction in the incidence of endometrial cancer, the magnitude of which is similar to that seen for ovarian cancer.<sup>53</sup> Because this reduction in risk persists more than 30 years after use has ceased, and the incidence of endometrial cancer increases steeply with age, the public health effect of oral contraceptive use on endometrial cancer is most apparent many years after use has stopped. The present results, taken together with what what is known about past patterns of use, suggest that in high-income countries oral contraceptives have, over the past 50 years (1965-2014), already prevented a total of about 400 000 endometrial cancers before the age of 75 years, including 200 000 in the past decade (2005-14).

# Contributors

NA, VB, SWK, RS, SS, and TOY identified studies, received and checked data, did analyses, and had full access to all materials and results. NA, VB, GR, SS, and RP drafted the report, and all writing committee members helped to revise it before and after circulation to the collaborators for comment.

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### **Declaration of interests**

We declare no competing interests.

#### References

- 1 IARC. Combined estrogen—progestogen contraceptives and combined estrogen—progestogen menopausal therapy. Lyon: International Agency for Research on Cancer, 2006.
- 2 Lacey JV Jr, Brinton LA, Lubin JH, Sherman ME, Schatzkin A, Schairer C. Endometrial carcinoma risks among menopausal estrogen plus progestin and unopposed estrogen users in a cohort of postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 2005; 14: 1724-31.
- 3 Schouten LJ, Goldbohm RA, van den Brandt PA. Anthropometry, physical activity, and endometrial cancer risk: results from the Netherlands Cohort Study. *J Natl Cancer Inst* 2004; **96**: 1635-38.
- 4 Colditz GA. Oral contraceptive use and mortality during 12 years of follow-up: the Nurses' Health Study. Ann *Intern* Med 1994; **120:** 821-26.
- 5 Terry PD, Miller AB, Rohan TE. A prospective cohort study of cigarette smoking and the risk of endometrial cancer. *Br J Cancer* 2002; **86**: 1430-35.
- 6 Anderson ICE, Anderson E, Mink PJ, et aL Diabetes and endometrial cancer in the Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prey* 2001; **10:** 611-16.
- 7 Wernli KJ, Ray RM, Gao DL, De Roos AJ, Checkoway H, Thomas DB. Menstrual and reproductive factors in

relation to risk of endometrial cancer in Chinese women. *Cancer Causes Control* 2006; **17:** 949-55.

- 8 Setiawan VW, Pike MC, Kolonel LN, Nomura AM, Goodman MT, Henderson BE. Racial/ethnic differences in endometrial cancer risk: the multiethnic cohort study. *Am J Epidemiol* 2007; **165**: 262-70.
- 9 Yang HP, Wentzensen N, Trabert B, et al. Endometrial cancer risk factors by 2 main histologic subtypes: the NIH-AARP Diet and Health Study. *Am J Epidemiol* 2013; **177**: 142-51.
- 10 Dossus L, Allen N, Kaaks R, et al. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2010; **127:** 442-51.
- 11 Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 2005; **294**: 47-55.
- 12 Gren L, Brosld K, Childs J, et al. Recruitment methods employed in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Clin Trials* 2009; **6:** 52-59.
- 13 Epstein E, Lindqvist PG, Olsson H. A population-based cohort study on the use of hormone treatment and endometrial cancer in southern Sweden. *Int* J Cancer 2009; **125**: 421-25.
- 14 Lof M, Sandin S, Hilaldvi-Clarke L, Weiderpass E. Birth weight in relation to endometrial and breast cancer risks in Swedish women. *Br J Cancer* 2007; 96: 134-36.
- 15 Friberg E, Orsini N, Mantzoros CS, Wolk A. Coffee drinking and risk of endometrial cancer-a population-based cohort study. *Int J Cancer* 2009; **125**: 2413-17.

- 16 Beral V, Bull D, Reeves G. Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2005; **365:** 1543-51.
- 17 The Cancer and Steroid Hormone Study. Combination oral contraceptive use and the risk of endometrial cancer. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. *JAMA* 1987; 257: 796-800.
- 18 Stanford JL, Brinton LA, Berman ML, et al. Oral contraceptives and endometrial cancer: do other risk factors modify the association? *Int J Cancer* 1993; **54**: 243-48.
- 19 Pike MC, Peters RK, Cozen W, et al. Estrogenprogestin replacement therapy and endometrial cancer. *J Natl Cancer Inst* 1997; **89:** 1110-16.
- 20 Newcomb PA, Trentham-Dietz A. Patterns of postmenopausal progestin use with estrogen in relation to endometrial cancer (United States). *Cancer Causes Control* 2003; **14**: 195-201.
- 21 Weiderpass E, Adami HO, Baron JA, Magnusson C, Lindgren A, Persson I. Use of oral contraceptives and endometrial cancer risk (Sweden). *Cancer Causes Control* 1999; **10**: 277-84.
- 22 Weiderpass E, Adami HO, Baron JA, et aL Organochlorines and endometrial cancer risk. *Cancer Epidemiol Biomarkers Prey* 2000; **9:** 487-93.
- 23 Strom BL, Schinnar R, Weber AL, et al. Case-control study of postmenopausal hormone replacement therapy and endometrial cancer. *Am J Epidemiol* 2006; **164**: 775-86.
- 24 Tao MH, Xu WH, Zheng W, et aL Oral contraceptive and IUD use and endometrial cancer: a population-

based case-control study in Shanghai, China. Int J Cancer 2006; **119:** 2142-47.

- 25 Brinton LA, Sakoda LC, Lissowska J, et al. Reproductive risk factors for endometrial cancer among Polish women. *Br J Cancer* 2007; **96:** 1450-56.
- 26 Cook LS, Dong Y, Round P, Huang X, Magliocco AM, Friedenreich CM. Hormone contraception before the first birth and endometrial cancer risk. *Cancer Epidemiol Biomarkers Prey* 2014; 23: 356-61.
- 27 Rowlands IJ, Nagle CM, Spurdle AB, Webb PM. Gynecological conditions and the risk of endometrial cancer. *Gynecol Oncol* 2011; **123:** 537-41.
- 28 Antunes CM, Strolley PD, Rosenshein NB, et al. Endometrial cancer and estrogen use. Report of a large case-control study. *N Engl J Med* 1979; **300**: 9-13.
- 29 Kaufman DW, Shapiro S, Slone D, et aL Decreased risk of endometrial cancer among oral-contraceptive users. *N Engl J Med* 1980; **303:**1045-47.
- 30 The Who Collaborative Study of Neoplasia and Steroid Contraceptives. Endometrial cancer and combined oral contraceptives. *Int J Epidemiol* 1988; **17**: 263-69.
- 31 La Vecchia C, Franceschi S, Decarli A, Gallus G, Tognoni G. Risk factors for endometrial cancer at different ages. *J Natl Cancer Inst* 1984; **73:** 667-71.
- 32 Moysich KB, Baker JA, Rodabaugh KJ, Villella JA. Regular analgesic use and risk of endometrial cancer. *Cancer Epidemiol Biomarkers Prey* 2005; **14:** 2923-28.
- 33 Levi F, La Vecchia C, Gulie C, et al. Oral contraceptives and the risk of endometrial cancer. *Cancer Causes Control* 1991; **2:** 99-103.

- 34 Parazzini F, Negri E, La Vecchia C, et aL Role of reproductive factors on the risk of endometrial cancer. *Int J Cancer* 1998; **76:** 784-86.
- 35 Zucchetto A, Serraino D, Polesel J, et al. Hormonerelated factors and gynecological conditions in relation to endometrial cancer risk. *Eur J Cancer Prey* 2009; **18**: 316-21.
- 36 Urban M, Banks E, Egger S, et al. Injectable and oral contraceptive use and cancers of the breast, cervix, ovary, and endometrium in black South African women: case-control study. *PLoS Med* 2012; **9:** e1001182.
- 37 Hirose K, Tajima K, Hamajima N, et al. Comparative case-referent study of risk factors among hormonerelated female cancers in Japan. *Jpn J Cancer Res* 1999; 90: 255-61.
- 38 Stevens VL, Jacobs EJ, Sun J, et al. Weight cycling and risk of endometrial cancer. *Cancer Epidemiol Biomarkers Prev* 2012; **21:** 747-52.
- 39 John EM, Koo J, Horn-Ross PL. Lifetime physical activity and risk of endometrial cancer. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 1276-83.
- 40 Arem H, Irwin ML, Zhou Y, Lu L, Risch H, Yu H. Physical activity and endometrial cancer in a populationbased case-control study. *Cancer Causes Control* 2011; 22: 219-26.
- 41 Voigt LF, Deng Q, Weiss NS. Recency, duration, and progestin content of oral contraceptives in relation to the incidence of endometrial cancer (Washington, USA). *Cancer Causes Control* 1994; **5:** 227-33.
- 42 Jacobs I, Gentry-Maharaj A, Burnell M, et aL Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. *Lancet Oncol* 2011; **12**: 38-48.

- 43 Razavi P, Pike MC, Horn-Ross PL, Templeman C, Bernstein L, Ursin G. Long-term postmenopausal hormone therapy and endometrial cancer. *Cancer Epidemiol Biomarkers Prev* 2010; **19:** 475-83.
- 44 Olson SH, Trevisan M, Marshall JR, et al. Body mass index, weight gain, and risk of endometrial cancer. *Nutr Cancer* 1995; **23:** 141-49.
- 45 Luo J, Beresford S, Chen C, et al. Association between diabetes, diabetes treatment and risk of developing endometrial cancer. *Br J Cancer* 2014; **111:** 1432-39.
- 46 The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of endometrial cancer. *Int J Cancer* 1991; **49:** 186-90.
- 47 Plummer M. Improved estimates of floating absolute risk. *Stat Med* 2004; **23**: 93-104.
- 48 Ness RB, Grisso JA, Mapper J, et aL Risk of ovarian cancer in relation to estrogen and progestin dose and use characteristics of oral contraceptives. SHARE Study Group. Steroid Hormones and Reproductions. *Am J Epidemiol* 2000; **152**: 233-41.
- 49 Piper JM, Kennedy DL. Oral contraceptives in the United States: trends in content and potency. *Int J Epidemiol* 1987; **16**: 215-21.
- 50 Thorogood M, Ward-Mackintosh L Combined oral contraceptives: risks and benefits. *Br Med Bull* 1993; 49: 124-39.
- 51 Setiawan VW, Yang HP, Pike MC, et al. Type I and II endometrial cancers: have they different risk factors? J *Clin Oncol* 2013; **31:** 2607-18.
- 52 Curado M, Edwards B, Shin H, et al. Cancer incidence in five continents, Vol. IX. Lyon: IARC Scientific Publications no. 160, 2007

- 53 Collaborative Group on Epidemiological Studies of Ovarian Cancer. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies induding 23,257 women with ovarian cancer and 87,303 controls. *Lancet* 2008; **371:** 303-14.
- 54 Maxwell GL, Schildkraut JM, Calingaert B, et al. Progestin and estrogen potency of combination oral contraceptives and endometrial cancer risk. *Gynecol Oncol* 2006; **103**: 535-40.
- 55 Felix AS, Cook LS, Gaudet MM, et al. The etiology of uterine sarcomas: a pooled analysis of the epidemiology of endometrial cancer consortium. *Br J Cancer* 2013; **108**: 727-34.
- 56 Clarke CL, Sutherland RL. Progestin regulation of cellular proliferation. *Endocr Rev* 1990; **11**: 266-301.
- 57 Key TJ, Pike MC. The dose-effect relationship between 'unopposed' oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. *Br J Cancer* 1988; **57**: 205-12.
- 58 Allen NE, Tsilidis KK, Key TJ, et aL Menopausal hormone therapy and risk of endometrial carcinoma among postmenopausal women in the European Prospective Investigation Into Cancer and Nutrition. *Am J Epidemiol* 2010; **172:** 1394-403.
- 59 Doherty JA, Cushing-Haugen KL, Saltzman BS, et al. Long-term use of postmenopausal estrogen and progestin hormone therapies and the risk of endometrial cancer. *Am J Obstet Gynecol* 2007; **197:** 139.e1-e7
- 60 Weiderpass E, Adami HO, Baron JA, et al. Risk of endometrial cancer following estrogen replacement with and without progestins. *J Natl Cancer Inst* 1999; **91**: 1131-37

61 US Census Bureau international database. www.census.gov (accessed Jan 31, 2014).

#### **APPENDIX R**

# Meta-Analysis of Intrauterine Device Use and Risk of Endometrial Cancer

ROBIN M. BEINING, MS, LESLIE K. DENNIS, MS, PHD, ELAINE M. SMITH, MPH, PHD, AND ANUJA DOKRAS, MD, PHD

**PURPOSE:** We sought to study the association between intrauterine device (IUD) use and endometrial cancer.

**METHODS:** A comprehensive search of literature published through April 2007 was conducted, studies reviewed, and data abstracted. Data from ten studies were pooled and analyzed using both fixed- and random-effects models to examine the association of ever use of an IUD and endometrial cancer.

**RESULTS:** Based on the random effects model, a protective crude association between IUD use and endometrial cancer was observed (odds ratio [OR] = 039; 95% confidence interval [CI] = 0.29-0.51; heterogeneity p < 0.001) with a pooled adjusted risk of OR = 0.54 (95% CI, 0.47-0.63; heterogeneity p = 0.40). A decreased risk of endometrial cancer also was seen for increased years of IUD use (OR for 5 years of use 0.88; 95% CI = 0.84-0.92; n = 5; heterogeneity p = 0.14), increased years since last IUD use (OR for 5 years of use 0.91; 95% CI, 0.86-0.95; n = 4; heterogeneity p = 0.02), and increased years since first IUD use (OR for 5 years of use 0.89; 95% CI, 0.83-0.95; n = 4; heterogeneity p = 0.04).

**CONCLUSIONS:** Our results suggest that nonhormonal IUD use may be associated with a decreased risk for endometrial cancer; however, the exact mechanism for this association is unclear. Future investigations should address

the difference in the proposed association by specific type of IUDs.

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KEY WORDS: Endometrial Cancer, Intrauterine Device, Meta-analysis, Review.

# **INTRODUCTION**

Endometrial cancer is the most prevalent female genital malignancy in the United States with an estimated 39,080 incident cases and 7,400 associated deaths expected in the United States during 2007 (1). Endometrial cancer primarily affects postmenopausal age women with a mean age at dignosis of 61 years (2). Factors associated with an increased risk of endometrial cancer are exposure to unopposed estrogen increasing age, elevated body mass index, nulliparity, infertility, polycystic ovary syndrome, amenorrhea, early age at first menarche, delayed onset of menopause, unopposed estrogen therapy, and tamoxifen therapy (2, 3). Previous studies have indicated a protective association between use of combination oral contraceptives and risk of endome-trial cancer. Progesterone acts to limit endometrial proliferation, thereby decreasing the overall risk of endometrial cancer (4).

Intrauterine devices (IUDs) are a common method of reversible contraception in many countries, with an estimated 106 million women worldwide who have used an IUD (5). However, the rate of IUD use in North America ranks among the lowest in the world, with an estimated 1.5% of married women in the United States using an IUD, compared with the highest rate, 33.0% in China, and a global rate of 11.9% (5). IUDs were first marketed for use in 1964 (6). The first generation of IUDs was inert devices, followed by a second generation of copper IUDs, first approved by the U.S. Food and Drug Administration (FDA) in 1984 (7), and most recently a third generation of progesterone IUDs, first introduced in 1990 in Finland (7, 8), and later approved by the FDA in December 2000 (7). Currently, two types of IUDs are marketed in the United States, the copper T380A (ParaGard) and the levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena) (5).

The overall aims of this study were to quantify the magnitude of the association between IUD use and risk of endometrial cancer, including potential contributing factors: duration of use, time since first use, time since last use, and type of device. A meta-analysis was conducted to evaluate these associations with endometrial cancer.

#### **Selected Abbreviatinos and Acronyms**

IUD = intrauterine device

LNG-IUS = levonorgestrel-releasing intrauterine system

SES = socioeconomic status

#### METHODS

#### **Literature Review**

For this meta-analysis, analytic studies that measured IUD use in relation to endometrial cancer were considered. First, a literature search from 1966 through the end of April 2007 was performed using PubMed. MeSH headings, key words, and text words searched included intrauterine devices, IUD, endometrial cancer, and endometrial neoplasms. The search of PubMed returned 42 articles, of which 11 (7, 9-18) were reviewed in detail. The 31 remaining articles were not relevant because they were commentaries, editorials, reviews, casereports, diagnostic or treatment techniques, or other biological discussions. The references in the 42 articles were examined for additional relevant studies; however, no additional relevant studies were identified. In an attempt to locate possible unpublished studies, we searched the ProQuest database of dissertations and theses. This found three dissertations (by Castellsague, Hill, and Wemili) that have been published

elsewhere and are included in our analyses. Non—Englishlanguage articles were also reviewed but determined not to be relevant. Among 11 articles reviewed in detail, several reported on the same populations. Two articles were published using the same data from a 1989-1992 study in Israel; therefore these articles were considered to represent one study (9, 10). Several articles published data from subjects in Shanghai, China (16-18), but their diagnosis dates (1997-2003, 1991-1998, 1988-1990) were only minimally overlapping, so they were treated as separate studies.

The relationship between IUD use and endometrial cancer was examined from multiple perspectives. Specifically, total years of IUD exposure, years since first IUD exposure, years since last IUD exposure, and type of IUD used were assessed. Only two studies reported age at first IUD use; thus we did not pool such data.

#### **Data Abstraction**

Data were abstracted from all articles by one reviewer (R. B.). For each factor, raw data, adjusted factors, reported odds ratios (ORs), and 95% confidence intervals (CIs) were recorded. Information on study design, location, study dates, ethnic majority, case/control source populations, matching factors, and age ranges were also collected. Whenever possible, the most adjusted OR, having controlled for the greatest number of potential confounders, was obtained. Since we could not run the original data, we had to assume each article adjusted for appropriate confounders in the data obtained.

#### **Statistical Methods**

ORs were reported as an estimate of the relative risks. For studies in which no OR was reported, a crude OR was calculated from the tabulated raw data. For each study, the natural log of the OR was calculated and the variance was based on the corresponding 95% confidence intervals (CIs). Dichotomous factors (e.g., ever versus never IUD use) were analyzed by using fixed-effects and random-effects models to compute pooled ORs (19). Assuming that there is a true overall quantity being estimated, inferences about the included studies can be obtained using the fixed-effects models. The amount of error in a fixed-effects model is assumed to be attributable to sampling error (19). Random-effects models apply inferences about hypothetical groups of studies, assumed to follow a probability distribution, rather than individual studies (19). To examine the consistency between associations, statistical tests of homogeneity (20) were performed. The estimated betweenstudy variance was utilized to quantify the magnitude of heterogeneity among the studies (20).

To examine multiple ordinal categories of duration (total years of IUD use), latency (years since first IUD use), and recency (years since last IUD use) for possible linear associations, the categories were analyzed by using fixed-effects dose-response method (20). This method provides the ability to adjust within study correlation while combining levels of exposure in a linear regression of the natural log of the OR. To determine whether the linear model was appropriate for the data, a goodness-of-fit test for linear and quadratic models was performed. The analyses of linear association were performed using SAS software (SAS Software, Inc., Cary, NC).

#### RESULTS

Eleven articles reporting on 10 studies were reviewed (6, 10-18). Study characteristics, including diagnosis years of cases, study location, age range, and number of subjects are described (Table 1). We reported the ORs for the associations between ever versus never IUD use and risk of endometrial cancer, along with the adjustment factors described in each study (Table 1). Only three studies reported on specific types of IUD used; thus the data for types of IUDs used were too sparse to pool (Table 1). Duration of use, reported in years of IUD use, was examined for a linear, protective dose-effect for endometrial cancer. A summary of the duration of use along with time since first and last use of an IUD for each study is provided (Table 1). Protective pooled effects were seen. Recency and latency effects were observed across studies; a protective association for endometrial cancer was observed with an increased period of time since first and last use of an IUD (Table 2). These data must only be interpreted within the range they cover.

The pooled ORs for the association between use of an IUD and endometrial cancer for both the fixed- and randomeffects models were calculated (see Table 2). All studies, except one (16), reported protective effects, and the pooled analyses showed a significant protective effect for ever-use of IUDs and endometrial cancer. Based on the random effects model, a protective crude association between IUD use and endometrial cancer was observed (OR = 039; 95% CI = 0.29-0.51; heterogeneity p < 0.001) with a pooled adjusted risk of OR = 0.54 (95% CI = 0.47-0.63; hetero-geneity p = 0.40).

#### Table 1

Stud characteristics and ever-use of intrauterine device exposure and endometrial cancer among 10 studies, type of device for three studies, and total years of use for six

studies

\* \* \*

#### Table 2

# Pooled odds ratios for intrauterine device used and endometrial cancer among 10 studies by study design along with duration of use reported for 5 year increments

\* \* \*

This meta-analysis found a significant inverse association between IUD use and endometrial cancer. The overall pooled OR of 0.54 suggests a significant reduction in risk of endometrial cancer with ever-use of an IUD (see Table 2). The studies appear to be homogeneous with respect to ever-use of IUDs and endometrial cancer; therefore, the fixed-effects model estimates may be more appropriate for the metaanalyses. The linear duration analyses for a 5-year increase in years of IUD use, latency, and recency effects are also reported (Table 2). An inverse association between IUD use and endometrial cancer was observed for duration of use (OR = 0.88 for 5 years), recency (OR = 0.91 for 5 years), and latency (OR = 0.89 for 5 years). The linear duration measures for years of IUD use, latency, and recency effects are reported as an increase for 5 years. The ORs pooled among studies reporting duration of use and duration since last use were not homogeneous.

The reported linear duration response ORs are the magnitude of association between IUD use and endometrial cancer that can be assumed for each 5 year increase in exposure within the range of the original studies (see Table 2). Among the four studies that examined recency, one had decreasing ORs, two decreased, then increased and the fourth study appeared to have no association. Thus the pooled risk estimates that show a 9% decrease over 5 years need to be interpreted within probably 5-10 years after last use based on the categories among the studies pooled (Table 2). Among the studies that examined first use, two showed a protective effect that was relatively flat, whereas the other two suggested more of a continued decrease, but showed no effect after 17 or 20 years since first use.

#### DISCUSSION

Hormonal (progesterone) IUDs have been marketed since. 1990 (7, 8). We assume all of the women included in these studies had used nonhormonal IUDs, since eight of the 10 studies had diagnosis dates of cancer prior to 1993 where participant exposure to IUDs would likely have occurred prior to the 1990s. When the two studies with diagnosis years in the 1990's were excluded, point estimates changed by 0.01 or less, suggesting that these two studies did not differ from the earlier studies. Considering the relative chronology of endometrial hyperplasia and subsequent cancer, it is unlikely that a significant portion of IUD users in the studies included in this analysis would have been exposed to hormonal IUDs at the time prior study data were collected.

The precise mechanism for the proposed protective association between IUD use and endometrial cancer is not clear. Cellular level changes in the normal endometrium include simple hyperplasia, complex hyperplasia, progressing to endometrial cancer. Two mechanisms through which IUD use may alter endometrial cancer risk have been enumerated: first, through influence on the production of estrogen and progesterone by inducing extrauterine effects on the ovary and the central hypothalamic-pituitary-ovarian axis; and second, through alteration of the endometrial response to hormones by exerting direct changes in the endometrial environment, resulting in chronic inflammation (11). Both mechanisms result in an overall reduction in endome-trial hyperplasia (11, 21, 22). An understanding of the magnitude and consistency of the association between IUD use and endometrial cancer may guide future recommendations in contraceptive health.

Mechanisms of different types of IUDs vary. Older, nonhormonal IUDs, including inert, copper, and stainless steel, 498 produce inflammation only. Studies have observed a significant reduction in both endometrial mitotic activity and estrogen receptor concentration, associated with copper IUD placement (23). Similarly, LNG-IUS acts by influencing the production of the hormone progesterone, which down-regulates estrogen receptors and results in a reduction of cellularproliferation of the endometrial lining. Clinically, women with a LNG-releasing IUD in place tend to have a thinner endometrial lining than women without an IUD (24). This observation supports the theory that the patho-physiological response to an IUD is due to cellular level changes that decrease the rate of hyperplasia, thereby limiting dysplasia and subsequent progression to endometrial cancer. Therefore, if the use of nonhormonal IUDs had a protective effect on cancer development, then an association of the IUD that contains progesterone will likely have a similar or additive protective effect. To date, there are insufficient published data to address

the difference in association between types of IUDs and risk of endometrial cancer.

Identified risk factors for endometrial cancer have the potential to bias risk estimates if not adjusted for in the analyses. The four important risk factors for endometrial cancer (age, obesity, nulliparity, and type 2 diabetes mellitus) were not consistently adjusted for across the 10 studies included in this meta-analysis. Each of the 10 studies, except for one (14), adjusted for age. None of the 10 studies adjusted for all four risk factors and only two studies adjusted for at least three of the risk factors (6, 15). Protective factors for endometrial cancer include any previous use of combined oral contraceptives, tobacco use, and increased parity. Only one of the 10 studies adjusted for all three protective factors (6). Surprisingly, only two studies adjusted for combined oral contraceptive use (6, 14), which confers a lifelong protective effect (25). Failure to adjust for combined oral contraceptive use could potentially bias the protective association between IUD use and endometrial cancer toward a greater magnitude.

Socioeconomic status (SES) often influences healthcare behaviors and may have influenced the study populations included in this meta-analysis, based on differences in access to contraceptive methods (26). Conversely, other literature has suggested that IUD use rates do not differ by SES (27). In this review we were not able to discern how SES may have influenced the study population and therefore cannot assess potential bias.

It may not be possible at this point in time to discern the true magnitude of the proposed association between IUD use and endometrial cancer in reproductive-aged women because of the low incidence of endometrial cancer in premenopausal women and the limited IUD exposure in postmenopausal women included in this meta-analysis. The age range of women included in this meta-analysis was 20-74 years. The percentage of cases in each age stratum was not well enumerated in the 10 studies; however, it is likely that the

majority of endometrial cancer cases were skewed toward older age, consisting primarily of postmenopausal women. The majority of women who are diagnosed with endometrial cancer are not likely to be current IUD users. Correspondingly, the number of endometrial cancer cases in women of reproductive age is limited. In the study with the youngest age bracket of women, 75% of the endo-metrial cancer cases were diagnosed in women between the ages of 45 and 54 years, which would likely correspond to perimenopausal status (11). Considering the disparity in age between IUD use and diagnosis of endometrial cancer, there is a potential for exposure recall bias.

An overall magnitude of association can be estimated, through increased statistical power, without the collection of new data. The collective review of individual studies can lead to the identification of gaps in previous research or knowledge, thus potentially leading to the generation of new hypotheses.

Endometrial cancer can be confirmed through an endometrial biopsy. Of the 10 studies that were reviewed in this meta-analysis, all except three (12, 17, 18) clearly stated that each of their cases had a histologically confirmed diagnosis of endometrial cancer. The other three studies were unclear. Since most registries and hospitals require confirmation of cancer diagnoses, we assume that these three studies had confirmed cases but did not report this detail in their publications. However, we examined this further by conducting sensitivity analyses that excluded these three studies. This showed similar point estimates (OR = 0.53 for ever-use of IUDs) with wider confidence intervals that remained significant. Similar results were seen for measures of duration.

There were several inherent limitations to this metaanalysis. It is difficult to assess the overall level of bias in a meta-analysis. When analyses were stratified by study design, no differences were seen. Therefore we can assume that the studies were comparable. In interpreting the associations, it must be considered that the individual studies adjusted for a variety of potential confounders, potentially influencing the level of bias in individual studies. In this meta-analysis, not every study controlled for each potential confounder. Thus the data for the individual studies may be biased in either a protective or an increased association depending on what factors were adjusted for. Since not all of the studies reported all duration measures of IUD use, the statistical power may be limited for several subanalyses. Additionally, it is unclear whether studies included in this meta-analysis that did not report on years of use or type of device originally collected such information. If the information was in fact collected, but not reported, then this would constitute a form of publication bias.

There have been a limited number of published studies addressing the association between IUD use and endome-trial cancer. It is more common for studies finding a positive association to be published than those concluding null associations (28). With only three or four studies reporting duration of use, latency, and recency, publication bias among measure of duration may exist, resulting in a bias of the overall magnitude and direction of the proposed association.

In conclusion, this meta-analysis found a protective association among women who reported ever-use of an IUD and risk of endometrial cancer. Future investigations should address the difference between exposure for the three types of IUDs-inert, copper, and hormonal. However, this study population may not be feasible because of exposure to multiple types of IUDs or exposure to nonhormonal IUDs and combined oral contraceptives. As time increases since IUDs were first marketed, it will be more feasible to study cohorts of women to assess the association between latency, recency, and duration of IUD use and risk of endometrial cancer, primarily in relation to the hormonal component. A large cohort study

would provide the ability to consistently control for potential confounders.

# REFERENCES

- 1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin. 2007;57:43-66.
- 2. Soliman PT, Oh JC, Schmeler KM, Sun CC, Slomovitz BM, Gershenson DM, et al. Risk factors for young premenopausal women with endometrial cancer. Obstet Gynecol. 2005;105:575-580.
- 3. Parslov M, Lidegaard O, Klintorp S, Pedersen B, Jonsson L, Eriksen PS, et aL Risk factors among young women with endometrial cancer: a Danish case-control study. Am J Obstet Gynecol. 2000;182:23-29.
- 4. Tung IC.H, Goodman MT, Wu AH, McDuffie K, Wilkens LR, Kolonel LN, et aL Reproductive factors and epithelial ovarian cancer risk by histologic type: a multiethnic case-control study. Am J Epidemiol. 2003;158:629638.
- 5. Johnson MJ, Morgan KW. Intrauterine contraception benefits extend beyond birth control. Nurse Pract. 2005;30:50-55.
- 6. IUDs-an update. Popul Rep B. 1995:1-35.
- Sturgeon SR, Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, et al. Intrauterine device use and endometrial cancer risk. Int J Epidemiol. 1997;26:496-500.
- 8. Chi IC, Farr G. The non-contraceptive effects of the levonorgestrel-releasing intrauterine device. Adv Contracept. 1994;10:271-285.
- Benshushan A, Paltiel O, Brzezinski A, Tanos V, Barchana M, Shoshani O, et aL Ovulation induction and risk of endometrial cancer: a pilot study. Eur J Obstet Gynecol Reprod BioL 2001;98:53-57.

- Benshushan A, Paltiel O, Rojansky N, Brzezinski A, Laufer N. IUD use and the risk of endometrial cancer. Eur J Obstet Gynecol Reprod Biol. 2002;105:166-169.
- 11. Castellsague X, Thompson WD, Dubrow R. Intrauterine contraception and the risk of endometrial cancer. Int J Cancer. 1993;54:911-916.
- 12. Hill DA, Weiss NS, Voigt LF, Beresford SA. Endometrial cancer in relation to intra-uterine device use. Int J Cancer. 1997;70:278-281.
- 13. Parazzini F, La Vecchia C, Moroni S. Intrauterine device use and risk of endometrial cancer. Br J Cancer. 1994;70:672-673.
- Rosenblatt KA, Thomas DB. Intrauterine devices and endometrial cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Contraception. 1996;54:329-332.
- 15. Salazar-Martinez E, Lazcano-Ponce EC, Gonzalez Lira-Lira G, Escudero-de los Rios P, Salmeron-Castro J, Hemandez-Avila M. Reproductive factors of ovarian and endometrial cancer risk in a high fertility population in Mexico. Cancer Res. 1999;59:3658-3662.
- 16. Shu XO, Brinton LA, Zheng W, Gao YT, Fan J, Fraumeni JF Jr. A population-based case-control study of endometrial cancer in Shanghai, China. Int J Cancer. 1991;49:38-43.
- 17. Tao MH, Xu WH, Zheng W, Zhang ZF, Gao YT, Ruan ZX, et al. Oral contraceptive and IUD use and endometrial cancer: a population-based case-control study in Shanghai, China. Int J Cancer. 2006;119:2142-2147.
- Wemli KJ, Ray RM, Gao DL, De Roos AJ, Checkoway H, Thomas DB. Menstrual and reproductive factors in relation to risk of endometrial cancer in Chinese women. Cancer Causes Control. 2006;17:949-955.

- 19. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Chin Trials. 1986;7:177-188.
- 20. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epide-miol. 1992;135:1301-1309.
- 21. Gardner FJ, Konje JC, Abrams KR, Brown LJ, Khanna S, Al-Azzawi F, et aL Endometrial protection from tamoxifen-stimulated changes by a lev-onorgestrel-releasing intrauterine system: a randomised controlled triaL Lancet. 2000;356:1711-1717.
- 22. Pekonen F, Nyman T, Lahteenmaki P, Haukkamaa M, Rutanen EM. Intrauterine progestin induces continuous insulin-like growth factor-binding protein-1 production in the human endometrium. J Clin Endocrinol Metab. 1992;75:660-664.
- 23. Guleria K, Agarwal N, Mishra K, Gulati R, Mehendiratta A. Evaluation of endometrial steroid receptors and cell mitotic activity in women using copper intrauterine device: can Cu-T prevent endometrial cancer? J Obstet Gynaecol Res. 2004;30:181-187.
- 24. Perino A, Quartararo P, Catinella E, Genova G, Cittadini E. Treatment of endometrial hyperplasia with levonorgestrel-releasing intrauterine devices. Acta Eur Fertil. 1987;18:137-140.
- 25. Voigt LF, Deng Q, Weiss NS. Recency, duration, and progestin content of oral contraceptives in relation to the incidence of endometrial cancer (Washington, USA). Cancer Causes Control. 1994;5:227-233.
- 26. Strinic T, Bukovic D, Bilonic I, Hirs I, Despot A, Bocan A. Socio-demo-graphic characteristics of women with endometrial carcinoma. Coll Antro-poL 2003;27:55-59.

- 27. Chick P, Nixon J. Who attends family planning clinics? Aust N Z J Obstet Gynaecol. 1984;24:213-216.
- 28. Ferrer RL. Graphical methods for detecting bias in meta-analysis. Fam Med. 1998;30:579-583.

# **APPENDIX S**

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# NONCONTRACEPTIVE HEALTH BENEFITS OF INTRAUTERINE DEVICES: A SYSTEMATIC REVIEW

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Most women and their clinicians are unaware that IUDs confer important noncontraceptive health benefits. This

review summarizes the evidence from published articles on this topic. We conducted a series of systematic literature searches to identify articles on the noncontraceptive health benefits of IUD use. We reviewed the potentially pertinent ones for content, grouped them according to type of IUD, and evaluated them using the U.S. Preventive Services Task Force rating system. Over 500 titles were identified and hundred abstracts were reviewed. several Use of nonhormonal IUDs (plastic and copper) was associated with a decrease in endometrial cancer. The levonorgestrel intrauterine system can treat a variety of gynecological disorders, including men-orrhagia and anemia. The levonorgestrel system has also been used successfully as part of hormone replacement therapy, as adjuvant therapy with tamoxifen, and as an alternative to hysterectomy for women with bleeding problems. Like oral contraceptives, intrauterine contracep-tives confer important noncontraceptive health benefits.

**Target Audience**: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this article, the reader will be able to describe the currently marketed IUDs in the U.S., to summarize the current literature about the noncontraceptive benefits of IUD use, and to list the noncontraceptive benefits of IUD use.

Intrauterine devices (IUDs) are known worldwide as contraceptives, but they also provide a variety of

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Dr. Hubacher has disclosed that he has no significant financial or other relationship with any commercial entity. Dr. Grimes has disclosed that he is a consultant for Alza,

Gynetics, GynoPharma, Mead-Johnson, Organon, Ortho-McNeil, Schering, Schmid, and Searle; is on the speakers bureau of Berlex Laboratories, Gyno-Pharma, Ortho-McNeil, Parke-Davis, Pharmacia-Upjohn, and Wyeth-Ayerst; and has received research grant support from Ber-lex Laboratories, Ortho-McNeil, and Wyeth-Ayerst.

The noncontraceptive uses of intrauterine devices discussed in this article have not been approved by the U.S. Food and Drug Administration. noncontraceptive health benefits. Although many ar¬ticles have chronicled the noncontraceptive benefits of oral contraceptives (1–4), the health benefits of intrauterine contraception are less well known and appreciated. Because IUDs are the most commonly used reversible contraceptive in the world today (5), the public health impact of disease protection and general health benefits that IUDs may provide may be substantial.

Two IUDs are currently marketed in the U.S. The copper T380A device (ParaGard, Ortho-McNeil Pharmaceutical Corp, Raritan, NJ) was approved by the FDA in 1984 and became available in the U.S. in 1988. Copper was first placed on plastic T-shaped devices in the 1960s, after researchers discovered the element's contraceptive properties. A dose-response relationship was established, culminating in the prod¬uct that now contains 380 mm2 of copper surface. The device is approved for 10 years of contraceptive protection, although data support high efficacy as long as 12 years (6). The T380A is the most used IUD worldwide.

In December 2000, the FDA approved the levonorgestrelintrauterine system (LNG-IUS); it is marketed under the name of Mirena (Berlex Labora¬tories, Wayne, NJ). This plastic device is also T-shaped and the vertical stem is a reservoir containing 52 mg of levonorgestrel. It releases 20 pg of levonorgestrel per day over a period of 5 years, although data support effectiveness for as long as 7 years (7).

In recent years, several review articles on the ther-apeutic uses of hormone-releasing IUDs have been written (8–10),

but none has summarized all the possible therapeutic uses in a systematic fashion. In the U.S., the LNG-IUS was approved as a contracep-tive only; we discuss research of other indications that represent unlabeled use. Older types of IUDs (nonmedicated and copper-bearing) seem to be asso-ciated with protection from numerous gynecological maladies, however, this information has not been assembled in one article. This article summarizes the noncontraceptive benefits of IUD use and expands on past reviews (11) by evaluating the strength of the evidence.

## **METHODS**

We conducted several online searches to collect pertinent English-language articles for this review. In Popline (June 2000 database), we located 103 articles with the following strategy: IUD [Beneficial Effects] or IUD [Therapeutic Use] or IUD, UNMEDICATED [Beneficial Effects] or IUD, UNMEDICATED [Therapeutic Use]. We also conducted separate PubMed (National Library of Medicine) searches: "intrauterine devices AND fibroids" (50 articles): "intrauterine devices AND (cancer OR neoplasm)" (379 articles); "intrauterine devices AND endometri-osis" (51 articles). To make sure key research on the levonorgestrel-IUS was not missed, we searched PubMed on that phrase and located 335 articles. Finally, we searched the Cochrane Library for arti-cles on hormone replacement therapy and heavy menstrual blood loss, and added any original re-search articles cited in the Cochrane topics to our review. For all the articles found in the initial searches, we removed duplicates and selected a subset for additional examination if they were original reports.

We divided the papers into two groups, depending on which type of IUD was investigated in the article. Nonmedicated and copper IUDs formed one group and hormone-releasing IUDs formed another group. The articles we found on nonmedicated and copper IUDs were epidemiologic studies focusing on cervi-cal cancer

(published reports on cervical intraepithe-lial neoplasia were excluded from this review), en-dometrial cancer, and endometriosis. In these studies, retrospective data were collected on previous IUD use and most articles reported odds ratios for the association between previous IUD use and the end point of interest. In some instances, as noted in the tables, the published papers did not report odds ratios in the form we required for this review; we used data from the published reports to compute the crude odds ratios and 95% confidence intervals. We distin-guished between crude and adjusted confidence in-tervals in our tables. Many of the papers provided subanalyses examining type of IUD, duration of use, and timing of use; we reported many of these find-ings from subanalyses in our tables. The literature on hormonal IUDs was generally derived from prospec-tive trials focusing on gynecological problems; all the articles involved the levonorgestrel system only. Treatment effects were compared with an alternative therapy, baseline measurements, or in some cases both. Where available, we reported whether such comparisons were statistically significant using a P value of ~.05. After collecting and reviewing the reports on both types of IUDs, we used the U.S. Preventive Services Task Force rating system (12) to grade the quality of evidence and the strength of recommendation that can be based on that evidence.

## RESULTS

Copper-bearing and nonmedicated (plastic only) IUDs have several noncontraceptive benefits, includ¬ing probable protection against endometrial cancer (Table 1). Seven studies reported the relationship between previous copper or nonmedicated IUD use and endometrial cancer (13–19). In all but one study, previous IUD use was associated with a decreased risk of endometrial cancer. The studies by Salazar-Martinez et al. (13), Hill et al. (15), and Castellsague et al. (18) all reported statistically significant associ¬ations between IUD use and a decrease in the risk of endometrial

cancer. Of note, the landmark Cancer and Steroid Hormone Study of the Centers for Dis-ease Control and Prevention was one of the studies to report significant protection against endometrial can¬cer (18). Three articles (14, 16, 17) suggested a protective effect of IUDs, but the measures of effect were not statistically significant. The final article (19) was based on research in China, where the steel ring IUD was used; the findings suggest that this type of IUD does not protect against endometrial cancer. The majority of articles on endometrial cancer also reported subgroup analyzes focusing on factors such as type of IUD and duration/timing of use. In general, no consistent pattern emerged from the articles to suggest that length or timing of use, or type of IUD was associated with an increase or decrease in the risk of endometrial cancer.

Cervical cancer was addressed in three articles (20–22) (Table 1). Although all three suggested a possible protective effect from previous IUD use, none was statistically significant. Each article re-ported subanalyses involving IUD use variables, and only the work by Li and colleagues (20) showed a statistically significant decrease in risk of cervical cancer in one subgroup: women who began intrauter¬ine contraception before age 33 years. Because the research by Li and colleagues (20) was done in China when the steel ring IUD was dominant, their findings apply to only this type of device.

We found seven articles (23–29) addressing the relationship between past use of an IUD and endo-metriosis (Table 2). Three of these articles (23, 24, 27) suggested an increased risk, but none was statis-tically significant. Of the two articles suggesting a possible protective effect (25, 26), only the results of Mahmood and Templeton (26) were statistically significant. As noted in Table 2, in all but one article, the odds ratios provided in this review were calculated from data presented in the published article.

The last two articles (28, 29) did not provide data from which overall odds ratios could be calculated, although Kirshon and Poindexter (28) suggested IUD use is positively associated with endometriosis.

The LNG-IUS has two distinct categories of benefits that will be described separately; the first concerns the ancillary health benefit or disease pro-tection that this device confers, relative to the copper IUD (Table 3). Two large, randomizedcontrolled trials, subsequently referred to as the European trial and the multicontinent trial, compared the LNG-IUS with the Nova-T (copper) IUD and the copper T380 device, respectively. In the European trial, pelvic inflammatory disease (PID) rates were significantly lower among LNG-IUS users at 5-year (30) and 3-year follow-up (31). In the multicontinent trial (7), PID rates did not differ significantly between LNG-IUS and copper-T users at 2, 5, and 7 years after insertion. In a retrospective cohort study, Merki-Feld and colleagues (32) compared the incidence of acti-nomyceslike organisms (ALO) in users of the LNG-IUS and users of copper IUDs; they found that ALO-positive PAP smears of the cervix were signif-icantly more common in users of copper IUDs com-pared with LNG-IUS users (20% vs. 3%).

In all four articles (7, 30, 33, 34) addressing hemoglobin changes, the LNG-IUS was shown to increase the concentration over measurements taken before insertion of the device (Table 3). The net gain in hemoglobin concentrations varied depending on the length of follow-up, ranging from as little as 0.5 gm/dl after 2 years (34) to as much as 1.6 gm/dl after 5 years (30). Both the European and multicontinent trials showed decreases in hemoglobin concentra-tions among users of copper IUDs.

#### TABLE 1

Estimates from case-control studies on cancer and previous use of nonmedicated and/or copper IUDs

\* \* \*

# TABLE 2

#### Studies on endometriosis and previous IUD use

\* \* \*

#### TABLE 3

# Selected health benefits/disease protection from using the levonorgestrel (LNG) intrauterine system

#### \* \* \*

The second category of papers on the LNG-IUS addresses the numerous therapeutic uses of this de-vice (Table 4). Idiopathic menorrhagia responds favorably to the levonorgestrel system; all nine stud-ies (35-43) using a variety of designs and measures, showed positive results. The seven articles that mea-sured menstrual blood loss estimated reductions of 74% to 97%. Four (37, 41-43) of the six studies used the alkaline hematin method (44, 45) for mea-suring the amount of menstrual blood, and three studies (35, 39, 40) used menstrual diaries (46) to estimate the amount of blood loss. Lahteenmaki and colleagues (38) used menstrual diaries to record the number of days of bleeding, not amount of bleeding; after 12 months, women using the levonorgestrel device reduced their number of days of bleeding by about 50%.

Many hysterectomies are performed because of heavy menstrual blood loss that has become intoler-able; two studies reported the LNG-IUS as a possible alternative to surgery. Both studies were random-ized trials, assigning either continued conservative (medical) treatments or the LNG-IUS for women who were contemplating hysterectomy. The proportion of women canceling their planned hysterectomy in the LNG-IUS arms of the two trials was 80% (47) and 64% (38); this compared with 9% and 14%, respectively, of women assigned to the medical treatments.

# TABLE 4

# Therapeutic uses of the levonorgestrel intrauterine system (LNG-IUS)

#### \* \* \*

Two articles addressed uterine fibroids; the be-fore-after study by Starczewski and Iwanicki (48) involved 12 participants and concluded that the LNG-IUS reduced bleeding from uterine fibroids but did not reduce the size of the fibroids, based on ultrasound measurements. The other publication, a case report (49), noted an increase in hemoglobin from 5 gm/dl to 11 gm/dl and a decrease in fibroid volume. The LNG-IUS has also been tested in a population of 25 women with adenomyosis-associ-ated menorrhagia (50); the therapy reduced bleeding and reduced uterine volume, as measured by ultra¬sound. Only one study (51) was located that exam¬ined anemia; the researchers found that the LNG-IUS reduces the prevalence compared with nonusers or users of other IUDs.

Because oral progestins used in hormone replace-ment therapy can cause frequent and irregular bleeding in some women (52), several groups of researchers sought to determine whether the LNG-IUS could avoid the effects of systemic progestin and mitigate bleeding. In all published articles on this topic (53-60), the LNG-IUS was found to reduce bleeding, as measured by the number of menstrual days, spotting days, or induced amenorrhea. In the subset of research that involved randomized trials comparing the LNG-IUS with other means of deliv-rering progestins (54–56, 58), the LNG-IUS was superior (in reducing bleeding) to the comparison methods in all but one study (55). Finally, as an adjuvant to tamoxifen therapy in women with breast cancer, the LNG-IUS caused a decidual response in the endometrium of all treated women (61); this in turn protected women from the uterine effects of tamoxifen.

# CONCLUSIONS
The collected evidence supports several conclu-sions about noncontraceptive benefits of contempo-rary IUDs (Table 5). Case-control studies (level II-2 evidence) provide fair evidence that use of nonmedicated or copper IUDs protect against endometrial cancer (class B recommendation). Because random¬ized, controlled trials cannot be done, level II-2 stud¬ies will be the most rigorous evidence available. Case-control studies of cervical cancer and endometriosis are inadequate to reach a conclusion (class C recommendation).

#### TABLE 5

#### U.S. Preventive Services Task Force ratings (12) as applied to research on the noncontraceptive benefits of IUD

\* \* \*

Concerning the LNG-IUS, randomized, controlled trials have produced conflicting conclusions regard-ing pelvic inflammatory disease; the European trial which compared the LNG-IUS with the Nova T copper IUD found a significant reduction in risk, whereas the multicontinent trial (using the copper T380 as a comparison) found no differences in risk. Compelling level I evidence indicates important improvements in hemoglobin concentration (class А recommendation), and level II-3 evidence supports a role in preventing anemia (class B recommendation). Strong evidence from randomized controlled trials shows the LNG-IUS to be an effective treatment for menorrhagia (class A recommendation). Small case-series reports (level III evidence) provide some evi-dence for a beneficial effect in treating heavy bleed-ing related to fibroids, although the evidence is too limited to make a recommendation.

The studies on the LNG-IUS as an alternative to hysterectomy were well conducted (level I evidence) and showed conclusively that when offered this method, women will cancel their procedure in pro-portions far exceeding that of women assigned to continue their current therapy. Level I evidence also strongly supports the usefulness of the levonorgestrel system as an adjunct to hormone replacement therapy (class A recommendation). One randomized, con¬trolled trial has also found benefit in preventing endometrial hyperplasia in women receiving tamoxifen (class B recommendation).

#### DISCUSSION

Like combined oral contraceptives (62) and inject-able depotmedroxyprogesterone acetate (63), non-medicated and copper IUDs seem to help prevent endometrial cancer. However, because of the diffi-culties in assessing causal relationships in case-con-trol studies, this protective effect must be viewed cautiously. The mechanism involved is unknown. The IUD might protect the endometrium against can¬cer by interfering with localized response to hor-mones and or by altering the production of hormones that are often associated with cancer development. Alternatively, the sterile inflammatory reaction may be hostile to atypical histology that might otherwise lead to cancer.

On a global scale, the public health impact of IUD use may be large. For example, in the U.S., endome-trial cancer is the most common gynecological ma-lignancy. Because over 100 million women world-wide currently use IUDs, even modest protection against endometrial cancer may avert thousands of deaths due to this cause. Although women are un-likely to choose an IUD expressly to prevent endo-metrial cancer, this information should probably be discussed as part of routine counseling. Given the powerful suppressive effect on the endometrium, the levonorgestrel system should also protect against en-dometrial cancer, although studies to date have been limited to women receiving tamoxifen (61).

Despite the seemingly strong evidence that the LNG-IUS is an alternative to hysterectomy (provided by level I evidence), we decided on a class B rec¬ommendation because of concerns that perhaps the women using the LNG-IUS were merely giving the method an honest chance to improve their condition; women who were not randomized to the LNG-IUS had nothing to compel them to cancel their hyster¬ectomy procedure. Longer follow-up periods are needed to document the incidence of hysterectomy among the women assigned to the LNG-IUS.

In contrast to the nonhormonal IUDs, the LNG-IUS will be used specifically for many noncontra-ceptive purposes. Current off-label uses in the U.S. include treatment of menorrhagia, treatment of dys-menorrhea, and use as hormone replacement therapy. The list of potential therapeutic applications will likely grow as its use expands around the world.

We broached the topic of IUDs and pelvic inflam-matory disease because some research has shown that the LNG-IUS confers protection compared with other IUDs. This possible protective effect has bio-logic plausibility in two major ways. First, because levonorgestrel thickens the cervical mucus, bacteria may have a more difficult time ascending into the upper genital tract. Second, because of reduced menstrual blood loss with a LNG-IUS, there is less opportunity for retrograde menstruation to occur. More research is needed to determine whether the LNG-IUS, indeed, provides clinically significant protection.

Our review has both strengths and weaknesses. The methods we used were comprehensive and standard¬ized; they included an explicit search strategy, a thorough search for relevant articles (64, 65), and a quantitative assessment of the strength of evidence using widely accepted criteria (12). However, several limitations may have biased our assessment. For ex¬ample, some relevant articles may have escaped our attention because the authors did not report outcomes of interest in their abstract. Although our review may have missed some articles, we do not believe this would introduce systematic bias. Publication bias (66) is another concern that must be raised; our conclusions may be biased if favorable findings on these topics were more likely to be published than unfavorable results. This might exaggerate the

poten¬tial benefits. Publication bias is probably more of an issue in research involving the levonorgestrel device.

The IUD today poses a global paradox. Although the most common reversible contraceptive method in the world, it has the worst reputation of all contra¬ceptives. . .except among those using IUDs (67). Mass media clearly influences women's decisions about contraceptive choices (68); over the past 20 years, the media have focused on adverse effects of IUDs. In recent years, many gynecologists have pointed out that today's IUDs deserve a fresh look (69–72). Clinicians and, importantly, the media now have an ethical obligation to inform women that IUDs are not only safe and effective contraception, but they also have important health benefits. Without this information, women cannot make truly informed choices about contraception.

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#### REFERENCES

- 1. Jensen JT, Speroff L. Health benefits of oral contraceptives. Obstet Gynecol Clin North Am 2000;27:705–721.
- Mishell DR Jr. Noncontraceptive benefits of oral contracep¬tives. J Reprod Med 1993;38(12 Suppl):1021–1029.
- 3. Mishell DR Jr. Noncontraceptive health benefits of oral steroi¬dal contraceptives. Am J Obstet Gynecol 1982;142(6 Pt 2): 809–816.
- 4. Burkman RT Jr. Noncontraceptive effects of hormonal con¬traceptives: Bone mass, sexually transmitted disease and pel¬vic inflammatory disease, cardiovascular disease, menstrual function, and future fertility. Am J Obstet Gynecol 1994;170(5 Pt 2):1569–1575.

- Trieman K, Liskin L, Kols A et al. IUDs: An update. Population Reports, Series B, No. 6. 95. Baltimore, MD: Johns Hopkins School of Public Health. Population Information Program.
- 6. Long-term reversible contraception. Twelve years of experi¬ence with the TCu380A and TCu220C. Contraception 1997; 56:341–352.
- Sivin I, Stern J, Coutinho E et al. Prolonged intrauterine con¬traception: A seven-year randomized study of the levonorg-estrel 20 mcg/day (LNg 20) and the Copper T380 Ag IUDS. Contraception 1991;44:473–480.
- 8. Luukkainen T. The levonorgestrel intrauterine system: Thera¬peutic aspects. Steroids 2000;65:699–702.
- 9. Coleman M, McCowan L, Farquhar C. The levonorgestrel-releasing intrauterine device: A wider role than contraception. Aust NZ J Obstet Gynaecol 1997;37:195–201.
- 10. Luukkainen T, Toivonen J. Levonorgestrel-releasing IUD as a method of contraception with therapeutic properties. Contra¬ception 1995;52:269–276.
- 11. McAlister FA, Clark HD, van Walraven C et al. The medical review article revisited: Has the science improved? Ann Intern Med 1999;131:947–951.
- 12. US Preventive Services Task Force. Guide to Clinical Preven-tive Services, 2nd Ed. Baltimore: Williams & Wilkins, 1995.
- 13. Salazar-Martinez E, Lazcano-Ponce EC, Gonzalez Lira-Lira G et al. Reproductive factors of ovarian and endometrial cancer risk in a high fertility population in Mexico. Cancer Res 1999; 59:3658–3662.
- 14. Sturgeon SR, Brinton LA, Berman ML et al. Intrauterine device use and endometrial cancer risk. Int J Epidemiol 1997;26:496–500.

- 15. Hill DA, Weiss NS, Voigt LF et al. Endometrial cancer in relation to intra-uterine device use. Int J Cancer 1997;70:278–281.
- 16. Rosenblatt KA, Thomas DB. Intrauterine devices and endo-metrial cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Contraception 1996;54:329–332.
- 17. Parazzini F, La Vecchia C, Moroni S. Intrauterine device use and risk of endometrial cancer. Br J Cancer 1994;70:672–673.
- 18. Castellsague X, Thompson WD, Dubrow R. Intrauterine con¬traception and the risk of endometrial cancer. Int J Cancer 1993;54:911–916.
- 19. Shu XO, Brinton LA, Zheng W et al. A populationbased case-control study of endometrial cancer in Shanghai, China. Int J Cancer 1991;49:38–43.
- 20. Li HQ, Thomas DB, Jin SK et al. Tubal sterilization and use of an IUD and risk of cervical cancer. J Womens Health Gend Based Med 2000;9:303–310.
- Parazzini F, La Vecchia C, Negri E. Use of intrauterine device and risk of invasive cervical cancer. Int J Epidemiol 1992;21: 1030–1031.
- 22. Lassise DL, Savitz DA, Hamman RF et al. Invasive cervical cancer and intrauterine device use. Int J Epidemiol 1991;20: 865–870.
- 23. Sangi-Haghpeykar H, Poindexter AN 3rd. Epidemiology of endometriosis among parous women. Obstet Gynecol 1995; 85:983–992.
- 24. Parazzini F, Ferraroni M, Bocciolone L et al. Contraceptive methods and risk of pelvic endometriosis. Contraception 1994;49:47–55.
- 25. Makhlouf Obermeyer C, Armenian HK, Azoury R. Endometri-osis in Lebanon: A case-control study. Am J Epidemiol 1986; 124:762–767.

- 26. Mahmood TA, Templeton A. Prevalence and genesis of en-dometriosis. Hum Reprod 1991;6:544–549.
- 27. Moen MH. Is a long period without childbirth a risk factor for developing endometriosis? Hum Reprod 1991;6:1404–1407.
- 28. Kirshon B, Poindexter AN 3rd. Contraception: a risk factor for endometriosis. Obstet Gynecol 1988;71(6 Pt 1):829–831.
- 29. Vessey MP, Villard-Mackintosh L, Painter R. Epidemiology of endometriosis in women attending family planning clinics. BMJ 1993;306:182–184.
- Andersson K, Odlind V, Rybo G. Levonorgestrelreleasing and copper-releasing (Nova T) IUDs during five years of use: A randomized comparative trial. Contraception 1994;49:56–72.
- 31. Toivonen J, Luukkainen T, Allonen H. Protective effect of intrauterine release of levonorgestrel on pelvic infection: Three years' comparative experience of levonorgestrel- and copper-releasing intrauterine devices. Obstet Gynecol 1991;77:261–264.
- 32. Merki-Feld GS, Lebeda E, Hogg B et al. The incidence of actinomyces-like organisms in Papanicolaou-stained smears of copper- and levonorgestrel-releasing intrauterine devices. Contraception 2000;61:365–368.
- Ronnerdag M, Odlind V. Health effects of long-term use of the intrauterine levonorgestrel- releasing system. A follow-up study over 12 years of continuous use. Acta Obstet Gynecol Scand 1999;78:716–721.
- Sivin I, Stern J, Diaz J et al. Two years of intrauterine contra¬ception with levonorgestrel and with copper: A randomized comparison of the TCu 380Ag and levonorgestrel 20 mcg/day devices. Contraception 1987;35:245–255.

- 35. Istre O, Trolle B. Treatment of menorrhagia with the levonorg-estrel intrauterine system versus endometrial resection. Fertil Steril 2001;76:304–309.
- 36. Romer T. Prospective comparison study of levonorgestrel IUD versus Roller-Ball endometrial ablation in the management of refractory recurrent hypermenorrhea. Eur J Obstet Gynecol Reprod Biol 2000;90:27–29.
- Irvine GA, Campbell-Brown MB, Lumsden MA et al. Random-ised comparative trial of the levonorgestrel intrauterine system and norethisterone for treatment of idiopathic menorrhagia. Br J Obstet Gynaecol 1998;105:592–598.
- Lahteenmaki P, Haukkamaa M, Puolakka J et al. Open ran¬domised study of use of levonorgestrel releasing intrauterine system as alternative to hysterectomy. BMJ 1998;316:1122–1126.
- Barrington JW, Bowen-Simpkins P. The levonorgestrel intra¬uterine system in the management of menorrhagia. Br J Ob-stet Gynaecol 1997;104:614– 616.
- 40. Crosignani PG, Vercellini P, Mosconi P et al. Levonorgestrel-releasing intrauterine device versus hysteroscopic endome-trial resection in the treatment of dysfunctional uterine bleed¬ing. Obstet Gynecol 1997;90:257–263.
- 41. Tang GW, Lo SS. Levonorgestrel intrauterine device in the treatment of menorrhagia in Chinese women: Efficacy versus acceptability. Contraception 1995;51:231–235.
- 42. Milsom I, Andersson K, Andersch B et al. A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel- releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. Am J Obstet Gynecol 1991;164:879–883.

- 43. Andersson JK, Rybo G. Levonorgestrel-releasing intrauterine device in the treatment of menorrhagia. Br J Obstet Gynaecol 1990;97:690–694.
- 44. Hallberg L, Nilsson L. Determiniation of menstrual blood loss. Scand J Clin Lab Invest 1964;16:244–248.
- 45. Newton J, Barnard G, Collins W. A rapid method of measuring menstrual blood loss using automatic extraction. Contracep¬tion 1977;16:269–282.
- 46. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol 1990; 97:734–739.
- 47. Hurskainen R, Teperi J, Rissanen P et al. Quality of life and cost-effectiveness of levonorgestrel-releasing intrauterine system versus hysterectomy for treatment of menorrhagia: a randomised trial. Lancet 2001;357:273–277.
- 48. Starczewski A, Iwanicki M. [Intrauterine therapy with levonorgestrel releasing IUD of women with hypermenorrhea secondary to uterine fibroids]. Ginekol Pol 2000;71:1221–1225.
- 49. Fong YF, Singh K. Effect of the levonorgestrelreleasing intra¬uterine system on uterine myomas in a renal transplant pa¬tient. Contraception 1999;60:51–53.
- 50. Fedele L, Bianchi S, Raffaelli R et al. Treatment of adenomy-osis-associated menorrhagia with a levonorgestrel- releasing intrauterine device. Fertil Steril 1997;68:426–429.
- 51. Faundes A, Alvarez F, Brache Vet al. The role of the levonorg-estrel intrauterine device in the prevention and treatment of iron deficiency anemia during fertility regulation. Int J Gynae-col Obstet 1988;26:429–433.
- 52. Girdler SS, O'Briant C, Steege J et al. A comparison of the effect of estrogen with or without progesterone on mood and physical symptoms in postmenopausal

women. J Womens Health Gend Based Med 1999;8:637–646.

- 53. Wollter-Svensson LO, Stadberg E, Andersson K et al. Intra¬uterine administration of levonorgestrel 5 and 10 Ag/24 hours in perimenopausal hormone replacement therapy. A random¬ized clinical study during one year. Acta Obstet Gynecol Scand 1997;76:449–454.
- 54. Suhonen SP, Holmstrom T, Allonen HO et al. Intrauterine and subdermal progestin administration in postmenopausal hor¬mone replacement therapy. Fertil Steril 1995;63:336–342.
- 55. Raudaskoski TH, Lahti EI, Kauppila AJ et al. Transdermal estrogen with a levonorgestrel-releasing intrauterine device for climacteric complaints: clinical and endometrial re¬sponses. Am J Obstet Gynecol 1995;172(1 Pt 1):114–119.
- 56. Andersson K, Mattsson LA, Rybo G et al. Intrauterine release of levonorgestrel—A new way of adding progestogen in hor¬mone replacement therapy. Obstet Gynecol 1992;79:963–967.
- 57. Suvanto-Luukkonen E, Kauppila A. The levonorgestrel intra¬uterine system in menopausal hormone replacement therapy: Five-year experience. Fertil Steril 1999;72:161–163.
- 58. Suvanto-Luukkonen E, Sundstrom H, Penttinen J et al. Per-cutaneous estradiol gel with an intrauterine levonorgestrel releasing device or natural progesterone in hormone replace¬ment therapy. Maturitas 1997;26:211–217.
- 59. Suhonen S, Holmstrom T, Lahteenmaki P. Three-year fol¬low-up of the use of a levonorgestrel-releasing intrauterine system in hormone replacement therapy. Acta Obstet Gy-necol Scand 1997;76:145–150.

- 60. Suhonen SP, Allonen HO, Lahteenmaki P. Sustainedrelease estradiol implants and a levonorgestrel-releasing intrauterine device in hormone replacement therapy. Am J Obstet Gy-necol 1995;172(2 Pt 1):562–567.
- 61. Gardner FJ, Konje JC, Abrams KR et al. Endometrial protec-tion from tamoxifen-stimulated changes by a levonorgestrel-releasing intrauterine system: A randomised controlled trial. Lancet 2000;356:1711–1717.
- 62. Combination oral contraceptive use and the risk of endome-trial cancer. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. JAMA 1987;257:796–800.
- 63. Depot-medroxyprogesterone acetate (DMPA) and risk of en-dometrial cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Int J Cancer 1991;49:186–190.
- 64. Mulrow CD. The medical review article: state of the science. Ann Intern Med 1987;106:485–488.
- 65. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: Syn¬thesis of best evidence for clinical decisions. Ann Intern Med 1997;126:376–380.
- 66. Dickersin K, Min YI. Publication bias: The problem that won't go away. Ann NY Acad Sci 1993;703:135–146; Discussion, pp. 146–148.
- 67. Forrest JD. U.S. women's perceptions of and attitudes about the IUD. Obstet Gynecol Surv 1996;51(Suppl):S30–S34.
- Jones EF, Beniger JR, Westoff CF. Pill and IUD discontinua-tion in the United States, 1970–1975: The influence of the media. Fam Plann Perspect 1980;12:293–300.

- 69. Darney PD. Time to pardon the IUD? N Engl J Med 2001;345: 608–610.
- 70. Cheng D. The intrauterine device: Still misunderstood after all these years. South Med J 2000;93:859–864.
- Fortney JA, Feldblum PJ, Raymond EG. Intrauterine devices. The optimal long-term contraceptive method? J Reprod Med 1999;44:269–274.
- 72. Dardano KL, Burkman RT. The intrauterine contraceptive de¬vice: An often-forgotten and maligned method of contracep¬tion. Am J Obstet Gynecol 1999;181:1–5.

#### **APPENDIX T**

#### EUROPEAN JOURAN OF OBSTETRICS & GYNECOLOGY AND REPRODUCTIVE BIOLOGY 105 (2002) 166-169

#### IUD USE AND THE RISK OF ENDOMETRIAL CANCER

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#### Abstract

*Objective*: Although the intrauterine device (IUD) is one of the most widely used forms of contraception throughout the world, its potential long-term effects on the uterus have not been thoroughly evaluated. This paper reports the long-term results of IUD use on the incidence of endometrial cancer. *Study design*: The data is part of a nationwide case-control, pilot study that was undertaken in order to evaluate the possible influence of ovulation induction drugs on the risk of endometrial cancer. The study included 128 living women 35–64 years old, with a histologically confirmed

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diagnosis of endometrial carcinoma. The controls were 255 women from the same dialing areas selected by random digit dialing. A multivariate logistic model, controlling for age, was used to assess the independent effects of factors found to be significantly associated with endometrial cancer on univariate

significantly associated with endometrial cancer on univariate analysis. *Results*: The following parameters were found to be independently associated with endometrial cancer controlling for age: nulliparity OR = 2.7 (95% CI 1.1–6.5, P = 0.03); history of infertility OR = 1.8 (95% CI 1.0–3.3, P = 0.05); BMI > 27 OR = 2.3 (95% CI 1.4–3.8, P = 0.001).

The use of oral contraceptives and IUD were found to be protective; OR = 0.29 and 0.37, respectively, (95% CI 0.14–0.61, P = 0.001, 0.19–0.70, and 0.003, respectively). *Conclusions*: IUD use may have a protective effect on endometrial cancer risk. The protective effect of IUD may be either, through the intense inflammatory response that leads to other lisosomal and inflammatory actions, which may include cells responsible for early elimination of hyperplastic endometrial epithelial cells or, the more complete shedding of the endometrium associated with IUD use may decrease hyperplasia of the endometrium, a known risk factor for endometrial carcinoma.

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*Keywords:* Contraception; Endometrial cancer; Epidemiology; Intrauterine device (IUD)

#### 1. Introduction

Although IUD use is one of the oldest and the most widely used form of contraception throughout the world, its potential long-term effects on the uterus have been poorly evaluated.

Since early this century, sporadic attempts have been made to design an intrauterine device (IUD) that would prevent pregnancy without serious adverse effects. In the 1960's, Lippes (1962) and Margulis (1964) described the flexible plastic devices, which are the basis for the present IUDs in use. The IUD is believed to induce an intense local inflammatory response, which leads to recruitment of phagocytic cells and mast cells, and to provoke

lysosomal activation, and proteolytic enzymes release from this cells into the uterine cavity [1–3]. Furthermore, scanning electron microscope studies of the endometrium in IUD-wearing women, show alterations in the surface morphology of cells, especially of the microvilli of ciliated cells [4] and reduction of ciliated cells with impairment of the secretory activity in the epithelium next to the device [5]. Other reports indicated alterations in the composition of proteins within the uterine cavity [6], and alterations in endometrial response to estrogen and progesterone [7,8].

The epidemiological data on the relationship between IUD use and endometrial cancer is scanty, and only few have examined the possibility of such a link. To expand the existing data we report a secondary analysis of a pilot case-control study from Israel.

#### 2. Material and methods

The general design of this study is fully described in our previous report [9]. In brief, cases of endometrial cancer were identified from the Israel Cancer Registry. Cases were eligible for this study if they had a histologically confirmed diagnosis of endometrial carcinoma that was first diagnosed and reported between 1 January 1989 and 31 December 1992; if they were born between 1 January 1929 and 31 December 1957; and if they were alive at the time of interview. Only living cases were used such that ascertainment of exposure was based on personal interviews exclusively.

Controls were obtained by telephoning randomly selected numbers within the same area codes as those of the cases, a method closely resembling that reported by Hartge et al. [10], and were interviewed during the same period as the cases. Thus, cases and controls were matched for geographic area by the sampling procedure. Eligibility for the control group was based on date of birth in the identical range to that of the cases. Once a household was reached, the interviewer asked if a woman born between 1 January 1929 and 31 December 1957 resided there. Women who had undergone hysterectomy were excluded as controls.

#### 3. Statistical analysis

The data were analyzed using SPSS for Windows (SPSS Inc., Chicago, IL). The association between case and control status and demographic and clinical parameters was assessed using w<sup>2</sup> for categorical variables and *t*-test for continuous variables. Variables found to have a statistically significant association with endometrial cancer on univariate analysis were entered into a stepwise logistic regression model, which controlled for age. The criterion for entry for the model was P = 0.05 and for removal from the model was P = 0.10. Ninety-five percent confidence interval for adjusted odds ratios for the logistic model were calculated using computer programs for epidemiological analysis PEPI version 2.06.<sup>1</sup>

The study protocol was submitted and approved by the institutional review board of Hadassah Medical Organization and the Ministry of Health. For legal reasons, women located via the Cancer Registry could not be contacted directly. Rather, their physicians were contacted and consent to interview the patient was obtained through them. Verbal consent was obtained from both cases and controls.

#### 4. Results

Before and during the study period, 21.6% of women with endometrial cancer reported to the Cancer Registry between the above dates had died. Of the 325 living women who could be included, we interviewed 128 (39.1%). The others were not interviewed because of inability to locate the patient or physician (69.3%), illness (5.0%), refusal of the physician (4.0%) or refusal by the patient (21.6%). Cases alive at the time of interview that were not interviewed, were compared with cases who participated and cases who were interviewed. There were no significant differences in age, area of residence, or histology. The distribution of cases and controls according to demographic and clinical characteristics is presented in Table 1. Cases tended to have a history of hypertension (24.8% versus 13.7%), and to be more obese (BMI greater or equal to 27). The study group had a mean BMI of 29.01 whereas the mean BMI was 25.93 in controls (P = 0.0001). Family

<sup>&</sup>lt;sup>1</sup> Galinger PM, Abramson JV. Copyright 1993–1997, USD Inc., Stone Mountain, Georgia.

history of endometrial cancer, a history of diabetes, and smoking were not different between the two groups. Obstetric and gynecologic characteristics, which were significantly different between controls and cases, were: a history of infertility (25.8% versus 16.5, P = 0.05), nulliparity (14.8% versus 5.1% P = 0.005), with no significant difference found for months of breast-feeding.

In our study, 19/128 (14.8%) of the cases and 121/256 (47.5%) of the controls were ever users of IUD. We found a significant negative association between IUD use and endometrial carcinoma. A similar negative association was demonstrated for oral contraceptive use, P = 0.00001 for both, Table 2.

Variables found to have statistically significant association with endometrial cancer on univariate analysis were entered into a stepwise logistic regression model, which controlled for age. According to the model, factors found to be significantly more prevalent in cases were; Obesity (BMI  $\ge 27$ ) with an adjusted OR = 2.47; infertility OR = 1.82; and nulliparity OR = 2.58.

Use of IUD and oral contraceptives were found to be protective (adjusted OR = 0.37 and 0.29, respectively).

#### 5. Discussion

The results of our study suggest that IUD use significantly reduces the risk of endometrial cancer. After controlling for confounding factors such as: age, nulliparity, family history of endometrial cancer and other factors, ever users of IUD had an OR of 0.37 (95% CI 0.19–0.70, P = 0.003) to develop endometrial cancer as compared to non-users of IUD.

Our results are in agreement with those of the few papers published on this subject.

Castellsague et al. [11], reported the data from a large, multicenter, population-based, case-control study of epithelial endometrial cancer. The study included 437 cases and 3200 randomly selected controls. The adjusted OR for the association of ever users of IUD and endometrial cancer was 0.51 (95% CI 0.3–0.8).

### Table 1 Selected sociodemographic and clinical characteristics of cases and controls

\* \* \*

Parazzini et al. [12], reported similar results from a case-control study conducted in Italy between 1983 and 1992. Their study included 453 cases with histologically confirmed endometrial cancer and 1451 controls. When compared to never users, ever users of IUD had a relative risk of 0.4 (95% CI 0.1–1.0).

Sturgeon et al. [13], examined the relation between use of IUD and endometrial cancer risk using data from a multicenter casecontrol study comprising 405 endometrial cancer cases and 297 controls. IUD use was associated with a decreased risk of endometrial cancer (OR = 0.56 for ever use; 95% CI 0.3–1.0).

### Table 2 IUD and oral contraceptives use of cases and controls \* \* \*

Hill et al. [14], reported similar results from a population-based case-control study. The study included women aged 45–74 from three counties in Washington State. They have found a risk of 0.61 (95% CI 0.41–0.89) of endometrial cancer in ever users of IUD as compared to a control group. The reduction in cancer risk was not found to be dependent on duration of IUD use. The relative risk among a small number of current users was 0.49 (95% CI 0.12–2.80).

However, data collected from seven countries [15], for a multinational case-control study, with 226 cases of endometrial cancer compared with 1529 matched controls, found no significant association between use of an IUD and risk of endometrial cancer (OR = 0.74, 95% CI 0.4–1.33). There were no trends in risk with respect to duration of use, time since first use, or ages at first or last use.

Theoretically IUD use may decrease endometrial cancer risk through at least two mechanisms: first the protective effect of IUD may be through the intense inflammatory response that leads to other lisosomal and inflammatory actions which may include recruitment of cells responsible for early elimination of abnormal, precancerous, hyperplasia endometrial epithelial cells. Another theoretical mode of action may be that the more complete shedding of the endometrium, and the changes in endometrial environment and endometrial response to hormones associated with IUD use may decrease hyperplasia of the endometrium, a known risk factor for endometrial carcinoma.

Our study had a number of limitations. One of the main limitations was that the study was not primarily designed to examine such an association. Furthermore, mainly for technical reasons, we were not able to interview the majority of cases who were still alive. This may have introduced considerable bias since non-interviewed cases, as well as those who had died prior to interview may have differed substantially from interviewed cases. We had no access to the medical records of subjects, thus we could not verify the information about IUD use that was obtained from the study participants, and under-reporting cannot be excluded. The potential for non-response bias is present due to the low response, which raises doubts for whether the study group is representative. However, a comparison between cases and those who did not participate in the study shows that the age, area of residency and histology in the two groups were not different.

Cases were at least 3 years and up to 7 years older than controls at time of interview, which might explain difference in contraceptive history, as well as recall of other exposures.

In conclusion, the scanty available epidemiological data, including ours, is reassuring and points toward a protective effect of IUD use on endometrial cancer risk. However, the existing data is based on case-control studies, which were not designed to address such an association. Thus, the results should be interpreted carefully. Larger especially designed studies are warranted, as the use of IUD is increasing.

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#### References

- [1] Alvarez F, Brache V, Fernandez E, et al. New insights on the mode of action of intrauterine contraceptive devices in women. Fertil Steril 1988;49:768–73.
- [2] Ortiz ME, Croxatto HB. The mode of action of IUDs. Contraception 1987;36:37–53.
- [3] Tursi A, Mastrorilli A, Ribatti D, Loiudice L, Contino R, Claudatus L. Possible role of mast cells in the mechanism of action of intra-uterine contraceptive devices. Am J Obstet Gynecol 1984;148:1064–6.
- [4] El-Badrawi HH, Haffez ESE, Barnhart NI, Fayad M, Shafeek A. Ultrastructural changes in the human endometrium with copper and non-medicated IUDs in utero. Fertil Steril 1981;36:41–9.
- [5] Gonzalez-Angulo A, Aznar-Ramos R, Feria-Valesco F. Ultrastructural changes found in endometrium of women using Lippes intrauterine devices. J Reprod Med 1973;10:44–51.
- [6] Umapathysivam K, Jones WR. Effects of contraceptive agents on the biochemical and protein composition of human endometrium. Contraception 1980;22:425–40.
- [7] Kontula K, Janne O, Luukkainen T, Vihko R. Progesterone binding protein in human myometrium, influence of metal ions on binding. J Clin Endocrinol Metab 1974;38:500–3.
- [8] Tamaya T, Nakata Y, Ohno Y, Nioka S, Furuta N, Okada H. The mechanism of action of copper intra-uterine device. Fertil Steril 1976;27:767–72.
- [9] Benshushan A, Paltiel O, Brzezinski A, Tanos V, Barchana A, Shoshani O, et al. Ovulation induction and risk of endometrial cancer: a pilot study. Eur J Obstet Gynecol Reprod Biol 2001;98:53–7.

- [10] Hartge P, Brinton LA, Rosenthal JF, Cahil JI, Hoover RN, Waksberg J. Random digit dialing in selecting a population-based control group. Am J Epidemiol 1984;120:825–33.
- [11] Castellsague X, Thompson D, Dubrow R. Intra-uterine device use and the risk of endometrial cancer. Int J Cancer 1993;54:911–6.
- [12] Parazzini F, La Vecchia C, Moroni S. Intrauterine device use and the risk of endometrial cancer. Br J Cancer 1994;70:672–3.
- [13] Sturgeon SR, Brinton LA, Berman ML, et al. Intrauterine device use and endometrial cancer risk. Int J Epidemiol 1997;26:496–500.
- [14] Hill Da, Weiss NS, Voigt LF, Beresford SA. Endometrial cancer in relation to intra-uterine device use. Int J Cancer 1997;70:278–81.
- [15] Rosenblatt KA, Thomas DB. Intrauterine devices and endometrial cancer. The WHO collaborative study of neoplasia and steroid contraceptives. Contraception 1996;54:329–32.

#### **APPENDIX U**

#### EUROPEAN JOURAN OF OBSTETRICS & GYNECOLOGY AND REPRODUCTIVE BIOLOGY 105 (2002) 166-169

#### ENDOMETRIAL CANCER IN RELATION TO INTRA-UTERINE DEVICE USE

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Data from a population-based case-control study were used to evaluate the risk of endometrial cancer among women who have used an intra-uterine device (IUD). Incident cases were identified between 1985 and 1991 among women aged 45-74 years who were residents of one of 3 counties in Washington State. Controls were selected by random digit dialing, and both groups of subjects received an in-person detailed interview. In this study population, women who had ever used an IUD were

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estimated to have a risk of endome-trial cancer that was 0.61 times that of other women (95% CI 0.41-0.89). The reduction in cancer risk was not found to be dependent on duration of IUD use. There was a suggestion that women who had used intra-uterine contraception relatively late in reproductive life experienced a greater reduction in risk than those whose use was more distant or at a younger age. The relative risk among the small number of women who were currently using an IUD was 0.49 (95% CI 0.12-2.80). These results apply to the use of inert and copper IUDs as there was no use of progestinreleasing IUDs among women in the study population. The data from this and several other studies of the question support the hypothesis that use of an IUD has a favorable effect on the subsequent risk of endometrial cancer. The reason(s) for such a reduced risk is unclear. Int. J. Cancer, 70:278-281, 1997.

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To date, 4 studies have examined the possibility that use of an intra-uterine device (IUD) alters a woman's subsequent risk of endometrial cancer. Two have observed that women who had ever used an IUD had half or less the risk of endometrial cancer as never-users (Castellsagué *et al.*, 1993; Parazzini *et al.*, 1994), while in a third, risk among users was 0.7 that of non-users (Rosenblatt *et al.*, 1994). However, the 4th study found that IUD users and non-users had a similar incidence (Shu *et al.*, 1991).

The presence of an IUD is known to alter the intra-uterine environment. The IUD evokes a number of immunological and biochemical changes, including localized acute and chronic inflammation (Moyer and Mishell, 1971) and increases in cytokine expression (Ammala *et al.*, 1995). IUDs also have been associated with elevations in uterine prostaglandins (Toppozada, 1985) and fibrinolytic activity (Liedholm *et al.*, 1983). IUDs induce morphological changes such as ulceration and erosion of surface epithelium and exposure of the underlying basement membrane (Shaw and Macaulay, 1979). It is not clear whether these or other responses to the presence of an IUD ought to alter the risk of endometrial cancer development after the device has been removed.

Although use has declined in the United States in recent years, an IUD is used by over 93 million women internationally (Shah, 1994), so the question of a relation to endometrial cancer is an important one. Furthermore, understanding the relationship between IUD use and development of endometrial cancer, if one exists, may suggest mechanisms by which endometrial cancer may be prevented.

Previous studies of endometrial cancer have included relatively few women who had used IUDs and, therefore, have not been able to examine specific patterns of use. As part of several case-control studies investigating endometrial cancer risk in western Washington, we were able to evaluate the association further.

#### **SUBJECTS AND METHODS**

The Cancer Surveillance System, a population-based cancer registry, identified women newly diagnosed with epithelial endometrial cancer in western Washington during the study period. Cases diagnosed during 1985 and 1986 were included in the study if they were residents of King County and 45–64 years of age. Women residing in King, Pierce and Snohomish counties were eligible if they were diagnosed during 1987–1990 and were 45–74 years of age or diagnosed during 1991 and 45–69 years of age.

Of the 1,254 identified cases, 100 were deemed ineligible: 72 women had a non-epithelial or *in situ* tumor, and the other 28 were excluded because they either were unable to communicate in English, were not residing in a household in the 3 county region or did not have a telephone when they were diagnosed. Of the remaining 1,154 eligible cases, 100 died before interview, 222 were not interviewed because of physician or subject refusal and one interview was lost. A total of 832 cases (72%) are included in this analysis.

Controls were identified using random digit dialing (Waksberg, 1978) and were broadly matched to cases by county of residence and by 5 year age group. Random digit dialing calls to identify controls were initiated to 52,045 numbers, of which 26,405 were found to be non-residential. Residential status could not be determined for an additional 2,113. Among the 23,527 identified households, in all but 877 it could be ascertained whether an eligible woman was a household member. Of the 2,619 women found to be eligible for the study, interviews were conducted with 1,975 (75.4%). Included in this analysis are the 1,114 controls who did not have a prior hysterectomy or prior endometrial cancer. Each control was assigned a reference date, analogous to the date of diagnosis of the cases, and all interviews collected data on the experiences of cases and controls prior to the reference date. Control reference dates were approximately matched to those of cases on year of diagnosis, and within that year reference months were assigned randomly.

All study subjects were interviewed in person by trained interviewers, except that 3% of cases and 5% of controls were interviewed over the telephone. Reproductive and medical histories were collected as well as routine demographic data. A detailed contraceptive history was obtained using calendars to aid recall and photographs of common IUDs, as well as contraceptive and noncontraceptive hormones. Subjects interviewed by telephone received photographs by mail prior to interview.

Information on IUD use available for analysis included type of device used, duration of use, age at first and last use and years since first and last use. Variables evaluated for potential confounding included demographic variables, such as age, ethnicity, county of residence, income and education, as well as factors known or suspected to be related to

endometrial cancer, such as oral contraceptive use; use of estrogen alone or combined with a progestin; smoking; number of births; incomplete pregnancies; age at menarche; weight, height and body mass index; history of diabetes, hypertension or infertility and treatment for any of these conditions; and family history of endometrial or breast cancer. We also evaluated potential confounding by factors known or suspected to be related to IUD use: amenorrhea, endometriosis, fibroids, ectopic pregnancy, age at last fullterm pregnancy, history of pelvic inflammatory disease or of other sexually transmitted diseases, number of sexual partners and use of other methods of birth control. Unconditional logistic regression was used to compute odds ratios (ORs) and associated 95% confidence intervals (CIs) for the relationship between IUD use and endometrial cancer and to evaluate possible confounding or modification of this relationship by other factors.

All analyses were adjusted only for variables that were found to alter the OR estimate: age (45-54, 55-64, 65-74), number of births (0, 1 vs. 2+) and use of unopposed estrogen for 3 or more years (yes, no).

#### RESULTS

Cases were somewhat older than controls and were more likely to be nulliparous or to have had only one birth, to have a higher body mass index and to have used unopposed estrogen for 3 or more years (Table I). A higher proportion of controls than cases reported having taken oral contraceptives. Cases and controls were broadly similar according to ethnicity, income and education.

A history of use of an IUD was reported by 5.2% of cases (n = 43) and 10.6% of controls (n = 118). Compared with nonusers, women who had ever used an IUD had a reduced risk of endometrial cancer (OR 0.61, 95% CI 0.41–0.89) (Table II). Few women (2 cases, 7 controls) reported that they currently used an IUD (*i.e.*, within 1 year of reference date), and their cancer risk was 0.49 (95% CI 0.12–2.80) that

of never-users. Although the relative risk did not vary substantially when evaluated among separate groups of women with and without other risk factors for endometrial cancer, estimates were imprecise because of small stratum sizes.

The length and timing of exposure to IUDs and age at first and last use were examined to ascertain any differential association with endometrial cancer risk. The duration of IUD exposure, once a woman became a user, was not associated with risk (Table II). There was a suggestion that use relatively late in reproductive life might be related to a reduced incidence of endometrial cancer.

# Table ICharacteristics of Endometrial Cancer Cases and<br/>Control Women

\* \* \*

We examined whether the type of intra-uterine contraception was related to development of endometrial cancer. The most frequently reported IUD was the Lippes loop (57.8%) (Table III). The reduction in risk seen among ever-users was not limited to a particular IUD. However, the total number of women who used some types was very small, and no women reported use of a progestin-releasing device. Among women who had used a Lippes loop, risk did not vary by duration of use.

#### DISCUSSION

Compared with women who had never used an IUD, the risk of endometrial cancer was more than one-third lower among those who had ever done so. The reduction in cancer risk was not dependent on duration of exposure and was only slightly influenced by use that was more recent or ended at a later age. Most women had ceased IUD use over 10 years prior to the reference date. Thus, the reduced risk was unlikely to be due to screening for precursor lesions (such as endometrial hyperplasia) that might take place among

women being considered for an IUD, the presence of which might prevent women from becoming IUD users (Weiss and Rossing, 1996).

## Table IIUse of An Intrauterine Device (IUD) Among Endometrial<br/>Cancer Cases and Control Women

\* \* \*

#### Table III

#### Intrauterine Device (IUD) Use Among Endometrial Cancer Cases and Control Women According to Type of Device

\* \* \*

Our observations that neither duration of use, time since first or last use or age at first or last use was appreciably related to risk among IUD users are consistent with those of previous studies (Castellsagué *et al.*, 1993; Rosenblatt *et al.*, 1994). The lower risk associated with IUD use was most apparent among women who were current users in one investigation (OR 0.10, 95% CI 0.01–0.78) (Rosenblatt *et al.*, 1994), but there were too few current users in our study to determine whether they had a notably decreased risk.

A number of potential biases should be considered in the interpretation of the results. The study included about 72% of eligible cases and 75% of eligible controls, and any differences in IUD use between participants and non-participants could result in biased estimates of risk. Differential recall between cases and controls is unlikely to have influenced our data. It is unlikely that cases or controls were aware of a potential association between IUD use and endometrial cancer at the time of the interview. We believe that women are likely to remember IUD use when interviewed as a physician visit is required for insertion and removal. Of potential concern is the fact that 16% of IUD users (n 5 26) did not recall the type of device. However, the

reduction in risk associated with use was not confined to a particular device.

Women who have practiced intra-uterine contraception may differ from women who have chosen other methods by their medical history or other factors that are related to endometrial cancer risk. Currently, IUDs are contra-indicated for women who have a history of pelvic inflammatory disease (PID) or ectopic pregnancy or who have recent unresolved conditions such as bleeding, infection or an abnormal Pap smear (Tatum and Connell, 1989). However, most women in our study used IUDs prior to the wide application of these restrictions. Inclusion in the analysis of variables indicating a history of PID or ectopic pregnancy did not alter the OR estimate. Data were not available on the remaining conditions. Compared to other women, those who have experienced conditions such as amenorrhea, uterine fibroids or infertility might have been less often given an IUD or might have less often tolerated it. Adjustment in the analysis for a history of fibroids further reduced the OR estimate slightly, while inclusion of amenorrhea or a history of infertility did not alter the risk estimate. Some residual confounding could be present due to lack of data on conditions, such as oligomenorrhea or anovulatory bleeding, that are possibly related to IUD use and to imprecise measurement of others, such as infertility, which required a physician visit to be included in the analysis. However, these conditions are at most only weakly related to endometrial cancer and could not completely account for our results. In summary, the characteristics of women who use IUDs do not appear to explain the lowered risk of endometrial cancer associated with IUD use in our data.

The presence of an IUD induces numerous physiologic changes that could alter risk of endometrial cancer. The IUD evokes a "foreign body" immune response in the endometrium, characterized by localized inflammation and increased concentrations of neutrophils, macrophages and

plasma cells (Moyer and Mishell, 1971) and increased expression of the cytokines interleukin 1 and tumor necrosis factor a (Ammala et al., 1995). Although the acute inflammation generally subsides, tissue concentrations of lymphocytes and macrophages remain elevated 2 years or more after beginning use (Moyer and Mishell, 1971). The sustained contact of an IUD with the endometrium is associated with minor tissue trauma, including ulceration, erosion and necrosis of the superficial layer of the epithelium and exposure of the underlying basement membrane or stroma (Shaw and Macaulay, 1979). Women using IUDs have been reported to experience heavier menses than they did prior to IUD insertion (Guillebaud et al., 1976). Among IUD users, increased fibrinolytic activity in endometrial biopsy tissue (Liedholm et al., 1983) or increased uterine fluid prostaglandin levels (Toppozada, 1985) have been found in comparison with control or baseline values and may be associated with the increased bleeding. Conceivably, some or all of the above could contribute to a reduction in endometrial cancer risk. However, the persistence of most of these changes after IUD removal has not been investigated.

Hormonal changes occur in the endometrial environment after IUD insertion, though their relevance to endometrial cancer incidence is uncertain. In animal studies, uterine concentrations of estrogen or progesterone receptors were lower among rats provided with suture-type IUDs than in control animals (Myatt *et al.*, 1980*a,b*). Estrogen uptake in the uterus was found to be increased but progesterone uptake unchanged among rats provided with copper IUDs, while no variation was found in association with inert devices (Aedo and Zipper, 1973). Few studies have examined hormonal changes in women in relation to IUD use. Among women using high-load copper IUDs, endometrial progesterone receptor concentrations were lower after 1 year than baseline levels, but there was no difference among other copper IUD users (De Castro and Gonzalez-Gancedo, 1986). Hormone

receptor concentrations were found to be similar among users and non-users of copper devices in another study (Punnonen et al., 1984). After 1 year of IUD use, endometrial biopsy did not reveal changes in estradiol or progesterone concentrations among users of inert IUDs compared with pre-insertion levels, but progesterone was decreased and estradiol increased in women provided with a copper IUD (Hagen-feldt and Landgren, 1975). Serum hormone levels have not been observed to differ between IUD users and nonusers (Nygren and Johansson, 1973), suggesting that the IUD does not exert an influence on ovarian hormone production. The persistence of hormonal changes, if any, after IUD removal has not been determined.

Our results provide evidence consistent with those of others that there is a reduced risk of endometrial cancer among women who have used an IUD. The reduced risk persists for many years after use is discontinued and is not restricted to one or a few types of IUDs, though the biologic basis for it remains unclear.

#### ACKNOWLEDGEMENTS

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#### REFERENCES

AEDO, A.R. and ZIPPER, J., Effect of copper intrauterine devices (IUDs) on estrogen and progesterone uptake by the rat uterus. *Fertil. Steril.*, **24**, 345–348 (1973).

AMMALA, M., NYMAN, T., STRENGELL, M. and RUTANEN, E.-M., Effect of intrauterine contraceptive

devices on cytokine messenger ribonucleic acid expression in the human endometrium. *Fertil. Steril.*, **63**, 773–778 (1995).

CASTELLSAGUE', X., THOMPSON, W.D. and DUBROW, R., Intra-uterine contraception and the risk of endometrial cancer. *Int. J. Cancer*, **54**, 911–916 (1993).

DE CASTRO, A. and GONZALEZ-GANCEDO, P., The effect of copper ions *in vivo* on specific hormonal endometrial receptors. *Adv. Contracept.*, **2**, 399–404 (1986).

GUILLEBAUD, J., BONNAR, J., MOREHEAD, J. and MATTHEWS, A., Menstrual blood-loss with intrauterine devices. *Lancet*, **1**, 387–390 (1976).

HAGENFELDT, K. and LANDGREN, B.M., Local effects of medicated IUDs. *In:* F. Hefnawi and S.J. Segal (eds), *Analysis of intrauterine contraception*, pp. 349–354, North Holland/American Elsevier, Amsterdam (1975).

LIEDHOLM, P., SRIVASTAVA, K., WINGERUP, L. and ASTEDT, B., Higher fibrinolytic activity in human endometrium in direct contact with an IUD. *Acta Obstet. Gynecol. Scand.*, **62**, 169–170 (1983).

MOYER, D.L. and MISHELL, D.R., Reactions of human endometrium to the intrauterine foreign body. II. Long-term effects on the endometrial histology and cytology. *Amer. J. Obstet. Gynecol.*, **111**, 66–80 (1971).

MYATT, L., CHAUDHURI, G., ELDER, M.G. and LIM, L., Effect of an intra-uterine device on intracellular relationships of the uterine oestrogen receptor, particularly during pregnancy. *J. Endocrinol.*, **87**, 357–364 (1980*a*).

MYATT, L., ELDER, M.G. and LIM, L., Alterations in progesterone receptors in the rat uterus bearing an intrauterine device during the oestrous cycle and early pregnancy. *J. Endocrinol.*, **87**, 365–373 (1980*b*).

NYGREN, K.-G. and JOHANSSON, E.D., Premature onset of menstrual bleeding during ovulatory cycles in

women with an intrauterine contraceptive device. Amer. J. Obstet. Gynecol., **117**, 971–975 (1973).

PARAZZINI, F., LA VECCHIA, C. and MORONI, S., Intrauterine device use and risk of endometrial cancer. *Brit. J. Cancer*, **70**, 672–673 (1994).

PUNNONEN, R., PETTERSSON, K. and VANHARANTA, R., Androgen, estrogen and progestin cytosol receptor concentrations in the normal human endometrium. *Gynecol. Obstet. Invest.*, **17**, 73–77 (1984).

ROSENBLATT, K.A., THOMAS, D.B. and THE WHO COLLABORATIVE STUDY OF NEOPLASIA AND STEROID CONTRACEPTIVES, Intrauterine device use and endometrial cancer [Abstract]. *Amer. J. Epidemiol.*, **139** (Suppl.), S36 (1994).

SHAH, I.H., The advance of the contraceptive revolution. *World Health Statist. Quart.*, **47**, 9–15 (1994).

SHAW, S.T. and MACAULAY, L.K., Morphologic studies on IUD-induced metrorrhagia. II. Surface changes of the endometrium and microscopic localization of bleeding sites. *Contraception*, **19**, 63–81 (1979).

SHU, X., BRINTON, L.A., ZHENG, W., GAO, Y.T. and FRAUMENI, J.F., A population-based case-control study of endometrial cancer in Shanghai, China. *Int. J. Cancer*, **49**, 38–43 (1991).

TATUM, H.J. and CONNELL, E.B., Intrauterine contraceptive devices. *In:* M. Filshie and J. Guillebaud (eds), *Contraception: science and practice*, pp. 160–161, Butterworths, London (1989).

TOPPOZADA, M., Prostaglandins and their inhibitors in IUD-induced bleeding. *In:* G.I. Zatuchni, A. Goldsmith and J.J. Sciarra (eds), *Intrauterine contraception: advances and future prospects*, pp. 319–334, Harper and Row, Philadelphia (1985).

WAKSBERG, J., Sampling methods for random digit dialing. J. Amer. Statist. Assoc., 73, 40–46 (1978).

WEISS, N. and ROSSING, M., Healthy screening bias in epidemiologic studies of cancer incidence. *Epidemiology*, **7**, 319–322 (1996).

#### **APPENDIX V**

#### **INTERNATIONAL JOURNAL OF EPIDEMIOLOGY**

#### INTRAUTERINE DEVICE USE AND ENDOMETRIAL CANCER RISK

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*Background.* Because intrauterine devices (IUD) invoke acute and chronic inflammatory responses in the endometrium, it is possible that prolonged insertion of an IUD could induce endometrial cancer.

*Methods.* We examined the relation between use of an IUD and endometrial cancer risk using data from a multicentre case-control study involving 405 endometrial cancer cases and 297 population controls.

*Results.* A total of 20 (4.9%) cases and 34 (11.4%) controls reported any use of an IUD. After adjustment for potential confounders, IUD use was not associated with an increased risk of endometrial cancer (RR = 0.56 for ever use; 95% CI : 0.3-1.0). Little reduction in risk was observed among women who last used an IUD within 10 years of the index date (RR = 0.84; 95% CI : 0.3-2.4) but risk was decreased among women who used an IUD in the more

distant past (RR = 0.45; 95% CI : 0.2-1.0). Risk did not vary

consistently with number of years of IUD use or with years since first use. Risk was not increased among women who used inert devices (RR = 0.46; 95% CI : 0.3-3.6) or those who used devices containing copper (RR = 1.08; 95% CI : 0.1-3.6).

*Conclusion.* These data are reassuring in that they do not provide any evidence of an increased risk of endometrial cancer among women who have used IUD.

*Keywords:* intrauterine device (IUD), endometrial cancer, contraception, epidemiology

Because intrauterine devices (IUD) invoke acute and chronic inflammatory responses in the endometrium, it is possible that prolonged insertion of an IUD could induce endometrial cancer.<sup>1</sup> IUD containing copper may be particularly suspect because they tend to produce more serious endometrial irritation than inert devices.<sup>2</sup> IUD could also theoretically increase endometrial cancer risk because they alter uterine sensitivity to oestrogen and progesterone.<sup>3</sup>

Although IUD are used by an estimated 85 million women worldwide,<sup>4</sup> only four small studies have examined the relation between their use and the occurrence of endometrial cancer <sup>5-8</sup> and none were able to examine risks associated with specific types of IUD. Thus, we used data from a large multicentre case-control study in the US to evaluate further the relation between IUD use and endometrial cancer.

#### METHODS

This case-control study was a collaborative effort with seven participating hospitals in five areas of the US— Chicago, Illinois; Hershey, Pennsylvania; Irvine and Long Beach, California; Minneapolis, Minnesota; and Winston-Salem, North Carolina. A total of 498 women between the ages of 20 and 74 years with newly diagnosed endometrial cancer were identified between 1 June 1987 and 15 May 1990. Detailed information on the selection of cases and
controls and other study methods are presented elsewhere.<sup>9</sup> Briefly, random digit dialling techniques were used to select controls for cases younger than age 65 whereas older controls were selected using information provided by the Health Care Financing Administration. We attempted to select one control for each case, matched for age (5-year age groups), race, and location of residence at diagnosis (telephone exchange or zip code).

Random digit dialling controls were selected by identifying a residential cluster matched for the telephone exchange for each eligible case. Telephone numbers were called, and an enumeration of female members aged 20-64 in each household was attempted. Of 15 820 telephone numbers sampled, 10 184 were assessed to be residential working numbers, and an enumeration of female members was obtained for 85%. Older controls were derived from Health Care Financing Administration computer records a subject of the same age, race and zip code as each eligible case. After the initial selection of subjects, a short telephone questionnaire was administered to determine whether the subjects had intact uteri. A total of 125 of the initially selected random digit dialling controls and 88 of the Health Care Financing Administration controls were eliminated because of their not being at risk of developing endometrial cancer. These subjects were replaced with other eligible controls so that there was an eventual accrual of 304 controls through random digit dialling techniques and 173 through Health Care Financing Administration records.

Trained interviewers completed home interviews on 434 (87%) of the eligible cases and 313 (66%) of the eligible controls. Eligible subjects who could not be interviewed were not replaced. Reasons for non response included refusal (5% of the cases and 22% of the controls), communication problems (4% versus 3%) and other problems (2.2% versus 9%). In addition, physician consent was not obtained for 2.0% of the cases. The response rate

was considerably higher for the random digit dialling than the Health Care Financing Administration controls (76% vs 47%).

Pathology reports were obtained and reviewed for all cases, with 93% of the interviewed cases having a classification of epithelial cancer. Because of the distinct epidemiological characteristics of sarcomas,<sup>10</sup> this analysis focused on data from interviews with 405 epithelial cancer cases and their 297 matched controls. The mean ages of the cases and controls were 59.2 (standard deviation [SD] = 9.96) and 58.0 years (SD = 10.4), respectively.

A structured interview, on average 76 minutes in length, was administered to obtain information on hypothesized risk factors. including demographics. pregnancy history, menstrual history, contraceptive behaviour, use of exogenous hormones, changes in body weight, diet and alcohol intake, family history of cancer, medical events and physical activity. The dietary section consisted of 60 food items and provided an estimate of usual adult caloric intake and intake of specific nutrients.<sup>11</sup> Anthropometric measurements, including waist-to-thigh circumference ratio as a measure of intra-abdominal fat,<sup>12</sup> were also taken at the time of interview. Information on birth control usage was obtained using lifetime calendars to record usage of specific methods on a monthly basis. For each mention of IUD use, information on brand was elicited. No subjects reported using progestagen containing IUD.

Because of the large number of cases without an interviewed matched control, adjusted maximum likelihood relative risk estimates (RR) and 95% confidence intervals (CI) are presented using unconditional logistic regression techniques.<sup>13</sup> The main results of the study were confirmed using conditional logistic regression on the smaller subset of 274 matched pairs of cases and controls.

Risk factors identified in this study, adjusted for each other, included education (RR = 2.0 for  $\ge 16$  versus < 12 years), age

at menarche (RR = 2.8 for <12 versus  $\geq$ 15 years), menopausal oestrogen use (RR = 15.3 for  $\geq$ 10 versus 0 years), diabetes (RR = 1.6), saturated fat intake (RR = 2.0 for highest versus lowest quartile), current body mass index (weight in kg/height in m<sup>2</sup>) (RR = 3.2 for  $\geq$ 32 versus <25) and waist to thigh circumference (RR = 2.7 for highest versus lowest quartile). Factors associated with reductions in risk included multiple livebirths (RR = 0.2 for  $\geq$ 5 versus 0 births), cigarette smoking (RR = 0.3 for current versus never smokers), and oral contraceptive use (RR = 0.4 for versus 0 years). Menopausal status and age at natural menopause were unrelated to risk.<sup>9</sup>

#### RESULTS

Table 1 presents the prevalence of risk factors among controls who never used any method of birth control, those who ever used an IUD and those who only used other forms of birth control. Compared to women who had never used any method of birth control, women who had used an IUD were younger, better educated and had a higher intake of saturated fat. Women who had used an IUD also had a lower waist to thigh circumference ratio, and were less likely to smoke and to be nulliparous. Differences tended to be less striking between women who had ever used an IUD and those who had only used other forms of birth control. Compared to those who only used other forms of birth control, women who had used an IUD were younger, better educated, had a later age at menarche and a lower waist to thigh circumference ratio. A total of 27 (79.4%) of the 34 controls who had ever used an IUD also had taken oral contraceptives (data not shown).

A total of 20 cases (4.9%) and 34 controls (11.4%) reported any use of an IUD, resulting in an age-adjusted relative risk of 0.43 (95% CI : 0.2-0.8). Further adjustment for oral contraceptive use attenuated this reduction in risk (RR = 0.53, 95% CI : 0.3-1.0). After further controlling for the other potential confounders identified in Table 1 (education, intake of saturated fat, waist to thigh circumference ratio, number of livebirths, cigarette smoking, and age at menarche), risk remained modestly lowered among women who used an IUD (RR = 0.56; 95% CI : 0.3-1.0) (Table 2). In this fully-adjusted model, risk did not vary with increasing years of use and years since first IUD use was unrelated to risk of endometrial cancer. Risk did, however, appear to vary by years since last IUD use. Little reduction in risk was observed among women who last used an IUD within 10 years of the index date (RR = 0.84; 95% CI : 0.3-2.4) but risk was reduced among those who last used an IUD more than 10 years before (RR = 0.45; 95% CI : 0.2-1.0).

#### Table 1

#### **Characteristics of controls by their birth control practices**

## \* \* \*

# Table 2Risk of endometrial cancer associated with use of an<br/>intrauterine device

#### \* \* \*

IUD were also categorized into two groups for analysis based on the presence or absence of copper. Inert device use was associated with a reduction in risk (RR = 0.46; 95% CI : 0.1-3.6) whereas copper device use was unrelated to risk (RR = 1.08; 95% CI : 0.3-3.6). The small number of IUD users precluded further stratification to investigate the separate effects of years since last use and type of IUD device on risk.

Additional adjustment for diabetes, current body mass index, cigarette smoking, menopausal oestrogen use, use of barrier methods of contraception, spermicides, female sterilization, and vasectomy of a partner did not materially change the risk estimates presented in Table 2. Excluding 86 women who had never used any form of birth control from the referent category also did not alter the results. Women who had used an IUD remained at modestly reduced risk of endometrial cancer (RR = 0.67; 95% CI : 0.3-1.6) in a separate analysis that excluded 188 women who bad ever used oral contraceptives.

Because IUD were first commercially available in the US in 1964, few of the women 65 years and older in this study would have had an opportunity to use IUD. Results were similar when we restricted the above analyses to women younger than 65 years.

#### DISCUSSION

Three of four previous studies have observed a modest overall reduction in endometrial cancer risk among women who bad ever used an IUD." No evidence of a positive relation between IUD use and risk was found among women under age 55 in an analysis of data from the Cancer and Steroid Hormones (CASH) study (RR = 0.5 for ever use versus none; 95% CI : 0.3-0.8).<sup>5</sup> In the analysis of data from a case-control study in Italy,<sup>6</sup> the relative risk associated with ever use of an IUD was 0.4 (95% CI : 0.1-1.0). A study carried out in developing countries also reported no increased risk associated with use of an IUD (RR = 0.7 for ever use versus none; 95% CI : 0.4-1.3).<sup>7</sup> One conducted in Shanghai, China found no relationship between IUD use and endometrial cancer risk (RR = 1.1 for ever use; 95% CI : 0.5-2.5).<sup>8</sup>

With respect to type of IUD device, we did not find any evidence of an increased risk of endometrial cancer among women who used either inert devices or those who used devices containing copper.

Studies have been inconsistent with respect to their findings on the effects of years of IUD use and years since last IUD use on risk. In the present investigation, the reduction in risk associated with IUD use was apparent only among women whose use had ceased more than 10 years ago. In the CASH study conducted in the early 1980s,<sup>5</sup> however, risk did not vary by time elapsed since last IUD use. By contrast, Rosenblatt *et al.*<sup>7</sup> found that risk was

lowest among current users (RR = 0.1; 95% CI : 0.01-0.8). In accord with the study by Rosenblatt *et al.*<sup>7</sup> we found no evidence that risk decreased with increasing years of IUD use. Castellsague *et al.*<sup>5</sup> however, observed that risk decreased from 0.62 among women who used IUD for less than 4 years to 0.41 for those who used an IUD for more than 8 years. No details were available on the relation between risk and various exposure measures from the other two studies.<sup>6-8</sup>

It is unclear why relationships with years since last IUD use and years of IUD use have differed across studies. This inconsistency may reflect the difficulty in obtaining stable risk estimates from studies involving small numbers of IUD users. Another possible explanation relates to the fact that the materials and shapes of IUD devices have varied across populations and calendar time.<sup>5</sup> If certain IUD have more of an effect on endometrial cancer risk, studies conducted in different populations could observe disparate findings. Alternatively, the lack of consistency across studies may indicate that the modest reduction in risk associated with IUD use is the result of indication bias. Such bias could result if women at increased risk of developing endometrial cancer were less likely to be prescribed IUD (e.g. those with uterine bleeding from endometrial hyperplasia).

The major limitation of the present study is that the response rate was low among the population-based controls. If the controls who were IUD users were disproportionately more likely to be interviewed than cases, this could result in a spurious reduction in risk associated with IUD use. It is somewhat reassuring, however, that findings from this study with respect to generally accepted endometrial cancer risk factors, are similar to those presented in previous studies.<sup>14</sup>

#### REFERENCES

<sup>1</sup> Tindall V R. *Jeffcoate's Principles of Gynaecology*. Boston: Butterworths, 1987. <sup>2</sup> Sciarra J J, Zatuchni G I. Speidel J J. Workshop on Risks, Benefits and Controversies in Fertility Control. New York: Harper and Row, 1978.

<sup>3</sup> Tamaya T, Nakata Y, Ohno Y, Nioka S, Furuta N, Okada H. The mechanism of action of the copper intra-uterine device. *Fertil Steril* 1976; 27: 767-72.

<sup>4</sup> Hatcher R A, Guest F, Stewart *F et al. Contraceptive Technology* 1988-1989. New York: Irvington Publishers, 1988.

<sup>5</sup> Castellsague X, Thompson W D, Dubrow R. Intra-uterine contraception and the risk of endometrial cancer. *Int J Cancer* 1993; 54: 911-16.

<sup>6</sup> Parazzini F, La Vecchia C, Moroni S. Intrauterine device use and risk of endometrial cancer. *Br J Cancer* 1994; 70: 672-73.

<sup>7</sup> Rosenblatt K A, Thomas D B and the WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Intrauterine device use and endometrial cancer (Abstract). *Am J Epidemiol* 1994; 139: S36.

<sup>8</sup> Shu Xiao-Ou, Brinton L A, Zheng W, Gao Y T, Fan I, Fraumeni J F Jr. A population-based case-control study of endometrial cancer in Shanghai, China. *Int J Cancer* 1991; 49: 38-43.

<sup>9</sup> Brinton L A, Berman M L, Mortel It *et al.* Reproductive, menstrual and medical risk factors for endometrial cancer: results from a case-control study. *Am J Obstet Gynecol* 1992; 167: 1317-25.

<sup>19</sup> Schwartz S M, Thomas D B. The World Health Organization collaborative study of neoplasia and steroid contraception. *Cancer* 1989; 64: 2487-92.

<sup>II</sup> Potischman N, Swanson C A, Brinton L A *et al.* Dietary associations in a case-control study of endometrial cancer. *Cancer Causes and Control* 1993; 4: 239-50.

<sup>12</sup> Swanson C A, Potischman N, Wilbanks G D *et al.* Relation of endometrial cancer risk to past and contemporary body size and body fat distribution. *Cancer Epidemiology, Biomarkers and Prevention* 1993; 2: 321-27.

<sup>13</sup> Breslow N E and Day N *E. Statistical Methods in Cancer Research: The Analysis of Case-Control Studies.* IARC Pub. no. 32. Lyon, France: International Agency for Research on Cancer, 1980.

<sup>14</sup> Kelsey J L, Hildreth N G. *Breast and Gynecologic Cancer Epidemiology*. Boca Raton: CRC Press, 1982.

(Revised version received September 1996)

### APPENDIX W

#### INTRAUTERINE DEVICE USE AND RISK OF ENDOMETRIAL CANCER

F. Parazzini<sup>1,2</sup>. C. La Vecchia<sup>1,33</sup> & S. Moroni<sup>1,2</sup>

Summary The relationship between intrauterine device (IUD) use and risk of endometrial cancer has been analysed in a case-control study conducted in Italy between 1983 and 1992, including 453 patients with histologically confirmed endometrial cancer and 1.451 controls admitted for acute, non-gynaecological, non-hormonal, non-neoplastic conditions to the same network of hospitals where cases had been identified. Two (0.4%) cases versus 36 (2.3%) controls reported ever using a IUD. The corresponding multivariate relative risk was 0.4 (95% CI 0.1-1.0). The results of this study and the few published available epidemiological data suggest a protective role of IUD use on endometrial carcinogenesis, but potential selective mechanisms for IUD utilisation (indication bias) should be carefully considered in the interpretation.

Intrauterine device (IUD) use may induce endometrial alterations, such as inflammatory changes (Sheppard, 1987), loss of epithelial surface (El-Badrawi *et al.*, 1981) and reduction in ciliated cells (Gonzalez-Angulo *et al.*, 1973), which may affect the risk of neoplastic changes of the endometrium. In terms of biological inference, the risk of

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endometrial cancer might be either increased or decreased by such changes.

Epidemiological data on the relation between IUD use and risk of endometrial cancer are, however, scanty. A recent analysis of data from the Cancer and Steroid Hormones (CASH) Study suggested that the risk of endometrial cancer is approximately halved in women reporting ever IUD use, and the protective effect tended to increase with duration of use (Castellsague *et al.*, 1993). To offer further data on the issue. we report the results from a case—control study conducted in Northern Italy (Parazzini *et al.*, 1991a).

#### **Patients and methods**

The general design of this study has been previously described (Parazzini *et al.*, 1991a). Cases included in the study were 453 patients with histologically confirmed endometrial cancer aged <65 years (median age 56 years. range 28-64). They were admitted to the Ospedale Maggiore (including the four largest teaching and general hospitals in the greater Milan area). to the University Obstetrics and Gynecology Clinics and to the National Cancer Institute of Milan between 1983 and 1992. They were interviewed during their stay in hospital for surgery. medical treatment, radiotherapy: their diagnosis of endometrial cancer dated back no more than 1 year (median time from diagnosis to interview 2 months, range 0-12 months).

Controls were patients younger than 65 years admitted for acute, non-gynaecological, non-hormone-related, nonneoplastic conditions to the same network of hospitals where cases had been identified. Women who had undergone hysterectomy were not eligible as controls. A total of 1,541 controls (median age 53 years, range 27-64) was included in the present analyses. Of these, 32% were admitted for traumatic conditions (mostly fractures and sprains). 35% had non-traumatic orthopaedic disorders (mostly low back pain and disc disorders), 15% had surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia) and 18% had other illnesses, such as ear, nose and throat or dental disorders. Less than 3% of identified cases and controls refused to be interviewed.

Trained interviewers identified and questioned cases and controls using a standard questionnaire. Information was collected on general characteristics and habits. gynaecological and obstetric data, related medical history and use of oral contraceptives, intrauterine devices (IUD) and female hormones for other indications.

Odds ratios, as estimators of relative risks (**RR**) of endometrial cancer, together with their 95% confidence intervals (CI). according to use of IUD were computed from data stratified for quinquennia of age by the Mantel-Haenszel procedure (Mantel & Haenszel. 1959). In order to allow simultaneously for the effects of several potential confounding factors. unconditional multiple logistic regression. with maximum likelihood fitting. was used (Breslow & Day. 1980). Included in the regression equations were terms for age and selected factors significantly associated in this data set with the risk of endometrial cancer (parity. Quetelet's index and oestrogen replacement therapy use).

#### **Results**

The distribution of cases and controls according to age and selected covariates is presented in Table I. Cases were more frequently null-parae (**RR** age adjusted. parae versus null-parae. 0.6: 95% CI 0.4-0.9). of higher body mass index (age adjusted **RR**. kg m<sup>-2</sup>  $\geq$ 25 is <25. 2.0: 95% CI 1.7-2.4) and more often oestrogen replacement therapy users (**RR** ever versus never 2.0. 95% CI 1.3-3.1).

The relation between IUD use and endometrial cancer risk is considered in Table II. Out of the 453 endometrial cancer cases, two (0.4%) reported ever having used an IUD: the figures for controls were 36 ever users (2.3%) out of the 1.541 controls. The corresponding **RR** of endometrial cancer

was, in comparison with never users, 0.4 (95% CI 0.1-1.0) for ever IUD users. The data were insufficient for analysis of duration of use or other time-related factors.

#### Discussion

The results of this analysis further suggest that IUD use reduces the risk of endometrial cancer, but the interpretation deserves caution. In fact, indication bias may. at least partially. explain this inverse association. IUD may be less frequently prescribed in women with long, heavy menstrual flows or reporting pre-, post- or inter-menstrual blood spotting, conditions that may be associated with unopposed oestrogen endometrial stimulation and consequently increased endometrial cancer risk. Another potential limitation of this study is the low number of IUD users in Italy, which did not provide the opportunity to analyse the role of duration and any other time-related factors. In relation to other potential biases, cases and controls were identified in institutions covering broadly comparable catchment areas, and participation was almost complete. Likewise, recall bias is unlikely, since the interviewed cases and controls and the interviewers were unaware of the potential association between IUD use and endometrial cancer risk.

#### Table l

# Distribution of 453 endoetrial cancer cases and 1.541 controls according to selected characteristics. Milan, Italy, 1983-1992

\*\*\* We did not have information on type of IUD used, thus we cannot evaluate the role of different types of IUD, particularly progestin-releasing ones. Despite these considerations. some biological evidence, the consistency of our results with data from the CASH study (Castellsague *et al.*, 1993) and the magnitude of the association offer some support to the hypothesis that IUD use reduces the risk of endometrial cancer. The CASH study showed a decreased risk of endometrial cancer in IUD users of about 50%; in that study the risk tended to decrease with duration of use, offering some support to the hypothesis of a causal relationship, although the trend in risk with duration was not significant (Castellsague *et al.*, 1993).

In biological terms, laboratory and animal studies have suggested that IUD use may alter the response to steroids of the endometrium. These changes are mediated by the device itself as well as by the copper ions present in some devices. These alterations inhibit binding of oestrogen and progesterone to the endometrial cell receptors (Tamaya *et al.*, 1976) and decrease the steroid nuclear receptor concentration in the endometrial cells (Myatt *et al.*, 1980). These changes, however, may influence both oestrogen and progesterone activity, which have opposing effects on endometrial carcinogenesis (Paramini *et al.*, 1991b).

In conclusion, the few available epidemiological data suggest a protective effect of IUD use on endometrial cancer risk, but potential indication or selection bias is difficult to overcome in any epidemiological study on the issue, and should therefore be carefully considered in the interpretation.

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#### References

- BRESLOW. N.E. & DAY. N.E. (1980). *Statistical Methods in Cancer Research*, Vol. 1. *The Analysis of Case-control Studies*. IARC Scientific Publication No. 32. IARC: Lyon.
- CASTELLSAGUE, X.. THOMPSON, W.D. & DUBROW, R. (1993). Intrauterine contraception and the risk of endometrial cancer. *Int. J. Cancer*, **54**, 911-916.
- EL-BADRAWI, H.H.. HAFFEZ, E.S.E.. BARNHART. M.I., FAYAD, M. & SHAFFEK. A. (1981). Ultrastructural changes in the human endometrium with copper and non-mediated IUDs in utero. *Ferri!*. *Steril.*, **36**, 41 49.
- GONZALEZ-ANGULO. A., AZNAR-RAMOS. R. & FERIA-VELASCO. A. (1973). Ultrastructural changes found in endometrium of women using Lippes intrauterine device. *J. Reprod. Med.*, *10*, 44-51.
- MANTEL. N. & HAENSZEL. W. (1959). Statistical aspects of data from retrospective studies of disease. *J. Nat! Cancer Inst.*, **22**, 719 748.
- MYATT, L. ELDER. M.G. & LIM. L. (1980). Alterations in progesterone receptors in the rat uterus bearing an intrauterine device during the oestrous cycle and early pregnancy. *J. Endo-crinol.*, **87**, 365-373.
- PARAZZINI, F., LA VECCHIA. C.. NEGRI. E., FEDELE. L. & BALOTTA, F. (1991a). Reproductive factors and risk of endomet-rial cancer. *Am. J. Obstet. Gynecol.*, **164**, 522-527.
- PARAZZINI. F., LA VECCHIA. C., BOCCIOLONE. L. & FRANCESCHI. S. (1991b). The epidemiology of endometrial cancer. *Gynecol. Oncol.*, **41**, **1-16**.
- SHEPPARD. B.L. (1987). Endometrial morphological changes in IUD users: a review. *Contraception*, **36**, 1-10.
- TAMAYA, T., NAKATA, Y., OHNO. Y., NIOKA. S., FURUTA. N. & OKADA. H. (1976). The mechanism of

action of the copper intra-uterine device. *Fertil. Steril.*, **27**, 767-772.

#### **APPENDIX X**

#### INTERNATIONAL JOURNAL CANCER 54, 911-916 (1993)

#### Xavier CASTELLSAGUO<sup>1,4</sup>, W. Douglas THOMPSON<sup>2</sup> and Robert DufiRow<sup>3</sup>

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Despite the increasing world-wide popularity of contraceptive intra-uterine devices (IUDs), their potential long-term effects on the risk of developing endometrial carcinoma have been poorly studied. This paper reports on the relationship between intrauterine contraception and endometrial cancer by analyzing epidemiological data from a large, multicenter, populationbased, case-control study of epithelial endometrial cancer. Cases were 437 women, 20 to 54 years of age, with histologically confirmed epithelial endometrial cancer ascertained through 6 population-based cancer registries in the United States. Controls were 3200 women selected at random from the populations of these areas. The age- and parityadjusted odds ratio (OR) for the association between ever having used intra-uterine contraception and endometrial cancer was 0.51 (95% confidence interval (CI) 0.3-0.8). Although the protective effect increased with duration of use, a dose-response relationship among users was not statistically demonstrable. The association did not vary significantly with age at first or last IUD use or with time elapsed since first or last IUD use. Years of education significantly modified the effect of intra-uterine contraception. Thus, intra-uterine contraception appeared to be strongly protective for women with at least 13 years of education (OR = 0.29, 95% CI, 0.15-0.6). It is proposed that intra-uterine contraception exerts its protective effect through local structural and biochemical changes in the endome-trium that may alter endometrial sensitivity and response to circulating estrogen and progesterone.

In this century, 3 major events in the field of contraception have occurred: the introduction of intrauterine contraception, the formulation of oral contraceptives, and the development of laparoscopic tubal sterilization. In contrast to oral contraceptives, the potential effects of intra-uterine contraception and tubal sterilization on the risk of endometrial carcinoma have been poorly studied. This paper focuses on the epidemiological relationship between intra-uterine contraception and endo-metrial cancer.

A contraceptive intra-uterine device (IUD) is not just an inert device seated inactively in the uterus. IUDs have been reported to induce profound endometrial changes, including sterile inflammatory changes (Sheppard, 1987; Sagiroglu and Sagiroglu, 1970), an increased number of mast cells (Tursi *et al.*, 1984; Kobayashi *et al.*, 1983), superficial loss of surface epithelium (Sheppard and Bonnar, 1980; El-Badrawi *et al.*, 1981), reduction of ciliated cells with impairment of the secretory activity in the epithelium contiguous to the device (Gonzalez-Angulo *et al.*, 1973), and alterations in endometrial response to estrogen and progesterone (Tamaya *et al.*, 1976; Ghosh *et al.*, 1975; Ghosh and Roy, 1976; Kontula *et al.*, 1974).

IUD use could theoretically alter endometrial cancer risk through at least 2 mechanisms: first, by inducing extrauterine effects on the ovary and the central hypothalamicpituitary-ovarian axis that could affect the production of ovarian estrogens and progesterone; and second, by exerting direct changes in the endometrial environment that could induce a chronic inflammatory process or an alteration of the endome-trial response to hormones.

To explore the relationship between IUD use and endometrial carcinoma, we analyzed data from the Cancer and Steroid Hormones (CASH) Study (CDC CASH Study, 1983), a large, multicenter, population-based, case-control study.

#### METHODS

Data for the CASH Study were collected in 8 areas of the USA that are part of the Surveillance, Epidemiology and End Results (SEER) program of the US National Cancer Institute. The areas included: the metropolitan areas of Atlanta, Detroit, San Francisco and Seattle; the states of Connecticut, Iowa and New Mexico; and the 4 urban counties of Utah.

The design and methods used in the CASH Study, which included breast- and ovarian-cancer patients as well as the endometrial-cancer patients reported here, have been detailed elsewhere (CDC CASH Study, 1983; Wingo *et al.*, 1988). Here we summarize those features of the CASH Study that are relevant to the association investigated.

#### Cases

Eligible cases were 905 women, 20 to 54 years of age, who resided in one of the 8 participating areas and who were newly diagnosed with a primary epithelial endometrial cancer between December 1, 1980, and December 31, 1982. Of those, 673 (74%) were interviewed. Cases from Utah and New Mexico were excluded because histologic reports and slides of endometrial cancer specimens were not retrieved. Of the 599 women identified and interviewed in the 6 remaining areas, the SEER centers were able to retrieve the histologic information and slides from 575 women (96%). These were independently reviewed by a panel of 3 pathologists, each an expert in endometrial cancer. The panel agreed that 437 women (76%) met the criteria for a primary epithelial malignant neoplasm of the endometrium.

#### *Controls*

The pool of eligible controls consisted of women 20 to 54 years of age selected through the Waksberg (1978) method of random digit dialing of households with telephones in the same geographic locations and during the same time interval as when the cases were diagnosed. A stratified sample, frequency-matched by geographic location and by the 5-year age distribution of breast-cancer cases, was selected from the pool (5698 women). Of these women, 4755 (83%) were interviewed; of that sub-group, 1271 were excluded because they had either had a previous hysterectomy or had reported having had a dilation and curettage procedure of unknown or questionable outcome prior to interview. All Utah and New Mexico controls (284) were further excluded, leaving a control group of 3200 women available for analysis.

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#### Data collection

Each study participant was interviewed in person in her home according to a pre-tested, standardized questionnaire. Details of the questionnaire and the information collected have been presented elsewhere (Wingo *et al.*, 1988).

Each woman was asked whether she had ever used an IUD, loop or coil as a form of birth control. If she had,

dates of use were recorded. Of the 3637 study participants, 520 (14%) reported having used some form of intra-uterine contraception, 3114 (86%) reported never having used intra-uterine contraception, and 3 (2 cases and 1 control) did not know if they had used IUDs. Therefore, 3634 women (435 cases and 3199 controls) were available for analysis.

#### Analyses

The measure of association used to compare the risk of developing endometrial cancer among exposed women with that in unexposed women was the odds ratio (OR) as an approximation to the rate ratio. Logistic-regression models with maximum-likelihood estimation of parameter values were used to estimate unadjusted and adjusted odds ratios and to test for linear trends. An alpha value of 0.05 was used as the criterion for statistical significance and, accordingly, 95% confidence intervals (CI) around the OR are reported.

A 3-step process for screening for confounding variables was performed: first, the Mantel-Haenszel procedure was used, treating IUD use dichotomously and the confounders categorically (one confounder at a time); second, logistic regression was used, treating IUD use and confounding variables as continuous (one confounder at a time); and finally, multivariate logistic regression was used to assess the joint confounding effects of those confounding variables selected individually in either of the 2 previous steps. Potential confounders assessed included, among others: age, parity, age at menarche, menopausal status, age at menopause, race, years of education, use of other non-hormonal contraceptive methods (tubal ligation, vasectomy, diaphragm, contraceptive foam/ cream suppositories, condom, rhythm and withdrawal), frequency of Pap smears, frequency of pelvic examinations, infertility, smoking, history of selected diseases (diabetes, hypertension, arthritis and

pelvic inflammatory disease), Quetelet's index, use of oral contraceptives, use of estrogens, data collection center, and family history of cancer.

To assess the specificity of effects of IUD use, adjusted odds ratios were estimated for 3 histologic sub-types of epithelial endometrial cancer: adenocarcinoma, adenoacanthoma and adenosquamous carcinoma. We also assessed the effects of duration of IUD use, age at first and last IUD use, and time since first and last IUD use.

To identify effect modifiers (factors that may alter the association between exposure and disease) a 2-step process was carried out. First, potential effect modifiers were examined one at a time in logistic-regression models that included IUD use (dichotomous), age and parity (confounders), the potential effect modifier, and an interaction term between IUD use and the potential effect modifier. Second, those variables that were statistically significant (p < 0.1) effect modifiers individually were included, along with their interaction terms with IUD use, in a single multiple logisticregression model. Through a backward elimination process, significant (p < 0.05) effect modifiers were retained. Potential effect modifiers assessed included: age, parity, age at menarche, menopausal status, age at menopause, race, years of education, frequency of Pap smears, infertility, smoking, history of selected diseases (diabetes, hypertension, arthritis and pelvic inflammatory disease), Quetelet's index, use of oral contraceptives, use of estrogens, data collection center, and family history of cancer.

The chi-square statistic proposed by Lemeshow and Hosmer (1982) was used to assess the goodness of fit of the final

adjusted and interaction logistic regression models. None of the models showed a statistically significant lack of fit.

#### RESULTS

In this population, the observed differences between cases and controls were consistent with those of other studies of risk factors for endometrial cancer. These results will not be presented here in detail, since they have been published elsewhere (CASH Study, 1987). In brief, as shown in Table I, endometrial cancer cases were more likely than controls to be of white race, obese, and nulliparous or of low parity. They tended to have completed fewer years of education and to have a slightly younger age at menarche. Cases were more likely to be peri-menopausal or to have had an early menopause. Cases were also more likely to have received treatment with estrogens and less likely to have used hormonal and non-hormonal contraceptive methods (tubal sterilization, diaphragm, condom). Cases reported more frequently than controls having received treatment for hypertension and diabetes and having a positive family history of cancer in a first-degree relative. Cases reported slightly less frequently than controls a history of cigarette smoking (Table I). Because controls were frequency matched by the 5-year age distribution of breast-cancer cases, differences in age between cases and controls are not interpretable.

Women who used intra-uterine contraception were less likely to develop endometrial cancer than women who did not use this contraceptive method (unadjusted OR, 0.32; 95% CI, 0.21 to 0.49). Only 6% (24/435) of the cases reported intrauterine contraception use, as compared with 16% (496/3199) in the control group (Table II). After the effects of 68 potential confounders had been assessed, only age and parity were found to appreciably reduce the estimated magnitude of the protective effect, but the association after adjustment remained statistically significant (adjusted OR, 0.51; 95% CI, 0.33 to 0.79; p = 0.003). All subsequent models were adjusted for age and parity. In the adjusted analysis, the protective effect of intra-uterine contraception increased with duration of use, but the dose-response relationship among IUD users did not reach statistical significance (Table II).

Table III summarizes the stratum-specific ORs by age group. IUD use was consistently protective in all age categories.

The protective effect of intra-uterine contraception use on the risk of endometrial cancer increased with younger ages at first IUD use, although this effect did not reach statistical significance. Women who first used IUDs before age 35 had an adjusted OR of 0.47 (95% CI, 0.27 to 0.81), whereas women who first used IUDs at later ages had an adjusted OR of 0.64 (95% CI, 0.33 to 1.25). The test for linear trend with age at first IUD use was not statistically significant (p = 0.41). Age at last IUD use did not substantially modify the association between endometrial cancer and IUD use (data not shown).

The association between endometrial cancer and IUD use varied with time since first IUD use, although not significantly (Table IV). Women who first used intrauterine contraception more recently had greater protection against endometrial cancer than women who first used intrauterine contraception in the more distant past. The OR for women who first used an IUD within 10 years before the index date was 0.35 (95% CI, 0.15 to 0.80), whereas the OR for women who first used an IUD at an earlier time was 0.63 (95% CI, 0.38 to 1.04). Intrauterine contraception appeared to be most protective among women who first used an IUD within the past 10 years and used it for at least 96 months (OR, 0.21; 95% CI, 0.06 to 0.77).

Recency of IUD use, on the other hand, did not substantially change the association between endometrial cancer and intrauterine contraception. Women who

stopped IUD use more recently (less than 72 months before the index date) had an adjusted OR of 0.49 (95% CI, 0.27 to 0.90) and women who stopped IUD use less recently (72 months or more) had an adjusted OR of 0.56 (95% CI, 0.31 to 1.02).

# Table ICharacteristics of Women with Epitherlial EndometrialCancer and Controls

#### \* \* \*

#### Table II

#### Crude and Adjusted Odds Ratios for the Associatin Between Epithelial Endoetrial Cancer and Intra-Uterine Contraception Use

\* \* \*

Table V shows the age- and parity-adjusted OR for the 3 histologic sub-types studied. A protective effect was consistently found for each of the 3 histologic sub-types, although the risk estimates did not reach statistical significance.

Of the 21 potential effect modifiers assessed, only years of education was found to be a statistically significant effect modifier. Per one-year differential in education, the OR for the association between endometrial cancer and intra-uterine contraception decreased by about 20% (OR, 0.80, 95% CI, 0.68 to 0.93). To better summarize the modifying effects of years of education, we fitted another logistic regression model in which years of education were divided into 2 categories, less than 12 years of education and more than 12 years of education. As shown in Table VI, women who had completed less than 13 years of education were not significantly protected by intrauterine contraception (OR, 1.02, 95% CI, 0.58 to 1.79), whereas women who had completed more than 12 years of education were strikingly protected by IUD use (OR,

0.29, 95% CI, 0.15 to 0.58). The ratio of these ORs is 0.29 (95% CI, 0.12 to 0.70), indicating that the OR among more educated women was about one third the magnitude of the corresponding OR among less educated women.

#### **Table III**

#### Odds Ratios for the Association Between Endometrial Cancer and Intra-Uterine Contraception Use by Age Group

\* \* \*

#### **Table IV**

Odds Ratios for the Association Between Endometrial Cancer and Intra-Uterine Contraceptin Use by Time Since First IUD Use

\* \* \*

#### Table V

Odds Ratios for the Association Between Endometrial Cancer and Intra-Uterine Contraception Use by Histologic Sub-Type

\* \* \*

#### Table VI

Odds Ratios for the Association Between Endometrial Cancer and Intra-Uterine Contraception Use by Years of Education

\* \* \*

#### DISCUSSION

This analysis of the data from the CASH Study shows an overall significant decrease in the risk of developing endome-trial cancer among women who used intrauterine contraception, as compared with women who never used it. After taking into account the combined confounding effects of age and parity, women who had used intra-uterine contraception were about half as likely to develop endometrial cancer as were women who had not used that method of contraception. Although the magnitude of the protective effect increased with duration of IUD exposure, a dose-response relationship was not statistically demonstrable among exposed women. However, due to low power, a fairly strong dose-response relationship could not be ruled out with statistical confidence.

The population-based design of the CASH Study reduced, but did not completely eliminate, the possibility of various types of bias that could distort the true relationship between intra-uterine contraception and endometrial cancer.

One of the main limitations was that the CASH Study was not primarily designed to investigate this association. As a consequence, procedures to specifically assist in the recall of IUD use were not incorporated in the study, thereby, at least theoretically, leading to mis-classification of exposure status.

However, poor recall of exposure to IUDs is unlikely to have played a role in the observed association. Intrauterine contraception should be readily remembered by women, since insertion of the device involves not only a procedure but also a number of visits to the gynecologist before and after insertion. Moreover, since equally poor recall of exposure status by both cases and controls would tend to bias the magnitude of the association toward the null value, the observed magnitude of the protective effect would be an underestimate of the real effect.

Another issue, however, is the role of reporting bias. A case may have been more likely than a control to overreport IUD use, since it is reasonable for a woman with cancer to focus on possible exposures, such as IUDs, that may be related to her disease. However, since the observed effect was protective, over-reporting of IUD use by cases would lead to underestimation of the observed protective effect. For differential reporting to account for the observed protective effect, either cases would have had to under-report IUD exposure more frequently than controls; or, alternatively, controls would have had to over-report IUD use more frequently than cases. Neither situation seems likely.

A second important limitation of this study was that information on the type of device used was not collected and thus it was not possible to assess whether the protective effect of intra-uterine contraception differed by type. It is likely that the nature and degree of the changes observed in the IUD-

exposed endometrium vary among inert, copperreleasing and progesterone-releasing devices. The shapes and materials of inert devices have changed over time, and in copper IUDs the amount of copper incorporated into the device, and consequently that released into the endometrial cavity, has also varied. Other epidemiologic, experimental and animal studies in which the effect of different types of IUDs on endometrial cancer risk can be evaluated are warranted to further investigate this protective relationship.

The finding that years of education significantly modified the association between IUD use and endometrial cancer is difficult to interpret. It can be speculated that more highly educated IUD users would be more likely than less educated IUD users to be involved in regular medical surveillance. However, this would more probably result in a positive relationship between IUD use and endometrial cancer among more highly educated women, rather than the negative relationship observed in this study. Failure to observe similar interactions between IUD use and actual screening behavior, such as frequency of Pap smears, further weakens an explanation based on detection bias. It should be borne in mind that the assessment of effect modification in this analysis was merely exploratory, and that education was one of many effect modifiers considered.

A number of animal and clinical studies suggest mechanisms by which IUDs may protect against endometrial cancer. Several lines of evidence suggest that IUDs may alter endome-trial sensitivity and response to the circulating steroid hormones estrogen and progesterone. Hormonal studies in animal uteri and clinical studies in women suggest that changes in the endometrial sensitivity to ovarian hormones caused by an IUD could be mediated through the effects of the copper ions released into the endometrial cavity and through the inherent structural and biochemical endometrial changes triggered by the device itself. More specifically, the effects of the copper ions and the changes in the endometrium may (a) inhibit binding of estrogen and progesterone to their endometrial cell receptors, (b) lower the concentration or synthesis of hormonal nuclear receptors and (c) alter the physical properties of estrogen and progesterone receptors. Tamaya et aL (1976) have observed in rabbits that copper IUDs inhibit both estrogen- and progesterone-receptor binding, suggesting that copper ions aggregated or dissociated hormonereceptor macromolecules, making the receptors biologically inactive. Other animal studies have shown that in an IUD-exposed endome-trium the response to progesterone is inhibited (Brown-Grant, 1969) or blocked (Nutting and Mueller, 1974), that estradiol and/or progesterone uptake is significantly decreased (Ghosh et al., 1975; Ghosh and Roy, 1976), and that hormonal nuclear-receptor concentrations are lower than in a non-IUD exposed endometrium (Myatt et al., 1978, 1980a.b).

Kontula *et al.* (1974) demonstrated that the presence of copper ions in concentrations similar to those prevailing in an human endometrium exposed to a copper-bearing IUD was capable of locally inhibiting progesterone binding in the human endometrium and that the inhibition was caused by decreased affinity of the receptors for progesterone.

The unopposed estrogen hypothesis of endometrial cancer causation maintains that exposure to estrogen that is not sufficiently opposed by progesterone increases endometrial

mitotic activity, and consequently, endometrial-cancer risk (Henderson *et al.*, 1982). According to this hypothesis, decreased endometrial sensitivity/response to estrogen would be protective, while decreased sensitivity/response to progesterone would increase risk. Thus, the animal and clinical observations made appear only partially consistent with the protective effect observed in the present study. More directed studies, including those specifically focussed on the effect of IUDs on endometrial mitotic activity, arc needed to clarify the mechanism by which IUDs may protect against endometrial cancer.

From a public-health view point, the significance of these findings is not the protective association itself, since it is unlikely that women will change contraception practices because of these results. What is informative in this study is that even a small positive association has been ruled out with a high degree of confidence (p = 0.003). This is important, because, although the literature does not provide any scientific evidence for a positive association between IUD use and endometrial cancer, neither does it rule out such a possibility. We should keep in mind that the etiology of various human cancers is thought to be associated with chronic inflammatory processes, which the IUD could well induce in the endometrium.

The finding of a 50% reduction in the risk of endometrial cancer among IUD users in this study is reassuring, but requires replication. Given the increasing worldwide popularity of IUDs, further research designed to address this association is warranted.

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#### REFERENCES

- BROWN-GRANT, K., Effect of an IUCD on an endometrial response to steroid hormones in the rat./ *Reprod. Fert.*, 18, 475-480 (1969).
- CANCER AND STEROID HORMONE (CASH) STUDY FOR DISEASE CONTROL. AND THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT, Combination oral contraceptive use and the risk of endometrial cancer. J. Amer. med. Ass., 257, 796-800 (1987).
- CENTERS FOR DISEASE CONTROL AND THE CANCER AND STEROID
- HORMONE STUDY (CASH), Long-term oral contraceptive use and the risk of breast cancer. J. Amer. med. Ass., 249, 1591-1595 (1983).
- EL-BADRAWI, 1<sup>-</sup>1.H., HAI-FEZ, E.S.E.. BARNHART, M.I., FAYAD, M. and SHAFEEK, A., Ultrastructural changes in the human endometrium with copper and non-medicated IUDs *in utero. Fertil. Steril.*, 36, 41-49 (1981).
- GHOSH, M. and ROY, S.K., Effect of intra-uterine Tdevice and copper-T on *in vitro* uptake of estradiol-17B-6,7 <sup>3</sup>H and progesterone-1,2-<sup>3</sup>H in monkey uterus and cervix. *Contraception*, 3, 355-364 (1976).
- GHOSH, M., ROY, S.K. and KAR, A.B., Effect of a copper intra-uterine contraceptive device and nylon suture on the estradiol 17B-6,7-W and progesterone 1,2-H<sup>3</sup> in the rat uterus. *Contraception*, *11*, 45-50 (1975).
- GONZALEZ-ANGULO, A., AZNAR-RAMOS, R. and FERIA-VELASCO, F., Ultrastructure changes found in endometrium of women using Lippes intra-uterine device. *J. reprod. Med.*, 10, 44-51 (1973).

- HENDERSON, B.E., Ross, R.K., PIKE, M.C. and CASAGRANDE, J.T., Endogenous hormones as a major factor in human cancer. *Cancer Res.*, 42, 3232-3239 (1982).
- KOBAYASHI, T.K., CASSLEN, B. and STORMBI, N., Cytologic atypias in the uterine fluid of intra-uterine contraceptive device users. *Acta cytologica*, 27, 138-141 (1983).
- KONTULA, K., JANNE, O., LUUKKAINEN, T. and VIHKO, R., Progesterone-binding protein in human myometrium. Influence of metal ions on binding. *J. clin. endocrinol. Metab.*, 38, 500-503 (1974).
- LEMESHOW, S. and HosmER, D.W., A review of goodness of fit statistics for use in the development of logistic-regression models. *Amer. I Epidemiol.*, 115, 92-106 (1982).
- MYATT. L., CHAUDHURI, G., ELDER, M.G. and LIM, L., The oestrogen receptor in the rat uterus in relation to intrauterine devices and the oestrous cycle. *Biochem. J.*, 176, 523-529 (1978).
- MYATT, L., CHAUDHURI, G., ELDER, M.G. and LIM, L., Effect of an intra-uterine device on intracellular relationships of the uterine oestrogen receptor, particularly during pregnancy. *I Endocr*, 87, 357-364 (1980a).
- MYATT, L., ELDER, M.G. and LIM, L., Alterations in progesterone receptors in the rat uterus bearing an intrauterine device during the oestrous cycle and early pregnancy. *J. Endocr.*, 87, 365-373 (1980b).
- NUTTING, E.F. and MUELLER, M.R., The effect of a copper intrauterine device on the uterine histology and progestational response in pregnant and immature rabbits. *Fertil. Steril.*, 26, 845-856 (1974).

- SAGIROGLU, N. and SAGIROGLU, E., Biological mode of action of the Lippes loop in intra-uterine contraception. *Amer. I Obstet. Gynecol.*, 106, 506-515 (1970).
- SHEPPARD, B.L., Endometrial morphological changes in IUD users: a review. *Contraception*, 36, 1-10 (1987).
- SHEPPARD, B.L. and BONNAR, J., The response of endometrial blood vessels to intra-uterine contraceptive devices: an electron microscopic study. *Brit. J. Obstet. Gynecol.*, 87, 143-154 (1980).
- TAMAYA, T., NAKATA, Y., OHNO, Y., NIOKA, S., FURUTA, N. and OKADA, H., The mechanism of action of the copper intra-uterine device. *Fertil. Steril.*, 27, 767-772 (1976).
- TURSI, A., MASTRORILLI, A., RIBArn, D., LOIUDICE, L., CONTINO, R. and CLAUDATUS, L., Possible role of mast cells in the mechanism of action of intra-uterine contraceptive devices. *Amer. J. Obstet. Gynecol.*, 148, 1064-1066 (1984).
- WAKSBERG, J., Sampling methods for random digit dialing. J. Amer. Stat. Ass., 73, 40-46 (1978).
- WINGO, P.A., ORY, H.W., LAYDE, P.M., LEE, N.C. and THE CANCER AND STEROID HORMONE STUDY GROUP, The evaluation of the data collection process for a multicenter, population-based, case-control design. *Amer. J. Epidemiol.*, 128, 206-217 (1988).

#### **APPENDIX Y**

#### CONTRACEPTION METHODS, BEYOND ORAL CONTRACEPTIVES AND TUBAL LIGATION, AND RISK OF OVARIAN CANCER

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**PURPOSE:** Few studies have examined methods of contraception, beyond oral contraceptives (OCs) and tubal ligation, in relation to ovarian cancer risk.

**METHODS:** Nine hundred two cases with incident ovarian/peritoneal/tubal cancer were compared with1800 population-based control subjects. Women self-reported all methods of contraception by using life calendars.

**RESULTS:** Each of the contraceptive methods examined reduced the risk of ovarian cancer as compared with use of

no artificial contraception. Comparing ever versus never use, after adjustment for potentially confounding factors and all other methods of contraception, the methods of contraception that emerged as protective were OCs (adjusted odds ratio [adj OR] 0.75, 95% confidence interval [CI] 0.61-0.93); tubal ligation (adj OR 0.63, 95% CI 0.51-0.77); intrauterine devices (IUDs) (adj OR 0.75, 95% CI 0.59-0.95); and vasectomy (adj OR 0.77, 95% CI 0.61-0.99). Although for OCs and tubal ligation we found that the longer the duration of use, the greater the effect, for IUDs the pattern was reversed: significant protection occurred with short duration and progressively greater risk (albeit nonsignificant) was seen with longer duration of use.

**CONCLUSIONS:** In the largest case-control study to date, a range of effective methods of contraception reduced the risk for ovarian cancer. OCs and tubal ligation reduced ovarian cancer risk with lower odds ratios with longer duration of use, whereas IUDs reduced risk overall, having the greatest impact with short duration of use.

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**KEY WORDS:** Contraception, Contraceptive Methods, IUDs, Oral Contraceptives, Ovarian Cancer, Tubal Ligation.

#### INTRODUCTION

Several forms of contraception have been shown to reduce the risk of developing ovarian cancer. Oral contraceptives (OCs) reduce risk in a duration-dependent fashion, and the effects of oral contraceptives last for at least 20 years after cessation of use (1-4). Tubal ligation has also been shown to consistently reduce risk (5-8). Increasingly, OCs are considered for chemoprophylaxis against ovarian cancer, particularly in high-risk women (9-11).

Few studies have examined use of other methods of contraception in relation to ovarian cancer risk. Small casecontrol studies demonstrated some risk reduction with

nonhormonal contraceptive methods; however, only small numbers of women used each method, the findings were not entirely consistent by method, and risk reductions were not significant (1, 12–14). Two larger studies reached somewhatconflicting conclusions. In a large, case-control study by our group, all methods of contraception (intrauterine devices or intrauterine devices [IUDs], barrier methods, and vasectomy, as well as OCs and tubal ligation) reduced ovarian cancer risk as compared with no contraception use; ever use versus never use also reduced risk in multiparous but not nulliparous women (15). An analysis from the prospective Nurses' Health Study cohort reported an increased risk associated with IUD use and no association for other contraceptive methods (16).

The finding that multiple contraceptive methods reduce ovary cancer risk must be scrutinized as possibly representing a bias by fertility status. Ovarian cancer rates are greater among infertile women (17, 18). In turn, many infertile women spend long periods of time practicing unprotected intercourse. Contraceptive users may thus appear to be protected from ovarian cancer only because they are less likely to be infertile. Alternatively, the finding that methods of contraception beyond OCs and IUDs are protective may provide insights into ovarian carcinogenesis.

Here we attempt to re-examine the results from our earlier case-control study in a newly conducted population-based case-control design. Our earlier study was conducted in the Delaware Valley in and around Philadelphia, and our current study was conducted in Western Pennsylvania and surrounding regions (15). As we did previously, we attempt to separate parity from contraceptive use and to examine the specificity of contraceptive effects on risk reduction for ovarian cancer. Here we examined OCs, IUDs, any barrier methods, tubal ligation, and vasectomy (in a partner) in relation to ovarian cancer risk.
# **Selected Abbreviations and Acronyms**

OC = oral contraceptive

IUD = intrauterine device

OR = odds ratio

CI = confidence inerval

#### SUBJECTS AND METHODS

Subjects were enrolled in a population-based case-control study conducted in a contiguous region comprising Western Pennsylvania, Eastern Ohio, and Western New York State. Cases were residents of this geographic region with histologically confirmed primary epithelial ovarian, fallopian tube, or peritoneal cancer diagnosed between February 2003 and November 2008. Both invasive and borderline tumors were included. Women were referred from hospital tumor registries, clinical practices, or pathology databases and contacted with the permission of their gynecologists. Eligible women were at least 25 years of age and within 9 months of initial diagnosis. Controls consisted of women at least age 25 who lived in telephone exchanges wherein cases resided. Random digit dialing was used to identify age-eligible women, and these were further screened by the study team to ensure that they had not had a previous oophorec-tomy or diagnosis of ovarian cancer. Eligible women were then invited to participate. Potential controls were frequency matched by 5-year age group and telephone exchange to cases in a ratio of approximately 2:1. Women were interviewed in their homes by trained interviewers. The questionnaire included a reproductive and gynecological history, a contraceptive history, a medical history, a family history, and information on lifestyle practices. All study subjects gave informed consent for participation.

From Pennsylvania and Ohio, we identified 2458 potential cases with histologically confirmed borderline or invasive epithelial ovarian cancer or tubal/peritoneal cancer. After excluding women who were ineligible on the basis of age and

time since diagnosis; deceased; residence outside of the counties in which referral hospitals were located; previous diagnosis of ovarian cancer; or inability to speak English, there were 997 who had incident cancer and were eligible for the study. Two hundred thirty one women were untraceable and 115 women refused to participate or their physicians refused on their behalf. Thus, 651 women completed case interviews. From New York, we identified 420 potential cases. After excluding women who were ineligible based on the aforementioned criteria, there were 273 who had incident cancer and were eligible for the study. Fourteen women were untraceable, and eight women refused to participate or their physicians refused on their behalf, resulting in a sample of 251 women who completed interviews.

Overall, 902 women with ovarian, tubal/peritoneal cancer completed an interview and are included in these analyses. For brevity, we subsequently use the term ovarian cancer to describe all cases.

Controls were identified from 90,540 random digit dialing calls. Of these, 46,752 reached nonworking numbers; 26,237 were unresolved (never reached a person); 14,899 reached an ineligible or indeterminate household (no woman within the age range or no information given); and 808 refused to participate. Of the 1844 eligible women willing to be interviewed in the initial screening, 1802 controls completed an interview. Two controls had an oophorectomy before the interview and were further excluded from our study, and 1800 controls completed an interview.

Cases included 677 women with invasive epithelial ovarian tumors, 97 with borderline epithelial ovarian tumors, 75 with peritoneal tumors, 32 with fallopian tumors, and 21 women with "other" or a missing type. The diagnosis of ovarian cancer was confirmed by local pathology in all cases.

# **Contraceptive Use**

Standardized 2-hour-long interviews were conducted by trained interviewers in the homes of participating women. A "life" calendar marked with important events that each participant recalled during her life was used to enhance memory of distant information. Using the calendar, the interviewer led each woman through a recall of her sexual activity, use of various contraceptive methods, pregnancy attempts, and reproductive events for every month from sexual debut until a reference date. The reference date was calculated as 9 months before the interview (for both cases and controls) to ensure that exposures occurred before ovarian cancer diagnoses in cases and within a similar time frame for cases and controls. All contraceptive use was recorded, including the type of contraception, frequency of use, duration of use, and reason for use. Finally, we asked women about any medical consultation for fertility problems.

# Covariates

Detailed information on demographic factors, physical characteristics, medical history, lifestyle, and family history was obtained by interview. These included factors that have been previously associated with ovarian cancer: race, education, family history of ovarian cancer, number of live births and pregnancies, and breast-feeding.

# Table 1 Demographic and reproductive characteristics of ovarian cancer cases and controls in the HOPE study

\* \* \*

# **Statistical Analysis**

All analyses were restricted to women who had ever had sexual intercourse with a man. Thirty-three cases and 23 controls that had never had intercourse were excluded on the basis that they would not have had the opportunity for exposure to contraceptive methods for contraception.

Because we did not engage in individual matching of cases and controls, we used unconditional logistic regression analyses. We adjusted the odds ratios (ORs) for any residual effect of age and for gravidity (each as continuous variables), race (white/black/other), self-reported infertility (yes/no for diagnosis or use of infertility medications), and history of ovarian cancer in any first-degree relative (yes/no). We included these covariates because they were the strongest covariates related to ovarian cancer in our data. The inclusion of education and breast-feeding did not affect our results. We subsequently adjusted for all other forms of contraception other than the one of interest (e.g., for OCs, this analysis included the covariates listed above plus ever use of IUD, tubal ligation, and vasectomy). Oral contraceptive use was categorized as use for contraception, for noncontraceptive uses such as to control abnormal bleeding or menstrual pain, or for both contraception and other uses. Barrier methods included condoms, diaphragms, foam, sponges, or cervical caps. The reference group of no contraception included women who reported never using OCs, birth control implants, IUDs, any barrier methods, tubal ligation, or vasectomy (in a partner). These women may have used natural family planning (that is, having intercourse during times when the woman believed she was not ovulating), withdrawal, or nothing. We do not report as a separate category of contraception birth control implants, because the number of women using these methods in our study was small (16 cases and 46 controls).

#### Table 2

#### Odds ratios for ovarian cancer comparison of ever-use of contraceptive methods with never-use

# \* \* \*

#### Table 3

Odds ratios for ovarian cancer: comparison of ever use of contraceptive methods with no artificial contraception

# RESULTS

Study subjects were predominantly white, post-high school graduates, 60 or older, and postmenopausal (Table 1). The commonly-found protections with increasing education, numbers of pregnancies/live births and breast-feeding were observed. Cases were more likely to be African American than controls, suggesting a selection bias among this small segment of subjects.

We found a reduction in the risk of ovarian cancer for ever versus never use of each of the methods for contraception analyzed (Table 2). However, after adjustment for age, race, family history of ovarian cancer, infertility, and gravidity, significant protection was seen only with IUDs as well as OCs for contraception and tubal ligation. After further adjustment for all other forms of effective contraception, IUDs, OCs for contraception, and tubal ligation remained significantly protective; now vasectomy also reached a level of significant protection.

Because ever use of contraceptive methods is complicated by admixing users of other methods, mixed methods, and none of these methods over a lifetime, we also compared users of each method with women who used no artificial contraception, defined as use of only natural family planning, withdrawal, rhythm, or no contraception (Table 3). Each of the methods significantly reduced the risk of ovarian cancer as compared to no artificial contraception.

Next, we examined the association between contraception and ovarian cancer among women with zero, one, two, or three or more pregnancies (Table 4). Both OCs for contraception and tubal ligation significantly reduced risk in some but not all gravidity categories, without a clear pattern of greater or lesser effects as gravidity increased. IUD use, despite generating protective odds ratios similar to those for OCs, did not produce significant results in any gravidity category, possibly because of small sample sizes. Vasectomy also did not produce significant reductions in risk in any gravidity category.

By duration, OCs had a progressively greater impact with 4 or fewer years, 5 to 9 years, and 10 or more years of use (Table 5). Similarly, longer duration of tubal ligation was associated with lower risk. For IUD use, the pattern was reversed: significant protection occurred with short duration (< 4 years) use and progressively greater risk was seen with longer duration of use (adjusted ORs 0.53 for <4 years; 1.11 for 5-9 years; 1.40 for >10 years). We further explored whether time since last IUD use might drive these observations. Although there was a trend toward reduced risk with increasing time since last use, this was eliminated with adjustment for (i.e., not independent of) IUD duration. We did not have data on duration of vasectomy.

Additional analyses showed our observations to be robust. Contraception use before the first pregnancy or episode of trying was protective (OCs for contraception, OR = 0.87, 95% confidence interval [CI] 0.69-1.11); IUD, OR = 0.81, 0.41-1.60). Adjustment for breast-feeding in the multivariate analyses had no substantial effect on our results for evernever use. Analyses including only epithelial ovarian cancer (excluding fallopian and peritoneal cancers) essentially replicated those shown here with the result for vasectomy slightly enhanced in these analyses when adjusted for confounders plus all other contraceptive methods (OR 0.73, 95% CI 0.56-0.94).

Finally, we examined use of concomitant methods of birth control over a lifetime (Table 6). The majority of women used more than one contraceptive method over a lifetime and of these, the most common combination was OC use plus another method. For instance, of the 424 women whose contraceptive use included vasectomy, only 89 (21%) did not also use OCs.

#### Table 4

Adjusted odds ratios for ovarian cancer: comparison of everuse of contraceptive methods with never-use by gravidity group

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#### DISCUSSION

We report here the largest case-control study to examine whether effective methods of contraception, beyond OCs and tubal ligation, reduce the risk of ovarian cancer. Consistent with the results of our previous case-control analysis (15), we found that use of a variety of different contraceptive methods generally reduced risk of ovarian cancer as compared to use of no artificial contraception. Such an analysis is almost certainly confounded by fertility in that women who are infertile or subfertile would be less likely to use effective methods of contraception and more likely to develop ovarian cancer. In our current, more discriminating analyses of ever versus never use, comparisons to OCs, and use within parity categories, the methods of contraception that emerged as protective were OCs, tubal ligation, IUDs, and vasectomy. Vasectomy is intriguing but we were less informed about this relationship with ovarian cancer since we had no data on duration of use. IUDs were particularly interesting because (i) they are not traditionally thought to reduce the risk of ovarian cancer; (ii) duration-response analyses showed a counter-intuitive pattern wherein shorter use reduced risk and longer use (albeit nonsignificantly) increased risk.

#### Table 5

Adjusted ORs and 95%CIs for ovarian cancer comparison of duration of use of contraceptive methods with never use

\* \* \*

 Table 6

 Contraception methods use by cases and controls

\* \* \*

Our results replicated a plethora of earlier studies linking OCs and tubal ligation to reduced ovarian cancer risk (5–7, 19, 20). In particular, our results mirror adjusted ORs for ever-use of OCs reported from a meta-analysis (0.7) and a pooled analysis (0.66) (2, 21). We partially, but did not fully, replicate a much more limited literature that has addressed the relation between other forms of contraception (barrier, IUD, or vasectomy) and the risk of ovarian cancer. In these studies, the reported ORs were generally less than 1.0; however, none of those studies had enough women in any contraception category, other than OCs, to show strong effects or to explore more fully comparisons between categories (1, 12–15, 22). In the only prospective study to examine contraception methods beyond OCs and tubal ligation, Tworoger et al. (16) found a significant relative risk of 1.76 associated with IUD use. Unfortunately, only 18 IUD users informed the analysis and thus duration and time since last use of IUDs was not reported. Here, we did not show significant risk reductions for barrier methods and vasectomy but we did find that shorter-duration IUD use reduced risk while longer duration IUD use increased risk.

In previous analyses stratifying by parity or gravidity groups, results have been mixed. In our previous study, we found risk reductions to be limited to multigravid women (15). In our current study, we found a patchy set of associations that did not clearly demonstrate a limitation by gravidity category but was not fully consistent between gravidity categories, perhaps on the basis of the sizes of individual stratification cells. All methods were protective before the first pregnancy, a time during which women might not yet know their fertility potential and thus not yet adjust their contraceptive strategy. All of this suggests that confounding by fertility status is an unlikely explanation for our observations.

A variety of biological explanations have been offered to explain the protective effect of OCs on ovarian cancer risk.

These include: (i) excessive ovulation promotes risk; (ii) elevated steroid hormone levels increaser risk; (iii) unopposed estrogen increases risk; and (iv) pelvic inflammation increases risk (23–27). Tubal ligation has been posited to have an effect via a reduction in utero-ovarian blood flow resulting in altered local hormonal and growth factor levels, or via its protection against the ascension of inflammants (26–28). Some IUDs contain progestin, which has been proposed to reduce the risk of ovarian cancer (25). However, only a tiny fraction of IUD users in the current analysis (n =14) reported using progestin-containing IUDs. IUDs. particularly older formulations, such as the Dalkon Shield, increased the risk for pelvic inflammatory disease. The hazard likely occurred because of the particular construction of the multifilament string attached to the Dalkon Shield. But it also may have related to insertion through a cervix infected with the bacterial sexually transmitted infections that cause pelvic inflammatory disease, as suggested by the close temporal relationship between insertion and pelvic inflammatory disease and the relative safety of modern-day use, which is confined to monogamous women without cervical infections (29). These facts may explain our counterintuitive finding of a reversed duration-response relationship (longer use associated with increasing risk). IUDs must be replaced every 5 to 10 years depending on the product; longer use would imply more insertions and thus greater risk of infection and inflammation. Shorter use might actually reduce upper genital tract inflammation by virtue of killing sperm. Indeed, the marginal reduction in risk from vasectomy might suggest some protection from reduced exposure to sperm.

Strengths of this study include the population-based ascertainment of cases and controls, the large number of women interviewed, the use of life calendars and emphasis on recall of contraceptive use and reproductive experiences, and the structured interviews to enhance recall. All of these

methodological features reduce the potential for selection and information bias. The greatest study limitation was the challenge of separating the effects of various contraceptive methods because the use of more than one method over a lifetime was the norm. We attempted to separately delineate methods by adjusting for all methods in logistic regression analyses and by comparing each method to no effective method. Nonetheless, residual confounding remains a real concern. Other study limitations included: (i) selection against women with short life expectancies postdiagnosis who may have become debilitated or died before interview and (ii) inaccurate recall of past contraceptive experiences. Women may have incorrectly recalled past events, such as the duration of use of contraceptive methods. It is less likely that women would misremember ever versus never-use of contraceptive methods (30, 31). Previous investigators (30-35) have found that among ever-users of OCs identified by medical records, 80% or more reported OC use; an even larger proportion of IUD users identified by medical records reported IUD use.

In summary, from this large study of contraceptive methods and ovarian cancer, we confirmed that OCs and tubal ligation reduced risk for ovarian cancer. Short-term IUD use reduced risk but long term IUD use tended toward elevating risk. Because contraceptive methods are modifiable and because ovarian cancer is highly lethal, these findings should be added to other considerations when selecting contraceptive methods.

# REFERENCES

- 1. The Cancer and Steroid Hormone Study Group. The reduction in risk of ovarian cancer associated with oral contraceptives use. N Engl J Med. *1987;316:650–655*.
- 2. Whittemore AS, Harris R, Itnyre J, the Collaborative Ovarian Cancer Group. Characteristics relating to ovarian cancer risk: collaborative analysis of *12* US case-control studies. II. Invasive epithelial ovarian

cancers in white women. Am J Epidemiol. 1992;136:1184–1203.

- 3. Purdie D, Green A, Bain C, Siskind V, Ward B, Hacker N, et al. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. Int J Cancer. 1995;62:678–684.
- 4. Ness RB, Grisso JA, Klapper J, Schlesselman JJ, Silberzweig S, Vergona R, et al., the SHARE Study Group. Risk of ovarian cancer in relation to estrogen and progestin dose and use characteristics of oral contraceptives. Am J Epidemiol. 2000;152:233–241.
- 5. Hankinson SE, Hunter DJ, Colditz GA, Willett WC, Stampfer MJ, Rosner B, et al. Tubal ligation, hysterectomy, and risk of ovarian cancer: a prospective study. JAMA. 1993;270:2813–2818.
- 6. Miracle-McMahill HL, Calle EE, Kosinski AS, Rodriguez C, Wingo PA, Thun MJ, et al. Tubal ligation and fatal ovarian cancer in a large prospective cohort study. Am J Epidemiol. *1997;145:349–357*.
- Rosenblatt KA, Thomas DB. Reduced risk of ovarian cancer in women with a tubal ligation or hysterectomy. The World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. Cancer Epidemiol Biomarkers Prev. 1996;5:933–935.
- 8. Kjaer SK, Mellemkjaer L, Brinton LA, Johansen C, Gridley G, Olsen JH. Tubal sterilization and risk of ovarian, endometrial and cervical cancer. A Danish population-based follow-up study of more than 65 000 sterilized women. Int J Epidemiol. 2004;33:596–602.
- Narod SA, Risch H, Moslehi R, Dorum A, Neuhausen S, Olsson H, et al. Oral contraceptives and the risk of hereditary ovarian cancer. N Engl J Med. 1998;339:424–428.

- Antoniou AC, Rookus M, Andrieu N, Brohet R, Chang-Claude J, Peock S, et al. Reproductive and hormonal factors, and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers: results from the International BRCA1/2 Carrier Cohort Study. Cancer Epidemiol Biomarkers Prev. 2009;18:601–610.
- Modugno F, Moslehi R, Ness RB, Nelson DB, Belle S, Kant JA, et al. Reproductive factors and ovarian cancer risk in Jewish BRCA1 and BRCA2 mutation carriers (United States). Cancer Causes Control. 2003;14:439– 446.
- Parazzini F, La Vecchia C, Negri E, Bocciolone L, Fedele L, Franceschi S. Oral contraceptive use and the risk of ovarian cancer: an Italian case-control study. Eur J Cancer. 1991;27:594–598.
- Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. Br J Cancer. 1989;60:592– 598.
- 14. Salazar-Martinez E, Lazcano-Ponce EC, Gonzalez Lira-Lira G, Escudero-De los Rios P, Salmeron-Castro J, Hernandez-Avila M. Reproductive factors of ovarian and endometrial cancer risk in high fertility population in Mexico. Cancer Res. 1999;59:3658–3662.
- 15. Ness RB, Grisso JA, Vergona R, Klapper J, Morgan M, Wheeler JE, for the Study of Health and Reproduction (SHARE) Study Group. Oral contraceptives, other methods of contraception and risk reduction for ovarian cancer. Epidemiology. 2001;12:307–312.
- Tworoger SS, Fairfield KM, Colditz GA, Rosner BA, Hankinson SE. Association of oral contraceptive use, other contraceptive methods, and infertility with ovarian cancer risk. Am J Epidemiol. 2007;166:894– 901.
- 17. Glud E, Kjaer SK, Troisi R, Brinton LA. Fertility drugs and ovarian cancer. Epidemiol Rev. 1998;20:237–257.

- 18. Ness RB, Cramer DW, Goodman MT, Kjaer SK, Mallin K, Mosgaard BJ, et al. Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. Am J Epidemiol. 2002;155:217–224.
- Hannaford PC, Sivasubramaniam S, Elliott AM, Angus V, Iversen L, Lee AJ. Cancer risk among users of oral contraceptives: Cohort data from the Royal College of General Practitioner's oral contraception study. BMJ. 2007:335–651.
- 20. Collaborative Group on Epidemiological Studies of Ovarian Cancer. Ovarian cancer and oral contraceptives: Collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet. 2008;371:303–314.
- 21. Stanford JL. Oral contraceptives and neoplasia of the ovary. Contracep- tion. 1991;43:543–556.
- 22. Dorjgochoo T, Shu XO, Li HL, Qian HZ, Yang G, Cai H, Gao YT, Zheng W. Use of oral contraceptives, intrauterine devices and tubal sterilization and cancer risk in a large prospective study, from 1996 to 2006. Int J Cancer. 2009;15(124):2442–2449.
- 23. Fathalla MF. Incessant ovulation a factor in ovarian neoplasia? Lancet. 1971;2:163.
- 24. Cramer DW, Welch WR. Determinants of ovarian cancer risk. II. Infer- ences regarding pathogenesis. J Natl Cancer Inst. 1983;71:717–721.
- 25. Risch HA. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of adrogens and progesterone. J Natl Cancer Inst. 1998;90:1774–1786.
- 26. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. J Natl Cancer Inst. 1999;91:1459–1467.

- 27. Ness RB, Grisso JA, Cottreau C, Klapper J, Veragona R, Wheeler JE, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. Epidemiology. 2000;11:111–117.
- 28. Cramer DW, Xu H. Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. Ann Epidemiol. 1995;5:310–314.
- 29. MacIsaac L, Espey E. Intrauterine contraception: the pendulum swings back. Obstet Gynecol Clin North Am. 2007;34:91–111.
- 30. West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall accuracy for prescription medications: self-report compared with database information. Am J Epidemiol. 1995;142:1103–1112.
- Coulter A, Vessey M, McPherson K. The ability of women to recall their oral contraceptive histories. Contraception. 1986;33:127–137.
- 32. Harlow SD, Linet MS. The agreement between questionnaire data and medical records: the evidence of accuracy of recall. Am J Epidemiol. 1989;129:233–248.
- 33. Maggwa BN, Man JK, Mbugua S, Hunter DJ. Validity of contraceptive histories in a rural community in Kenya. Int J Epidemiol. 1993;22: 692–697.
- Stolley PD, Tonascia JA, Sartwell PE, Tuckman MS, Tonascia S, Rutledge A, et al. Agreement rates between oral contraceptive users and prescribers in relation to drug use histories. Am J Epidemiol. 1978;107:226–235.
- 35. Wingo PA, Lee NC. Use of life calendar to enhance the quality of exposure and risk factors histories. Am J Epidemiol. 1988;128:921.

# **APPENDIX Z**

#### **AMERICAN ASSOCIATION FOR CANCER**

# CONDITIONS ASSOCIATED WITH ANTIBODIES AGAINST THE TUMOR-ASSOCIATED ANTIGEN MUC1 AND THEIR RELATIONSHIP TO RISK FOR OVARIAN CANCER

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# Abstract

Many cancers, including ovarian, overexpress epithelial mucin (MUC1) and promote anti-MUC1 antibodies that may correlate with more favorable prognosis. By extension, risk for ovarian cancer might be reduced by preexisting MUC1-specific immunity. We measured anti-MUC1 antibodies in 705 control women, identified events predicting antibodies, and estimated ovarian cancer risk by comparing profiles of events generating antibodies in controls with those in 668 ovarian cancer cases. Factors predicting antibodies included oral contraceptive use, breast mastitis, bone fracture or osteoporosis, pelvic surgeries, nonuse of talc in genital hygiene, and to a lesser extent intrauterine device use and current smoking. There was a significant increase in the

likelihood of having anti-MUC1 antibodies from 24.2% in women with 0 or 1 condition, to 51.4% in those with five or more conditions. By the same index of events, the risk for ovarian cancer was inversely associated with number of conditions predisposing to anti-MUC1 antibodies. Compared with having experienced 0 or 1 event, the adjusted risk for ovarian cancer decreased progressively with relative risks (and 95% confidence limits) of 0.69 (0.52-0.92), 0.64 (0.47-0.88), 0.49 (0.34-0.72), and 0.31 (0.16-0.61), respectively for women with two, three, four, and five or more events related to the presence of antibodies ( $P_{trend} < 0.0001$ .) We conclude that several traditional and new risk factors for ovarian cancer may be explained by their ability to induce MUC1 immunity through exposure of MUC1 to immune recognition in the context of inflammatory or hormonal processes in various MUC1-positive tissues. (Cancer Epidemiol Biomarkers Prev 2005;14(5):1125–31)

#### Introduction

Human mucin (MUC) family member, MUC1, is a high molecular weight protein expressed in a highly glycosylated form and low levels by many types of normal epithelial cells and in a hypoglycosylated form and high levels by most epithelial adenocarcinomas, including breast and ovarian cancer (1). Anti-MUC1 antibodies have been described and correlated with a more favorable prognosis (2-5) showing that patients generate immunity against MUC1 produced by their tumors and defining MUC1 as a tumor-associated antigen and candidate for cancer vaccines (6). Anti-MUC1 antibodies are also found in healthy individuals, especially in women during pregnancy and lactation. It has been hypothesized that a natural immunity against tumor MUC1 might develop and account for the long-term protective effect of pregnancy or breast-feeding on breast cancer risk (7), an elaboration on the so called "fetal antigen theory"(8). Indeed it has been shown that sera from multiparous women, but not from nulliparous women or from men, are able to mediate killing of breast cancer cells (9). Supporting a key role for MUC1 in these reactions, core peptide sequences from MUC1 can induce proliferation of T cells and cytotoxic Tcell responses in multiparous women (10). Recently, the "fetal antigen" hypothesis was extended to ovarian cancer after it was shown that sera from multiparous women also reacted with multiple antigens from ovarian cancer cells more strongly than sera from nulliparous women or men (11), although MUC1 was not specifically examined in these experiments.

In this study, we used an ELISA to determine the presence and relative amounts of MUC1-specific antibody in women from the general population who served as controls in a study of ovarian cancer. In analyses confined to these controls, we identified the predictors of anti-MUC1 antibodies and used case-control comparisons to evaluate these predictors in relation to ovarian cancer risk. We hypothesized that events predicting anti-MUC1 antibodies would be inversely associated with ovarian cancer risk and that there would be a cumulative effect of such events.

# **Materials and Methods**

Subject Recruitment and Study. This report is based on the second phase of a population-based case-control study of ovarian cancer conducted between 7/98 and 7/03 and involving eastern Massachusetts and all of New Hampshire, approved by the Brigham and Women's Hospital and Dartmouth Medical Center's Institutional Review Boards. We identified 1,267 cases from tumor boards and Statewide Registries and excluded 119 cases who died, 110 who moved from the study area, one who had no telephone, 23 who did not speak English, and 46 found to have a nonovarian primary upon review. Of the remaining 968, physicians denied permission to contact 106 and 171 declined to participate, leaving 691 cases interviewed. Of these, 668 had epithelial an ovarian cancer (including borderline

malignancies) and are included in this report. A small number of cases (n = 48) were enrolled before surgery.

Controls were identified through town books in Massachusetts and Drivers' License lists in New Hampshire and sampled to match the age and residence of previously accumulated cases. Invitations to participate were sent to 1843 potential controls. Of these 318 had moved and could not be located or had died, 197 (in Massachusetts) could not be recontacted because subjects returned an "opt out" postcard required by the hospital's Institutional Review Boards, and 47 no longer had a working telephone. Of the remaining 1,281 who were contacted, 152 were ineligible because they had no ovaries or were not the correct age, 59 were incapacitated or did not speak English, and 349 declined, leaving 721 who were interviewed and included in this report.

After written informed consent, an in-person interview dealing with demographic, medical, and family history was conducted. Subjects also completed a self-administered dietary questionnaire. Heparinized blood specimens were collected from subjects agreeing to provide one; separated into red cell, buffy coat, and plasma components; and stored at -80°C.

**ELISA Assay for Anti-MUC1 Antibodies**. Plasma specimens were available for measuring anti-MUC1 antibodies in 48 cases with preoperative bloods and 705 controls. Antibodies were measured against a synthetic 100-mer MUC1 peptide corresponding to five tandem repeats of the MUC1 polypep-tide core tandem repeat region, according to our previously published protocol (2). Briefly, 0.5 Ag of MUC1 peptide in 100 AL of PBS was added to each well of Immulon 4 plates (Dynax, Chantilly, VA) and incubated overnight at 4°C. Control plates without the MUC1 peptide were also prepared. The plates were washed thrice with PBS and 100 AL of 2.5% bovine serum albumin in PBS added for 1 hour at room temperature to coat remaining sites in the well

(blocking step). Fifty microliters of serially diluted plasma (1:20 to 1:80 in PBS) were added to the MUC1 peptidecoated and control plates and incubated for 1 hour at room temperature. The plates were washed 5x with 100 AL PBS and 0.1% Tween 20 detergent. Fifty microliters of secondary antibody, alkaline phosphatase- labeled goat anti-human polyvalent IgM, IgG, IgA (Sigma-Aldrich, St. Louis, MO), diluted 1:1,000, was added for 1 hour at room temperature, and plates again washed 5x with PBS-Tween. One hundred microliters of alkaline phosphatase substrate pNPP (Sigma-Aldrich) were added at 3 mg/mL in 0.05 mol/L NaCO3 and 0.5 mmol/L MgCl2 and the plates incubated in the dark for exactly 1 hour before adding 50 AL of the stop solution (0.5 mol/L NaOH). The absorbance at 405 to 410 nm was measured using the plate reader MRX Revelation (Thermo Labsystems, Chantilly, VA). Absorbance values for each sample in the MUC1-coated plate were compared with values in the antigen-negative plates to subtract nonspecific binding. Based upon the previous responses in over 500 cancer cases and controls, absorbance reactions at the 1:20 dilution at < 0.6are scored as negative, reactions in the 0.6 to 0.79 range as low, reactions in the 0.8 to 0.99 range as intermediate, and reactions z1.0 as high. In the current study, 20 blinded replicate specimens were included and the Spearman correlation coefficient between the paired absorbances was 0.93 (*P* < 0.0001).

**Statistical Methods**. Logistic regression analysis was used to compare those with an antibody reaction at any level against those considered negative for MUC1 antibody (A < 0.6), while adjusting for potential confounding variables. Spearman rank correlations or generalized linear modeling was used to assess differences in absorbance levels (using log-transformed values of absorbance) for a more quantitative assessment of factors affecting anti-MUC1 antibody production. Combinations of factors were examined to identify the best cumulative index of experiences

associated with likelihood of having antibodies. Ovarian cancer cases and controls were then categorized by the presence or absence of events found to affect the likelihood of antibodies and risk for ovarian cancer calculated using unconditional multivariate logistic regression to adjust for potential confounders. In our models, we adjusted for the matching variables, age (continuous), and study site (Massachusetts, New Hampshire), as well as ethnicity (White, non-White), religious background (Jewish, non-Jewish), and parity as a continuous variable except where noted in the text or footnotes.

#### Results

The distributions of absorbance readings (corresponding to the amount of anti-MUC1 antibodies measured in the ELISA assay) seemed bimodal in cases with preoperative bloods and skewed right in controls prompting log transformation for statistical testing (Fig. 1). By a cutoff of  $A \ge 0.6$ , 33.8% of controls and 45.8% of cases were positive for antibodies. By a cutoff of  $A \ge 1.0$ , 12.3% of controls and 25% of cases had a high level of antibodies, a significant difference that likely reflects an ongoing immune response to tumor in the cases.

**Events** Predicting Occurrence of Anti-MUC1 Antibodies. A number of demographic, reproductive, and medical conditions were examined as they affected the likelihood of controls having a low, intermediate, high level, or any anti-MUC1 antibody (Table 1). The last two columns show the (geometric) mean absorbance value, its SE, and the P from the linear regression model. Age was a strong predictor with 50% having antibodies at ages <35, declining to 29.3% at ages 55 to 64 years, and increasing back up to 32.6% in those ages z65 years, prompting age adjustment when testing for the significance of further variables. The proportion of women who were positive for anti-MUC1 antibody was similar for women who had never been pregnant (33.3%), had at least one live birth (34.1%), or had breast-fed without experiencing a mastitis (33.0%) but

elevated for women who had experienced mastitis while breast-feeding (46.1%). Notably, 25.0% of women reporting mastitis had high antibody levels compared with 10% to 14% of parous women who either never breast-fed or breast-fed and reported no mastitis (P = 0.05). Women who had used oral contraceptives (OC), compared with those who had not, were more likely to have antibodies; and this was most apparent among premenopausal women in whom 40.7% of OC users had antibodies compared with 26.7% of nonusers (P = 0.05). The proportion of women with antibodies was also higher for those who reported a bone fracture or osteoporosis after age 40 or within 20 years of their age at interview (36.0%) than in those who had not (33.0%) and 17.1% of women with fracture/osteoporosis had high antibody levels compared with 10.8% of women who had not (P = 0.03). Several types of pelvic/gynecologic surgery, including tubal sterilization, cervical conization, and cesarean section increased the likelihood of a positive antibody reaction and 47.2% of women who had more than one surgery had antibodies compared with 30.9% of women who never had pelvic surgery (P = 0.01). A surprising finding was that 38.1% of women who reported no use of cosmetic talc in hygiene had antibody compared with 28.6% of women who regularly used talc in genital hygiene (P = 0.04). The final entry shows the trend for elevated anti-MUC1 antibody levels by increasing number of antibody-promoting conditions. These included all variables significant in univariate analyses, such as OC use, bone fracture, mastitis, pelvic surgery, and genital talc use (where no use was considered the "condition") as well as variables of marginal significance in the univariate analysis, which nevertheless improved the overall model including current smoking and use of an intrauterine device (IUD). A significant trend (P =0.0005) in the likelihood of having antibodies was observed such that 24.2% of women who had zero or one of condition had antibodies compared with 51.4% of women who had experienced five or more of these conditions.

#### Figure 1

# Distribution of absorbances from anti-MUC1 antibody assay in cases with preoperative bloods and all controls

\* \* \*

# Table 1 Occurrence of anti-MUC1 antibodies in control women by epidemiologic variables

\* \* \*

Spearman (rank) correlations were calculated between the absorbance reading and several variables quantifiable on a numerical scale. No significant correlations were noted with number of live births, months of breast-feeding, or pack-years of smoking (data not shown). Weak but significant positive correlations were noted between absorbance values and months of OC use (r = 0.09, P = 0.02) and number of cesarean sections (r = 0.10, P = 0.02). A nonsignificant inverse correlation was noted between absorbance and estimated total applications of talc. When genital talc users were characterized by <weekly, weekly, and daily use, there was a trend of borderline significance (P = 0.11) for women using talc more frequently to have the lower antibody levels after adjustment for age, smoking, bone fractures, and OC or IUD use.

**Risk for Ovarian Cancer Associated with Antibody-Promoting Events**. The variables examined in relation to anti-MUC1 antibodies were then examined in relation to ovarian cancer risk, based upon case-control comparisons (Table 2). Odds ratios for ovarian cancer with each of these variables (except for age which was a matching variable) were calculated and adjusted for age, study site, exact parity, non-White race, and Jewish religion. Our study confirmed the influence of known ovarian cancer risk factors including parity, breast-feeding, and OC use. In addition, we identified previously unreported risk factors, including mastitis, relative risk (and 95% confidence limits) of 0.35 (0.16-0.77); IUD use, relative risk of 0.68 (0.50-0.91); and bone fracture, relative risk of 0.70 (0.530.91). The final entry shows the antibody-promoting association between number of conditions and ovarian cancer risk. Compared with women with zero or one condition, the risk for ovarian cancer decreased progressively with relative risks (and 95% confidence limits) of 0.69 (0.52-0.92), 0.64 (0.47-0.88), 0.49 (0.34-0.72), and 0.31 (0.16-0.61), respectively, for women with two, three, four, and five or more conditions (Ptrend <0.0001). This pattern mirrored the effect of these same conditions on the likelihood that control women had anti-MUC1 antibody (Fig. 2). Finally, risk by number of antibody-promoting conditions was examined separately for major histologic subtypes of ovarian cancer (Table 3). The inverse association was most evident for endometrioid cancers followed by undifferentiated and then invasive serous cancers. Numbers were too limited to make any definitive comments about predictors of antibodies among the 48 cases with preoperative bloods in whom anti-MUC1 antibodies were measured.

#### Discussion

To date, this is the largest study to examine determinants of anti-MUC1 antibodies and the first to show that conditions that generally increase the likelihood of having antibodies decrease the risk for ovarian cancer. MUC1 is normally present in a glycosylated, membrane-bound form on the apical surface of most polarized epithelial cells of the respiratory, genitourinary, and digestive tracts as well as breast ducts (12). With malignant transformation, epithelial cells lose polarity and overexpress MUC1 on their entire cell surface. A soluble, underglycosylated form circulates in cancer patients, thus becoming available for recognition by the immune system (6, 13). Some healthy women and men also have detectable MUC1 (albeit much lower levels) as well as anti-MUC1 antibodies. In women mostly ages 50 to 70 years, McGuckin et al. assessed the presence of circulating MUC1 using the cancer-associated serum antigen

assay. Cancer-associated serum antigen concentrations were elevated in smokers and increased progressively with age (14). In a sample of women from the same study, Richards et al. then measured anti-MUC1 antibodies and found that virtually all women less than age 40 had antibodies and this percentage declined with age (4), somewhat similar to the pattern we observed. It is well established that women have MUC1 and anti-MUC1 antibodies during pregnancy and breast-feeding, presumably due to changes within the breast or uterus that alter MUC1 expression, glycosylation, or shedding (4, 15, 16). In addition, Hinoda et al. observed antibodies specific for the peptide backbone of MUC1 in patients with ulcerative colitis and speculated that inflammation may change MUC1 glycosylation and enhance its immunogenicity (17). One difficulty in evaluating these studies is that assays both for MUC1 and anti-MUC1 antibodies may differ. In measuring antibodies, assays will vary by the specific epitope of MUC1 and the secondary immunoglobulin antibody used. The assay in our study is based on the peptide backbone of MUC1 that we believe is closer to tumor MUC1 and we assessed total immunoglobulin levels including all isotypes, IgG, IgM, and IgA.

In our data, anti-MUC1 antibodies were associated with events affecting the reproductive tract, whose epithelia heavily express MUC1 (18). Injury and/or inflammation of these tissues, surgery, and other events might allow enhancement of MUC1 expression, spillage into circulation, and presentation to the immune system. Thus, the mechanism by which tubal sterilization reduces ovarian cancer risk, previously attributed to preventing substances like talc or endometrial cells from reaching the ovaries (19, 20), may include production of protective antibodies. In our data, cervical conization involving injury and repair of endocervical tissue was also associated with a nonsignificant increase in antibody formation and decrease in risk for

ovarian cancer. Antibody formation was also directly correlated with number of cesarean sections, which involve incision and repair of the uterine wall and endometrium. Endometrial expression of MUC1 might also be affected by IUD use, as suggested by biopsies showing a low-grade, chronic inflammation with enhanced mucin staining (21). We found that IUD use increased the likelihood of antibodies in the "low"range and significantly decreased the risk for ovarian cancer. This is the first study to identify an inverse association between ovarian cancer and IUD use, whereas there is considerably more evidence that IUD use reduces risk for endometrial cancer (22), another tumor with high MUC1 expression (23).

An increased likelihood of MUC1-specific antibodies in the "high" range was found in women reporting bone fracture or a diagnosis of osteoporosis. Both conditions are known to be associated with high interleukin 6 levels (24, 25), an important regulatory cytokine for MUC1 expression (26). Furthermore, a bone fracture might be associated with release of hemato-poetic precursors into the circulation, some of which may express MUC1 and be immunogenic (27). We also found an inverse association between bone fracture/osteoporosis and ovarian cancer risk, which to our knowledge has not been shown previously. Interestingly, bone fracture is associated with reduced endometrial and breast cancer risk (28). Whereas this may simply reflect low estrogen, an influence of anti-MUC1 antibodies should also be considered. Besides bone fracture and IUD use, a third factor, which may link the etiology of ovarian and endometrial cancer, is smoking. A decreased risk for endometrial cancer is found in smokers, especially current smokers (29, 30). The data are less clear for ovarian cancer with two recent studies suggesting that smoking may increase the risk only for mucinous histologic subtypes (31, 32). Although current smoking was not clearly related to either anti-MUC1 antibody development or ovarian cancer

risk in our univariate analyses, it did improve the cumulative index models in Tables 1 and 2. Furthermore, McGuckin's observation that smokers have higher serum MUC1 levels (presumably from damaged lung epithelium) provides a basis for linking current smoking to anti-MUC1 antibody production (14).

#### Table 2

# Adjusted risk of ovarian cancer by epidemiologic variables in ovarian cancer cases and controls

\* \* \*

#### Figure 2

# Likelihood of anit-MUC1 antibodies by index of number of conditions and risk for ovarian cancer by same index

\* \* \*

OC use is a strong protective factor for ovarian (and endometrial) cancer and also seemed to generate anti-MUC1 antibodies, particularly among premenopausal women. CA15-3 (MUC1) levels in saliva were found to be 75% higher in OC users compared with nonusers, a nonsignificant difference in that small study (33). Other studies suggest that MUC1 expression in the endometrium is progesterone dependent (34) and up-regulated by exogenous progesterone (35). Considered together, these observations support the speculation that OC users may have higher MUC1 levels that could translate into higher antibody production.

History of mastitis was associated with both increased anti-MUC1 antibodies and decreased ovarian cancer risk in our study. We believe this is an important finding in light of our previous report of a long-term breast cancer survivor in whom MUC1-specific antibody production and mucinspecific T lymphocytes became elevated following mastitis in pregnancy (36). The lactating breast secretes a form of MUC1 that is similar to the underglycosylated form of MUC1 produced by tumors. Thus, mastitis may lead to a potent anti-MUC1 and antitumor immune response, which could explain the substantial decreased risk for ovarian cancer associated with mastitis found in our current study.

Curiously, we found that use of talc in the genital area was associated with significantly decreased levels of anti-MUC1 antibodies. Use of talc in the genital area would expose at least lower genital tract epithelia to talc and conceivably affect MUC1 expression in these tissues. In serial assays of pleural fluid in patients who received talc pleurodesis, inflammatory mediators eventually became depressed (37). Use of talc in the genital area has been consistently found to increase the risk for ovarian cancer in several meta-analyses (38-40). However, some investigators have challenged the association because of uncertainty about its biological basis and the absence of a dose-response relationship (38, 40). Although our present finding may also meet with skepticism, a testable hypothesis is now suggested by the possible link between genital talc exposure and systemic diminution of anti-MUC1 antibodies.

Existing theories of ovarian cancer pathogenesis have invoked incessant ovulation, gonadotropin excess, androgen excess, progesterone deficiency, or deleterious effects of inflammation to explain risk factors for ovarian cancer (41-44). Our findings offer an additional perspective on how OC use, tubal sterilization, and even talc use might exert their effects on ovarian cancer risk and suggests an entirely new set of protective factors such as mastitis, IUD use, and bone fracture that might be explained by the same immunemediated mechanism. Interestingly, this mechanism may also explain the decreased risk for ovarian cancer associated with mumps parotitis noted in older studies conducted before the widespread use of vaccination (45, 46). Analogous to mastitis, infection of MUC1-rich salivary glands might also lead to an anti-MUC1 immune response and antibody production. Clearly, we have not explained all features of ovarian cancer including the "dose-related" decrease in risk associated with multiple pregnancies and length of breastfeeding. Based on the studies reporting anti-MUC1 antibodies in women currently pregnant or breast-feeding, we had expected, but did not observe, that antibodies would increase with the more pregnancies a woman had or the longer she breast-fed. However, it should also be appreciated that anti-MUC1 antibodies are just one of several immuneeffecter mechanisms that may also include helper and cytotoxic MUC1-specific T cells that are generated by MUC1 presentation to the immune system. Indeed, the reactions described in sera and T cells from multiparous women suggest that a complete picture of the link between ovarian cancer risk and MUC1 immunity will require assessment of cell-mediated reactions. In addition, immunity to other human mucins, including MUC16 (CA 125), may also need to be examined.

The principal limitation of our study comes from its casecontrol design. Exposure information was collected by selfreport after the diagnosis in cases, introducing the possibility of misclassification. More importantly, we were unable to directly compare anti-MUC1 antibody levels in cases and controls and directly calculate odds ratios based on antibody levels because the cancer itself leads to production of antibodies. Consequently, assessing antibodies in cases after the diagnosis is not useful for identifying earlier events that influenced antibody generation or the predictive value of such antibodies. Prospective studies, in which blood samples are obtained decades or years before the development of ovarian cancer, will be necessary to assess directly the predictive value of anti-MUC1 antibodies on ovarian cancer risk. In addition, prospective studies before and after events like tubal sterilization, IUD use, mastitis, etc. that document the precise changes in the status of anti-MUC1 antibodies will refine our "cumulative index model" with its crude assumption that all events might be of equal potency in ability to generate antibodies. Thus, we make no claim this model is final but rather represents a simple foundation for a

paradigm shift that will incorporate MUC1 immunity as a key mechanism through which many risk factors for ovarian cancer may exert their influence.

#### Table 3

# Adjusted risk, 95% confidence intervals, and trends for ovarian cancer of different histologic types associated with number of conditions predisposing to MUC1 antibodies

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In summary, evidence from this case-control study of ovarian cancer suggests that events predicting the presence of anti-MUC1 antibodies are inversely associated with ovarian cancer risk and that the more conditions a woman experienced to raise antibodies the lower is her risk for ovarian cancer. We believe these data support the immune response as one mechanism of action of "traditional" ovarian cancer risk factors such as OC use and tubal sterilization, as well as novel ones observed in this study including mastitis, bone fracture, and IUD use. If, as we would like to propose, the immune response is a major mechanism, the implications are profound because it may eventually offer new avenues for ovarian cancer prevention through vaccines to stimulate immunity against MUC1 and perhaps other antigens expressed in ovarian cancer. Much work would need to be done, including prospective documentation of the precise changes in cell-mediated and humoral responses to MUC1 associated with pregnancy, breast-feeding, mastitis, and other events. Such studies may have implications beyond ovarian cancer and apply to other cancers with high MUC1 expression including endometrial and breast cancer.

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# References

- Ho SB, Niehans GA, Lyftogt C, et al. Heterogeneity of mucin gene expression in normal and neoplastic tissues. Cancer Res 1993;53:641–51.
- 2. Kotera Y, Fontenot JD, Pecher G, Metzgar RS, Finn OJ. Humoral immunity against a tandem repeat epitope of human mucin MUC-1 in sera from breast, pancreatic, and colon cancer patients. Cancer Res 1994;54:2856–60.
- 3. von Mensdorff-Pouilly S, Gourevitch MM, Kenemans P, et al. Humoral immune response to polymorphic epithelial mucin (MUC-1) in patients with benign and malignant breast tumours. Eur J Cancer 1996;32:1325 31.
- 4. Richards ER, Devine PL, Quin RJ, Fontenot JD, Ward BG, McGuckin MA. Antibodies reactive with the protein core of MUC1 mucin are present in ovarian cancer patients and healthy women. Cancer Immunol Immunother 1998;46:245 –52.
- 5. Hamanaka Y, Suehiro Y, Fukui M, Shikichi K, Imai K, Hinoda Y. Circulating anti-MUC1 IgG antibodies as a favorable prognostic factor for pancreatic cancer. Int J Cancer 2003;103:97–100.
- 6. Vlad AD, Kettel JC, Alajez NM, Carlos CA, Finn OJ. MUC1 immunobiology: from discovery to clinical applications. Adv Immunol 2004;82:249–93.
- Agrawal B, Reddish MA, Krantz MJ, Longenecker BM. Does pregnancy immunize against breast cancer? Cancer Res 1995;55:2257–61.
- Janerich DT. The influence of pregnancy on breast cancer risk: is it endocrinological or immunological? Med Hypotheses 1980;6:1149 –55.
- 9. Forsman LM, Jouppila PI, Andersson LC. Sera from multiparous women contain antibodies mediating

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cytotoxicity against breast carcinoma cells. Scand J Immunol 1984;19:135–9.

- Shields LB, Gercel-Taylor C, Yashar CM, et al. Induction of immune responses to ovarian tumor antigens by multiparity. J Soc Gynecol Investig 1997;4:298–304.
- 11. Agrawal B, Reddish MA, Longenecker BM. *In vitro* induction of MUC-1 peptide-specific type 1 T lymphocyte and cytotoxic T lymphocyte responses from healthy multiparous donors. J Immunol 1996;157:2089–95.
- 12. Gendler SJ, Spicer AP. Epithelial mucin genes. Annu Rev Physiol 1995;57: 607–34.
- 13. Fontenot JD, Mariappan SV, Catasti P, Domenech N, Finn OJ, Gupta G. Structure of a tumor associated antigen containing a tandemly repeated immunodominance epitope. J Biomol Struct Dyn 1995;3:245–60.
- McGuckin MA, Ramm LE, Joy GJ, Devine PL, Ward BG. Circulating tumor associated mucin concentrations determined by the CASA assay in healthy women. Clin Chim Acta 1993;214:139–51.
- Bon GG, Kenemans P, Verstraeten AA, et al. Maternal serum Ca125 and Ca 15-3 antigen levels in normal and pathological pregnancy. Fetal Diagn Ther 2001;16:166 –72.
- 16. Croce MV, Isla-Larrain MT, Price MR, Segal-Eiras A. Detection of circulating mammary mucin (Muc1) and MUC1 immune complexes (Muc1-CIC) in healthy women. Int J Biol Markers 2001;16:112 –20.
- 17. Hinoda Y, Nakagawa N, Nakamura H, et al. Detection of a circulating antibody against a peptide epitope on a mucin core protein, MUC1, in ulcerative colitis. Immunol Lett 1993;35:163 –8.

- 18. Gipson IK, Ho SB, Spurr-Michaud SJ, et al. Mucin genes expressed by human female reproductive tract epithelia. Biol Reprod 1997;56:999 –1011.
- 19. Hankinson SE, Hunter DJ, Colditz GA. Tubal ligation, hysterectomy, and risk of ovarian cancer. JAMA 1993;270:2813 –8.
- 20. Green A, Purdie PD, Bain C, et al. Tubal sterilization, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. Int J Cancer 1997;71:948–51.
- 21. Hester LL Jr, Kellett WW III, Spicer SS, Williamson HO, Pratt-Thomas HR. Effects of the intrauterine contraceptive device on endometrial enzyme and carbohydrate histochemistry. Am J Obstet Gynecol 1970;106:1144–54.
- 22. Hubacher D, Grimes DA. Noncontraceptive health benefits of intrauterine devices: a systematic review. Obstet Gynecol Surv 2002;57:120 –8.
- Sivridis E, Giatromanolaki A, Koukourakis MI, Georgiou L, Anastasiadis P. Patterns of episialin/MUC1 expression in endometrial carcinomas and prognostic relevance. Histopathology 2002;40:92 – 100.
- Papadopoulos NG, Georganas K, Skoutellas V, Konstantellos E, Lyritis GP. Correlation of interueukin-6 serum levels with bone density in postmenopausal women. Clin Rheumatol 1997;16:162–5.
- Strecker W, Gebhard F, Rager J, Bruckner UB, Steinbach G, Kinzl L. Early biochemical characterization of soft-tissue trauma and fracture trauma. J Trauma Injury Infect Crit Care 1999;47:358– 64.
- 26. Gaemers IC, Vox HL, Volders HH, van der Valk SW, Hilkens J. A stat-responsive element in the promoter of

the episialin/MUC1 gene is involved in its overexpression in carcinoma cells. J Biol Chem 2001;276:6191–9.

- 27. Brugger W, Buhring HJ, Grunebach F, et al. Expression of MUC-1 epitopes on normal bone marrow: implications for the detection of micrometastatic tumor cells. J Clin Oncol 1999;17:1535–44.
- 28. Newcomb PA, Trentham-Dietz A, Egan KM, et al. Fracture history and risk of breast and endometrial cancer. Am J Epidemiol 2001;153:1071 –8.
- 29. Terry PD, Miller AB, Rohan TE. A prospective cohort study of cigarette smoking and the risk of endometrial cancer. Br J Cancer 2002;86:1430 –5.
- Brinton LA, Barrett RJ, Berman ML, Mortel R, Twiggs LB, Wilbanks GD. Cigarette smoking and the risk of endometrial cancer. Am J Epidemiol 1993; 137:281– 91.
- 31. Pan SY, Ugnat AM, Mao Y, Wen SW, Johnson KC. Association of cigarette smoking and the risk of ovarian cancer. Int J Cancer 2004;111:124 –30.
- Zhang Y, Coogan PF, Palmer JR, Strom BL, Rosenberg L. Cigarette smoking and increased risk of mucinous epithelial ovarian cancer. Am J Epidemiol 2004;159:33 –9.
- McIntyre R, Bigler L, Dellinger T, Pfeifer M, Mannery T, Stredkfus C. Oral contraceptive usage and the expression of CA 15-3 and c-erB-2 in the saliva of healthy women. Oral Surg Med Pathol Radiol Endod 1999;88: 687–90.
- 34. Hild-Petito S, Fazleabas AT, Julian J, Carson DD. Mucin (Muc-1) expression is differentially regulated in uterine luminal and glandular epithelia of the baboon (*Papio anubis*). Biol Reprod 1993;54:939–47.

- 35. Hewetson A, Chilton BS. Molecular cloning and hormone-dependent expression of rabbit Muc1 and the cervix and uterus. Biol Reprod 1997; 57:468–77.
- Jerome KR, Kir AD, Pecher G, Ferguson WW, Finn OJ. A survivor of breast cancer with immunity to MUC-1 mucin, and lactational mastitis. Cancer Immunol Immunother 1997;43:355–60.
- 37. D'Agostino P, Camemi AR, Arcoleo F, et al. Matrix metalloproteinases production in malignant pleural effusions after talc pleuodesis. Clin Exp Immunol 2003;34:138–42.
- 38. Gross AJ, Berg PH. A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer. J Expo Anal Environ Epidemiol 1995;5:181–95.
- Cramer DW, Liberman RF, Titus-Ernstoff L, et al. Genital talc exposure and risk of ovarian cancer. Int J Cancer 1999;81:351–6.
- 40. Huncharek M, Gerschwind JF, Kupelnick B. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. Anticancer Res 2003; 23:1955–60.
- 41. Fathalla MF. Incessant ovulation: a factor in ovarian neoplasia? Lancet 1971; 2:163.
- 42. Cramer DE, Welch WR. Determinants of ovarian cancer risk. II. Inference regarding pathogenesis. Natl Cancer Inst 1983;1:717–21.
- 43. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. J Natl Cancer Inst 1999;91:1459–67.
- 44. Risch HA. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of

androgens and progesterone. J Natl Cancer Inst 1998; 90:1774-86.

- 45. West RD. Epidemiologic study of malignancies of the ovaries. Cancer 1966; 19:1001.
- 46. Newhouse ML, Pearson RM, Fullerton JM, Boesen EA, Shannon HS. A case control study of carcinoma of the ovary. Br J Prev Soc Med 1977;31: 148–53.

# **APPENDIX AA**

# INTRAUTERINE DEVICE USE, CERVICAL INFECTION WITH HUMAN PAPILLOMAVIRUS, AND RISK OF CERVICAL CANCER: A POOLED ANALYSIS OF 26 EPIDEMIOLOGICAL STUDIES

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# Summary

**Background** Intrauterine device (IUD) use has been shown to reduce the risk of endometrial cancer, but little is known about its association with cervical cancer risk. We assessed whether IUD use affects cervical human papillomavirus (HPV) infection and the risk of developing cervical cancer.

Methods We did a pooled analysis of individual data from two large studies by the International Agency for Research on Cancer and Institut Catala d'Oncologia research programme on HPV and cervical cancer; one study induded data from ten case-control studies of cervical cancer done in eight countries, and the other induded data from 16 HPV prevalence surveys of women from the general population in 14 countries. 2205 women with cervical cancer and 2214 matched control women without cervical cancer were induded from the case—control studies, and 15 272 healthy women from the HPV surveys. Information on IUD use was obtained by personal interview. HPV DNA was tested by PCR-based assays. Odds ratios and 95% CIs were estimated using multivariate unconditional logistic regression for the associations between IUD use, cervical HPV DNA, and cervical cancer.

**Findings** After adjusting for relevant covariates, induding cervical HPV DNA and number of previous Papanicolaou smears, a strong inverse association was found between ever use of IUDs and cervical cancer (odds ratio 0.55, 95% CI 0.42-0.70; p<0.0001). A protective association was noted for squamous-cell carcinoma (0.56, 0.43-0.72; p<0.0001), adenocarcinoma and adenosquamous carcinoma (0.46, 0.22-0.97; p=0.035), but not among HPV-positive women (0.68,0.44-1.06; p=0.11). No association was found between IUD use and detection of cervical HPV DNA among women without cervical cancer.

**Interpretation** Our data suggest that IUD use might act as a protective cofactor in cervical carcinogenesis. Cellular

immunity triggered by the device might be one of several mechanisms that could explain our findings.

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# Introduction

Epidemiological studies have consistently shown that intrauterine device (IUD) use reduces the risk of endometrial cancer.<sup>1-4</sup> However, the question of whether IUDs might also affect the risk of cervical cancer remains unanswered. Clinical and epidemiological studies done in several countries have reported inconsistent results,<sup>3,5,6</sup> and none of these studies accounted for human papillomavirus (HPV) status in their analyses. Since HPV is now firmly established as the cause of cervical cancer, HPV should be considered when exploring the potential effects of IUD use on cervical cancer risk, and the association between IU exposure and cervical HPV infection should be assessed.

During the past 20 years, the International Agency for Research on Cancer (IARC; Lyon, France), in collaboration with the Institut Català d'Oncologia (ICO; Barcelona, Spain), has done several large epidemiological studies on HPV and cervical cancer in different countries. We analysed pooled individual data from the IAR programme to explore the potential effects of IUD use on the risk of cervical HPV infection in healthy women, and on the risk of developing cervical cancer.

# Methods

#### Patients

Women included in these analyses were recruited from two large series by the IARC and ICO programmes on HPV and cervical cancer: a series of HPV prevalence surveys, and a series of case-control studies of HPV and cervical cancer.

#### Procedures

A series of population-based HPV prevalence surveys was done by IARC in 15 areas in four continents between 1993 and 2007. Methods of population sampling have been described previously for the individual areas: Hanoi and Ho Chi Minh City, Vietnam; Lampang and Songkla, Thailand; South Korea; Shanxi, Shenzhen, and Shenyang, China; Mongolia; Mexico; Argentina; Colombia; Chile; Nigeria; Spain; and Poland.<sup>7-2</sup>° Briefly, in each area an attempt was made to obtain a random age-stratified sample of the population that induded at least 100 women in each 5-year age group, from 15-19 years to 65 years and older. Participation ranged from 48% in Songkla, Thailand, to 96% in Colombia. Trained interviewers questioned study participants face-to-face with a standardised questionnaire that induded information on IUD use and duration. Study participants had a pelvic examination during which samples of exfoliated cells from the cervix were obtained for cytology and HPV testing. All participants gave written informed consent according to the recommendations of IARC and the local ethical review committees.

# Table 1Characteristics of Participants Included in IARC HPV<br/>Surveys, by HPV Status

\* \* \*

From 1985 to 1997, 13 case-control studies of cervical cancer were done in 11 countries with a broad range in the incidence of cervical cancer. Regions covered induded Africa (Algeria, Morocco, and Mali), South America (Brazil,

Paraguay, Peru, and Colombia), southeast Asia (India, Thailand, and the Philippines), and Europe  $(Spain)2^{1-28}$ Studies from Brazil, Paraguay, and Mali were exduded from the pooled analyses because they did not contribute information on IUD use. Case patients were women with incident, histologically confirmed, invasive squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix. Control patients were hospital-based or clinicbased and were frequency matched to case patients by 5-year age groups, in all studies except in Colombia and Spain, where random population-based controls were used for the invasive cervical cancer cases. All study participants were interviewed using a standardised questionnaire to elicit information on potential risk factors for cervical cancer, including IUD use and duration. All women had a pelvic examination and two cervical scrapes were obtained for cytology and HPV-DNA detection. A tumour biopsy was also taken from case patients and kept frozen. All protocols were approved by IARC and local ethics committees. All participants gave written informed consent.

The detailed protocol for detection of HPV DNA by PCR in cervical specimens obtained in the case-control studies has already been published.<sup>21-28</sup> Briefly, L1 consensus primers MY09-MY11, as modified by Hildesheim and colleagues,<sup>29</sup> were used in the Colombia and Spain studies, and GPS+/6+ general primers in the remaining studies. PCR products were assessed for HPV positivity using a cocktail of HPV-specific probes and were further genotyped by hybridisation of the PCR products with type-specific probes for 33 HPV types.<sup>30,31</sup>

For all HPV surveys, apart from the one in Mexico, cervical cells were tested with general GPS+/6+ primermediated PCR.<sup>30</sup> PCR products were tested using lowstringency Southern blot analysis of PCR products with a cocktail probe of HPV-specific DNA fragments. Typing of samples positive for HPV was done by enzyme immunoassay or reverse line-blot analysis of GPS+/6+ PCR products using HPV type-specific oligoprobes for 36 HPV types.<sup>30,32</sup> The oligoprobe cocktail was extended to indude HPV types 30, 32, 64, 67, 69, cand85, 86, and JC9710 in the most recent HPV surveys done in Chile, Poland, Mongolia, and China (Shanxi, Shenzhen, and Shenyang). HPV testing and genotyping of samples collected in the Mexican HPV survey was done as previously described,<sup>14</sup> using biotinylated MY09/11 consensus primers and a single-hybridisation, reverse line-blot detection method.<sup>33</sup>

### Figure 1

# Adjusted odds ratios\* for the association between IUD use and cervical HPV-DNA detection in IARC HPV prevalence surveys.

\* \* \*

# **Statistical analysis**

Unconditional logistic regression models were used to estimate odds ratios (ORs) and 95% CIs for associations between IUD use and both cervical HPV and cervical cancer. We did three analyses. The main analysis explored the association between IUD use and cervical cancer risk overall, by country, histology, years of use, and categories of reproductive and behavioural covariates possibly related to cervical cancer risk. We also estimated the association between IUD use and cervical HPV DNA among control women enrolled in the case-control study. Finally, we explored the association between IUD use and cervical HPV DNA among women enrolled in the HPV prevalence surveys.

Unless otherwise specified, all logistic regression models using the case-control data were adjusted by study area, age in tertiles (18-42, 43-53,  $\geq$ 54 years), years of schooling in quartiles (0, 1-4, 5-9,  $\geq$ 10), age at first sexual intercourse in quartiles ( $\geq$ 23, 20-22, 18-19,  $\geq$ 17 years), number of previous screening Pap smears the woman had until 12 months before

enrolment in the study  $(0, 2-5, \ge 6)$ , and cervical HPV-DNA status. Logistic regression models using data from the HPV prevalence surveys were adjusted for study area, age group ( $\le 24, 25-34, 35-44, 45-54, \ge 55$  years), years of schooling (0, 1-5, 6-10,  $\ge 11$ ), lifetime number of sexual partners (0-1, 2,  $\ge 3$ ) and Pap history (number of Paps unless otherwise specified: 0, 1, 2-4, .5). Heterogeneity in OR between study areas was tested using the likelihood ratio test for interaction between the study area and exposure of interest.

Statistical analyses were done with SAS version 9.2 and the computing environment R, version 2.12.0. Graphs were created using the plot.meta function of the R software.

# Figure 2 Adjusted odds ratios\* for the association between IUD use and cervical cancer in IARC case-control studies.

\* \* \*

#### **Role of the funding source**

The funding institutions of the studies included in this pooled analysis had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; in the writing, review, and approval of the manuscript; or in the decision to submit the report for publication. The corresponding author had full access to all the data and the final responsibility to submit for publication.

# Results

Table 1 summarises the main characteristics of participants recruited from the IARC HPV prevalence surveys, according to HPV status, and table 2 summarises characteristics of participants recruited from the IARC case-control studies, according to cervical cancer status.

The original series of HPV prevalence surveys induded 13 924 HPV-negative and 2556 HPV-positive women from 16 studies, of whom 745 (5.4%) and 463 (18.1%), respectively,

were exduded because of missing information on IUD use. A total of 13 179 HPV-negative and 2093 HPV-positive women were induded in the final pooled analysis. Compared with HPV-negative women, women who tested positive for HPV were younger, had a lower educational level, fewer pregnancies, fewer screening Pap smears, more sexual partners, more exposure to cigarette smoking, and an earlier age at sexual debut. Overall, 4.7% (721 of 15 272) of the recruited women had an abnormal result in the cytological sample obtained for the study, ranging from 0.7% (seven of 994) in Hanoi, Vietnam, to 13.1% (127 of 969) in Mongolia (data not shown).

#### Figure 3

# Adjusted odds ratios\* for the association between IUD use and cervical cancer, by years of use in IARC casecontrol studies.

\* \* \*

The original series of case-control studies included 2905 cases and 2906 controls from 11 studies. Women from Brazil, Mali, and Paraguay were excluded because they did not contribute information on IUD use, leaving 2508 cases and 2483 controls. A total of 2205 cases with cervical cancer and 2214 control women with information on IUD use were included in the final pooled analysis.

#### Figure 4

# Adjusted odds ratios\* for the association between IUD use and cervical cancer, by strata of selected variables in IARC case-control studies

\* \* \*

The percentage of women with unknown IUD use status was similar between cases and controls (12.1% [303 of 2508] *vs* 10.8% [269 of 2483]). By contrast, the percentage of women with unknown IUD use was somewhat higher among HPV-positive than among HPV-negative women (14.4% [301 of 2094] vs 9.7% [182 of 1882]), although the

corresponding 95% CIs greatly overlapped (webappendix p 2). Women with cervical cancer were more likely than control women to be single, divorced, or widowed, to have a lower educational level, more pregnancies, higher number of lifetime sexual partners, fewer screening Pap smears, and a younger age of sexual debut.

The potential effect of IUD use on cervical HPV infection was assessed in two groups: among control women recruited in the case-control studies and among women recruited in the HPV prevalence surveys. No association was found between IUD use and cervical HPV-DNA detection among control women in the case-control studies (OR 0.95, 95% CI 0.64-1.39); webappendix p 4 shows the ORs by country and years of IUD use. Further analyses stratified by potential risk factors and cofactors did not show any relevant associations across subgroups of age, education, menopausal status, number of sexual partners, number of pregnancies, use of hormonal oral contraception, and number of previous screening Pap smears within 12 months before study enrolment (data not shown).

Figure 1 shows the ORs for the association between IUD use and cervical HPV-DNA detection in the IARC HPV prevalence surveys, overall, and by study area and years of use. Although there is some significant heterogeneity between studies, none of the 16 surveys yielded a significant association between IUD use and cervical HPV. The overall combined adjusted OR was very dose to unity and not significant (OR 0.96, 95% CI 0.85-1.08; p=0.47). As shown in figure 1, years of IUD use was not associated with risk of cervical HPV. Further analyses stratified by selected characteristics did not show any significant associations in any of the subgroups explored (data not shown).

The potential effect of IUD use on cervical cancer risk was assessed in women enrolled in the case-control studies. Figure 2 shows data on IUD prevalence and ORs for cervical cancer overall, by country, and by cancer histology. The

combined prevalence of IUD use was 13.0% among women with cervical cancer and 22.5% among control women. Inverse associations between IUD use and cervical cancer risk were found for all study areas except Morocco. Inverse associations were dearly or borderline significant, apart from in Thailand, the Philippines, and India. After adjusting for relevant covariates, a strong and significant inverse association was found between ever use of an IUD and cervical cancer risk for all cervical cancers combined (OR 0.55, 95% CI 0.42-0.70; p<0.0001), and for each of the two histological groups: squamous-cell carcinoma (OR 0.56, 0.43-0.72; p<0.0001) and combined adenocarcinoma and adenosquamous carcinomas (OR 0.46, 0.22-0.97; p=0.035; These estimates were not substantially altered figure 2). when adjusting for finer age categories (ie, 18-24,35-42, 43-53, z54 years) instead of tertiles (data not sown).

Figure 3 shows the relationship between years of IUD use and cervical cancer. Compared with never users, the risk was reduced nearly by half in the first year of use (OR 0.53, 95% CI 0.27-1.02) and was maintained with longer durations of use. The formal test for linear trend with years of use was not significant (p=0.69).

To address further the potential effect of residual confounding we did a stratified analysis to assess the association between IUD use and cervical cancer risk within subcategories of selected covariates known to be potential confounders or cofactors in cervical carcinogenesis. These stratified analyses showed a consistent inverse association between cervical cancer and IUD use within each category of age, education, marital status, number of screening Paps, number of sexual partners, parity (except in nulliparous women), among premenopausal (but not postmenopausal) women, and in HPV-positive women (figure 4). The ORs in the younger age categories were 0.16 (95% CI 0.02-1.12) and 0.51 (0.51-0.37) for the 18-24 and 25-42 years age groups, respectively. The OR among HPV-negative women (0.44;

0.26-0.74) was similar to that among HPV-positive women (0.68; 0.44-1.06) and to that among women with unknown HPV status (0.46; 0.30-0.69). An inverse association was also seen among ever users (0.62, 0.39-0.98) and never users of oral contraceptives (0.50; 0.29-0.84), and among shortterm (<2 years) users (0.79, 0.29-2.16) and long-term (<10years) users of oral contraceptives (0.23, 0.09-0.62; webappendix table 2). The percentage of oral contraceptive users was somewhat higher among IUD users than in nonusers, in cases (71.0% [191 of 269] vs 50.6% [736 of 1455], respectively) and in controls (66.4% [303 of 456] vs 49.8% [629 of 1262], respectively; webappendix p 3). Finally, condom use did not modify the inverse association found between IUD use and cervical cancer risk, among women who never or rarely used condoms (0.59, 0.44-0.79), and among women who regularly or always used condoms (0.55,0.29-1.05; p for interaction 0.76).

# Discussion

Several studies show that contraceptive methods such as oral contraceptives and condom use can affect the risk of cancer<sup>34,35</sup> infection.<sup>36</sup> cervical and cervical HPV respectively. Use of contraceptive IUDs has consistently been shown to reduce the risk of endometrial cancer;" however, little is known about the potential effects of IUD use on the risk of developing cervical cancer or cervical HPV To our knowledge, this is the first large infection. epidemiological study, with almost 20000 women induded, to explore such potential associations taking into account cervical HPV status and Pap screening history.

We found a strong and consistent inverse association between IUD use and cervical cancer risk; women who reported previous IUD use had half the risk of developing cervical cancer compared with women with no history of IUD use. An inverse association was detected for the two major cervical cancer histological types, squamous-cell carcinoma and adenocarcinoma or adenosquamous carcinoma, as well as in most of the subgroups explored, although many were not significant. The lack of association among postmenopausal women is puzzling, but might be due to the fact that IUD exposure history was low: less than 10% of postmenopausal women reported having ever used an IUD. They were also substantially older and with a lower parity than the premenopausal women (data not shown).

The inverse association between IUD use and cervical cancer risk was not significantly affected by duration of use: an association was found within 1 year of use and it remained significant even after 10 years of use, but did not significantly increase or wane with increasing years of use. By contrast, neither the analysis among the 2214 control women from the case—control studies nor among the 15 272 women recruited in the international HPV surveys identified an association between IUD status or years of use and cervical HPV infection, as assessed by PCR methods. The lack of association between IUD use and cervical HPV was generally consistent across studies and among the covariates explored (data not shown).

Although the hypothesis that IUD use might promote cervical cancer has been considered since the introduction of these devices in 1930s, studies are inconclusive. A large multicentre case—control study in the USA found a non-significant reduced risk of cervical cancer associated with copper IUD use (adjusted OR 0.6, 95% CI 0.3-1.2), but almost no effect was found for the inert IUD (1.1; 0.9-1.7). Decreased risk with increased duration of copper IUD use supported a possible protective effect for copper IUDs on development of invasive cervical cancer.' By contrast, a 2007 review that included four case—control studies did not find an association between IUD use and cervical cancer risk.<sup>3</sup>

Overall, the associations found in our study strongly suggest that IUD use does not modify the likelihood of prevalent HPV infection, but might affect the likelihood of HPV progression to cervical cancer. Thus, IUD use could possibly be regarded as a protective cofactor in cervical carcinogenesis. One of the mechanisms by which IUDs might exert this protective effect is through the induction of a reactive, chronic, low-grade, sterile inflammatory response in the endometrium, endocervical canal, and cervix that could modify, via changes in the local mucosal immune status, the course of HPV infections. Microscopic observation of typical cellular changes in the cervices of IUD users support this theory?' It is possible that these IUD-related subjacent mechanisms induce an immune deviation with a Th1 type of biased immune response, which might affect IUD users' risk of HPV persistence, progression to cervical cancer, or both. Also, for hormonal IUDs, release of progestins or progesterone into the uterus might affect the natural history of HPV infection. Unfortunately, information on IUD type was not obtained in any of the studies, preduding our assessment of the effect of copper IUDs and hormonereleasing IUDs on cervical cancer risk or cervical HPV DNA.

Alternatively, it can be postulated that the local trauma to the cervical tissue associated with insertion or removal of the device induces local small foci of chronic inflammation and a long lasting immune response similar to that noted in patients after colposcopically guided punch biopsies. This alternative hypothesis would explain better the immediate protective effect found for short-term users, and the observation that there was no difference in the protective effect by years of IUD use.

Another possible explanation for the protective effect of IUDs against cervical cancer is elimination of preinvasive cervical lesions when the device is inserted or removed. This hypothesis would help explain the lack of effect with duration of IUD use. More importantly, removal of preinvasive cervical lesions is compatible with some of our subgroup findings—ie, the strongest protective effect was in women 37-45 years, among whom preinvasive cervical lesions might have already accumulated in inadequately screened populations but not yet progressed to invasive cancer. These possible mechanisms are speculative and provocative, but emphasise our limited knowledge and the need for other study designs to explore the underlying mechanisms by which IUDs might exert a protective effect on cervical cancer risk.

We also attempted to assess whether the protective effect on cervical cancer risk was driven by reduced persistent infection, as opposed to reduced progression to cervical intraepithelial neoplasia. We assumed that, by contrast with younger women, a substantial proportion of HPV infections detected in older women were more likely to be persistent rather than transient. If IUDs reduce the persistence of HPV, we should find a larger inverse association in older than in younger women. However, our analysis showed that the OR for association between IUD use and cervical HPV infection was exactly the same in women younger (OR 0.99, 95% CI 0 83-1.19) and older (OR 0.95, 0.81-1.11) than 35 years.

An important challenge in interpreting these results is to assess the possible effect of screening bias, induced by IUD use, on explaining the inverse association with cervical cancer risk. Insertion, follow-up, and removal of IUDs are often done in adult, parous women. In developed countries, these procedures involve several visits to the gynaecologist, providing many opportunities for these women to be directly diagnosed or screened for cervical cancer, through visual identification or repeated cervical cytology. Therefore, the reduced risk of cervical cancer seen in IUD users might not be due to the biological effect of the device, but rather to the higher likelihood of more intensive cervical screening or diagnosis in these women compared with non-users. To address whether IUD-induced screening bias had a confounding effect on the observed results, we estimated associations by specific strata of number of previous Pap smears women had until 12 months before diagnosis or study entry. As shown in figure 4, an inverse association was consistent among women who never had a screening Pap smear (OR 0.62), and those who had one (OR 0.64), two to five (OR 0.45), and six or more Pap smears (OR 0.48). Thus, history of previous Pap smears did not significantly affect the observed inverse association between IUD use and risk of cervical cancer. Furthermore, since most of the populations included in these analyses are from developing areas of the world, where screening is opportunistic and has little effect in preventing cervical cancer, it is unlikely that screening bias would explain the observed inverse association.

Finally, information bias regarding self-reporting of IUD use and other covariates might also have had a confounding role in the observed associations. This bias is inherent to all epidemiological studies that rely on data collected through a questionnaire or interview. However, since the hypothesis that IUD use might affect HPV infection or cervical cancer risk was unknown to all study participants, it is unlikely that IUD-use misclassification was differential with regard to case-control status or HPV status, the latter being impossible because HPV status was unknown to the participants and interviewers. It is well established that nondifferential misclassification of the exposure of interest (ie, IUD use) can attenuate the real OR, but it can never artificially increase it. Thus, the most likely effect of this potential bias on our study would be an underestimation of the true underlying effect.

In conclusion, our data suggest that use of IUDs substantially reduces the risk of cervical cancer and that this effect does not seem to be due to differences in screening histories between users and non-users. By contrast, IUD use is not associated with risk of cervical HPV infection, suggesting that the presence of the device does not affect HPV acquisition and detection in the exfoliated cells of the

We postulated that repeated microtrauma and cervix. subsequent chronic mucosal inflammation processes induced by the device might be the underlying mechanism through which IUDs can reduce the risk of cervical HPV progression, consequently reducing the risk of cervical cancer. Alternatively, even though our stratified analyses do not support this possibility, we cannot totally rule out the potential effects of residual confounding, and screening and diagnosis bias. In view of the wide use of IUDs worldwide. women, gynaecologists, and reproductive-health professionals can be reassured that IUDs do not seem to increase the risk of cervical HPV infection; and our study contributes solid evidence that IUD use might even reduce the risk of developing cervical cancer.

# Contributors

XC, NM, SdS, RH, SF, CJLMM, and FXB were responsible for the conception, design, and supervision of the study. NM, SS, RH, SF, CJLMM, and FXB were responsible for data acquisition and obtaining funding. XC drafted the report. XC, MD, and SV did the statistical analysis. All authors analysed and interpreted data, revised the report, and provided administrative, technical, and material support.

# **Conflicts of interest**

We declare that we have no conflicts of interest.

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# References

- 1 Beining RM, Dennis LK, Smith EM, Dokras A. Metaanalysis of intrauterine device use and risk of endometrial cancer. *Ann Epidemid* 2008; **18**: 492-99.
- 2 Castellsague X, Thompson WD, Dubrow R Intrauterine contraception and the risk of endometrial cancer. *Int J Cancer* 1993; **54:** 911-16.
- 3 Curtis KM, Marchbanks PA, Peterson HB. Neoplasia with use of intrauterine devices. *Contraception* 2007; 75 (suppl 6): 60-69.
- 4 Hubacher D, Grimes DA. Noncontraceptive health benefits of intrauterine devices: a systematic review. *Obstet Gynecoi Surv* 2002; 57: 120-28.
- 5 Lassise DL, Savitz DA, Hamman RF, Baron AE, Brinton LA, Levines RS. Invasive cervical cancer and intrauterine device use. *Intl Epidemiol* 1991; **20:** 865-70.
- 6 Castellsague X, Diaz M, de Sanjose S, et al. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. *J Natl Cancer Inst* 2006; **98**: 303-15.
- 7 Pham TH, Nguyen TH, Herrero R, et al. Human papillomavirus infection among women in South and North *Vietnam*. *Int J Cancer* 2003; **104:** 213-20.
- 8 Sukvirach S, Smith JS, Tunsakul S, et al. Populationbased human papillomavirus prevalence in Lampang and Songkla, Thailand. *J Infect Dis* 2003; **187**: 1246-56.

- 9 Shin HR, Lee DH, Herrero R, et aL Prevalence of human papillomavirus infection in women in Busan, South Korea. *Int J Cancer* 2003; **103**: 413-21.
- 10 Dai M, Bao YP, Li N, et aL Human papillomavirus infection in Shanxi Province, People's Republic of China: a population-based study. *Br J Cancer* 2006; 95: 96-101.
- 11 Wu RF, Dai M, Qiao YL, et al. Human papillomavirus infection in women in Shenzhen City, People's Republic of China, a population typical of recent Chinese urbanisation. *Int J Cancer* 2007; **121:** 1306-11.
- 12 Li LK, Dai M, Clifford GM, et al. Human papillomavirus infection in Shenyang City, People's Republic of China: a population-based study. *Br J Cancer* 2006; **95:** 1593-97.
- 13 Dondog B, Clifford GM, Vaccarella S, et al. Human papillomavirus infection in Ulaanbaatar, Mongolia: a population-based study. *Cancer Epiclemiol Biomarkers Prev* 2008; **17**: 1731-38.
- 14 Lazcano-Ponce E, Herrero R, Munoz N, et al. Epidemiology of HPV infection among Mexican women with normal cervical cytology. *Int J Cancer* 2001; **91:** 412-20.
- 15 Maths E, Loria D, Amestoy GM, et al. Prevalence of human papillomavirus infection among women in Concordia, Argentina: a population-based study. Sex Transm Dis 2003; 30: 593-99.
- 16 Molano M, Posso H, Weiderpass E, et al. Prevalence and determinants of HPV infection among Colombian women with normal cytology. *Br J Cancer* 2002; **87**: 324-33.
- 17 Ferreccio C, Prado RB, Luzoro AV, et al. Populationbased prevalence and age distribution of human papillomavirus among women in Santiago, Chile.

Cancer Epiclemiol Biomarkers Prev 2004; 13: 2271-76.

- 18 Thomas JO, Herrero R, Omigbodun AA, et aL Prevalence of papillomavirus infection in women in Ibadan, Nigeria: a population-based study. *Br J Cancer* 2004; 90: 638-45.
- de Sanjose S, Ahnirall R, Lloveras B, et al. Cervical human papillomavirus infection in the female population in Barcelona, Spain. *Sex Transm Dis* 2003; 30: 788-93.
- 20 Bardin A, Vaccarella S, Clifford GM, et al. Human papillomavirus infection in women with and without cervical cancer in Warsaw, Poland. *Eur J Cancer* 2008; 44: 557-64.
- 21 Hammouda D, Munoz N, Herrero R, et al. Cervical carcinoma in Algiers, Algeria: human papillomavirus and lifestyle risk factors. *Int J Cancer* 2005; **113:** 483-89.
- 22 Chaouki N, Bosch FX, Munoz N, et al. The viral origin of cervical cancer in Rabat, Morocco. *Int J Cancer* 1998; **75:** 546-54.
- 23 Bosch FX, Munoz N, de Sanjose S, et aL Human papillomavirus and cervical intraepithelial neoplasia grade III/carcinoma in situ: a case-control study in Spain and Colombia. *Cancer Epiclemiol Biomarkers Prev* 1993; **2**: 415-22.
- 24 Munoz N, Bosch FX, de Sanjose S, et al. The causal link between human papillomavirus and invasive cervical cancer: a population-based case-control study in Colombia and Spain. *Int J Cancer* 1992; **52**: 743-49.
- 25 Bosch FX, Munoz N, de Sanjose S, et al. Risk factors for cervical cancer in Colombia and Spain. *Int J Cancer* 1992; **52:** 750-58.

- 26 Franceschi S, Rajkumar T, Vaccarella S, et al. Human papillomavirus and risk factors for cervical cancer in Chennai, India: a case-control study. *Int J Cancer* 2003; **107:** 127-33.
- 27 Chichareon S, Herrero R, Munoz N, et al. Risk factors for cervical cancer in Thailand: a case-control study. J Natl Cancer Inst 1998; **90:** 50-57
- 28 Ngelangel C, Munoz N, Bosch FX, et al. Causes of cervical cancer in the Philippines: a case-control study. *J Natl Cancer Inst* 1998; **90**: 43-49.
- 29 Hildesheim A, Schiffman MH, Gravitt PE, et al. Persistence of type-specific human papillomavirus infection among cytologically normal women. *J Infect Dis* 1994; **169:** 235-40.
- 30 Jacobs MV, Roda Husman AM, van den Brule AJ, Snijders PJ, Meijer CJ, Walboomers JM. Groupspecific differentiation between high- and low-risk human papillomavirus genotypes by general primermediated PCR and two cocktails of oligonudeotide probes. *J Clin Microbiol* 1995; **33**: 901-05.
- 31 Roda Husman AM, Walboomers JM, Meijer CJ, et al. Analysis of cytomorphologically abnormal cervical scrapes for the presence of 27 mucosotropic human papillomavirus genotypes, using polymerase chain reaction. *Int J Cancer* 1994; **56**: 802-06.
- 32 van den Brule AJ, Snijders PJ, Raaphorst PM, et al. General primer polymerase chain reaction in combination with sequence analysis for identification of potentially novel human papillomavirus genotypes in cervical lesions. *J Clin Microbiol* 1992; **30**: 1716-21.
- 33 Gravitt PE, Peyton CL, Apple RJ, Wheeler CM. Genotyping of 27 human papillomavirus types by using Ll consensus PCR products by a single-hybridization, reverse line blot detection method. *J Clin Microbiol* 1998; **36:** 3020-27.

- 34 Moreno V, Bosch FX, Munoz N, et al. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. *Lancet* 2002; **359:** 1085-92.
- 35 Smith JS, Green J, Berrington dG, et al. Cervical cancer and use of hormonal contraceptives: a systematic review. *Lancet* 2003; **361:** 1159-67
- 36 Wmer RL, Hughes JP, Feng Q, et aL Condom use and the risk of genital human papillomavirus infection in young women. *N Engl J Med* 2006; **354:** 2645-54.
- 37 Solomon D, Nayar R (eds). The Bethesda System for reporting cervical cytology: definitions, criteria, and explanatory notes, 2nd edn. New York: Springer, 2004.

# **APPENDIX BB**

# ORIGINAL RESEARCH ARTICLE IMPACT OF THE FEDERAL CONTRACEPTIVE COVERAGE GUARANTEE ON OUT-OF-POCKET PAYMENTS FOR CONTRACEPTIVES: 2014 UPDATE<sup>°, °°</sup>

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## Abstract

**Background:** The Affordable Care Act requires most private health plans to cover contraceptive methods, services and counseling, without any out-of-pocket costs to patients; that requirement took effect for millions of Americans in January 2013.

**Study design:** Data for this study come from a subset of the 1842 women aged 18–39 years who responded to all four waves of a national longitudinal survey. This analysis focuses on the 892 women who had private health insurance

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and who used a prescription contraceptive method during any of the four study periods. Women were asked about the amount they paid out of pocket in an average month for their method of choice.

**Results:** Between fall 2012 and spring 2014, the proportion of privately insured women paying zero dollars out of pocket for oral contraceptives increased substantially, from 15% to 67%. Similar changes occurred among privately insured women using injectable contraception, the vaginal ring and the intrauterine device.

**Conclusions:** The implementation of the federal contraceptive coverage requirement appears to have had a notable impact on the out-of-pocket costs paid by privately insured women, and that impact has increased over time.

**Implications:** This study measures the out-of-pocket costs for women with private insurance prior to the federal contraceptive coverage requirement and after it took effect; in doing so, it highlights areas of progress in eliminating these costs.

*Keywords:* Contraception; Oral contraceptive pills; Insurance; Health reform; Out-of-pocket costs

### **1. Introduction**

One high-profile provision of the Affordable Care Act is a requirement that private health plans cover contraceptive methods, services and counseling for women, without any copayments, deductibles or other patient out-of-pocket costs [1]. This federal contraceptive coverage guarantee part of a broader provision requiring coverage without cost sharing for dozens of recommended preventive care services was phased in starting in August 2012 and began affecting health plans widely in January 2013.

Even before that requirement took effect, coverage of a wide range of contraceptive methods was standard in U.S. private health plans [2]. Where the federal requirement broke new ground, at least for private health plans, was in its

prohibition on patient cost sharing. That change brought with it the potential to eliminate cost as a reason for choosing one method of contraception over another, a change that could be particularly important for low-income women and women considering methods with substantial upfront costs.

This report provides new, national-level data about the reach and impact of the contraceptive coverage requirement. It utilizes information collected from a longitudinal survey of women, comparing women's responses in fall 2012, before the contraceptive coverage requirement would have taken effect for most women, with their responses to three subsequent rounds of the survey (at 6-month intervals) that were fielded after the requirement was implemented for millions.

An earlier analysis, using just the first two waves of this survey (fall 2012 and spring 2013), was published in December 2013 and found substantial increases in the proportions of privately insured women paying zero dollars out of pocket for oral contraceptives and the vaginal ring over just the first few months of the federal guarantee [3]. An April 2014 report from the IMS Institute for Healthcare Informatics found similar trends and estimated that women saved nearly half a billion dollars in out-of-pocket costs for contraception in 2013 in the wake of the guarantee [4]. Our report provides more up-to-date information to bolster this body of knowledge.

# 2. Materials and Methods

Data for this analysis come from all four waves of the Guttmacher Institute's Continuity and Change in Contraceptive Use Study, which surveyed women about their contraceptive use repeatedly over an 18-month time period. This analysis is based on the methodology used for the Guttmacher Institute's first analysis described above [3]. More details on the methodology can be found in that article, but we provide a brief description below.

The survey was administered online to a national sample of omen aged 18–39 years. It was administered by the market

women aged 18–39 years. It was administered by the market research firm GfK using their KnowledgePanel, a national household panel recruited using a probability-based methodology.

The survey was conducted over 3-week periods in fall 2012, spring 2013, fall 2013 and spring 2014. Of the 4634 women who participated in the baseline study, 3207 participated at Wave 2, 2398 participated at Wave 3 and 1842 participated at Wave 4, resulting in between-survey response rates of 69%, 75% and 77%, respectively. The sample for the current analysis was limited to women who participated in all four waves of the study or 40% of the baseline sample. The sample used for this analysis was further limited to women who had private health insurance and used a prescription contraceptive method during any of the four study periods (892 women).

In this analysis, we focused on survey questions about outof-pocket payments for contraception among women who used hormonal methods in the last 30 days or obtained an intrauterine device (IUD) between surveys. We examined the percentage of women who reported paying nothing, as well as the mean and median amounts that women paid for the pill; the number of women paying for methods other than the pill was too small for an analysis of means and medians.

Women who reported that they used the pill, injectable or vaginal ring during the last 30 days were asked how much they paid for the method out of pocket each month. We assessed change over time in cross-tabulations using Rao-Scott–corrected  $\chi^2$  tests in order to include as many women as possible in all analyses while also taking into account the clustering of data within individuals. Our focus is change over time, and  $\chi^2$  statistics allow us to assess differences across all waves at once rather than whether specific waves are statistically different from each other. Our analysis is based on a total of 1916 observations of pill use, 107 observations of injectable use and 151 observations of ring use as reported by 892 women; some women contributed up to four observations per method, while others only contributed one.

IUD users were only asked about cost the first time they reported use of the method. Because we captured relatively few new IUD users covered by private health insurance in waves two through four (n=45), we used t tests to assess for differences between the proportions who paid nothing for the method at Wave 1 compared to the users at Waves 2, 3 and 4 grouped together. Our analysis is based on 165 IUD users. We did not ask about type of IUD — copper vs. hormonal — and both are grouped together.

The number of users of the patch and implant were too small to be reliable; thus, those methods were excluded from this analysis. Analyses were performed using Stata 13. All findings presented were statistically significant at the p<.05 level.

# 3. Results

Among women who reported using the pill and having private health insurance, the proportion who did not pay anything out of pocket increased from 15% to 67% between Waves 1 and 4 (Fig. 1). The most substantial increase occurred between Wave 1 and Wave 2 (from 15% to  $44\%^{1}$ ), but there was a continuing upward trend over the 18-month time period.

<sup>&</sup>lt;sup>1</sup> The previously published article in Contraception reported that 40% of pill users paid nothing out of pocket during Wave 2. The difference is because the prior study restricted analyses to women who were privately insured and using the pill at both points in time, while the current study incorporated women who may have experienced changes in insurance coverage or method use. Moreover, respondents included in the earlier analyses who failed to participate in subsequent waves are excluded from the current study.

We conducted a sensitivity analysis that examined changes in out-of-pocket costs when the sample was restricted to women who were privately insured and using the pill during all four waves (n=308, obs=1227). The proportions paying US\$0 were virtually the same, 15%, 45%, 57% and 69% (p<.001), respectively (data not shown). In addition, we also examined these changes when the sample was restricted to women who were privately insured and using the pill at both Waves 1 and 4 (n=350). The proportions paying US\$0 were 16% and 69%, and a paired t test indicated that the difference was significant at p<.001 (data not shown). Both analyses confirmed the patterns found in analyses using all available observations.

Similar increases in the proportion paying zero dollars out of pocket were observed for injectable contraception users and vaginal ring users with private insurance. For injectable users, the proportion increased from 27% to 59% between Wave 1 and Wave 4. For ring users, it increased from 20% to 74% over the same time period.

Among IUD users with private health insurance at Wave 1, 45% indicated that they paid nothing for the method. This increased to 62% among new users in all three subsequent waves combined (data not shown).

## Fig. 1

# Percent of privately insured women who paid US\$0 out of pocket for their method

\* \* \*

#### Fig. 2

## Mean and median out-of-pocket costs for privately insured women using the pill

\* \* \*

Among privately insured women using the pill, the Wave 1 mean out-of-pocket payment was US\$14.35 and the median was US\$10; by Wave 4, this had declined to US \$6.48 and US\$0, respectively (Fig. 2).

## 3.1. Limitations

This study is subject to some limitations. Although our response rates were comparable to those of other studies using online administration, only 40% of the baseline sample participated in all four waves of the study, which compromises the representativeness of the data. The findings might be further biased if our respondents differed from the national population in ways that correlate with contraceptive use. Nonetheless, the data are still useful because they serve as one of the only sources of information about trends in contraceptive copays among the same group of women over time.

Despite the abovementioned concerns, it is reassuring that the findings here are similar to prior published research: The mean (US\$14.35) and median (US\$10) out-of-pocket payments for the pill in Wave 1 of our study are almost identical with the mean (US\$15.13) and median (US\$10) out-of-pocket payments from another nationally representative study carried out before the new federal policy took effect [5].

Some 45% of baseline IUD users reported that they had paid US\$0 for the method, a higher proportion than reported paying US\$0 for the pill, the ring or the injectable at Wave 1. Prior to the contraceptive coverage guarantee, many women had to pay several hundred dollars out of pocket for the IUD. One potential interpretation of the pattern in our data is that many women unable to obtain the method at no cost were unable to afford it at all. That is, prior to coverage guarantee, women may have opted to pay a relatively modest copayment each month for the pill rather than come up with several hundred dollars to cover out-of-pocket costs for the IUD.

### 4. Discussion

The findings of this study suggest that the federal contraceptive coverage guarantee has had a substantial

impact in eliminating out-of-pocket costs among privately insured women using some methods of contraception including oral contraceptives, the most popular reversible method in the United States. Between fall 2012 and spring 2014, the proportion of pill users paying zero dollars out of pocket increased from 15% to 67%, with similar trends for injectable, ring and IUD users.

Further progress may still be expected as more private health plans become subject to the requirement. Notably, existing plans are grandfathered exempt from the requirement so long as they make no significant negative changes, such as benefit reductions or cost sharing increases. That status is designed to be temporary to allow for a smoother transition to new federal rules, and the number of people enrolled in grandfathered plans has been declining rapidly, from 48% of covered workers in 2012 to 36% in 2013 and 26% in 2014 [6].

However, the proportion of women paying zero dollars will never reach 100%, for several reasons:

- Federal guidance allows insurers to charge copayments in limited situations, such as when a woman chooses a brand-name drug with a generic equivalent or when a woman receives services from an out-of-network provider [7].
- Federal regulations exempt some employer-sponsored health plans sponsored by houses of worship from the contraceptive coverage requirement on religious grounds, [8] and the U.S. Supreme Court's June 2014 decision in *Burwell v. Hobby Lobby* has extended that to certain closely held for-profit employers.

In addition, several other problems may result in women paying out of pocket for contraceptive methods despite the federal guarantee:

• There is evidence that some private health plans are not adequately complying with what the law clearly requires

coverage of "the full range" of contraceptive methods approved by the Food and Drug Administration when prescribed for a woman and are instead denying coverage, requiring cost sharing or otherwise restricting access to specific methods [9].

• Other religiously affiliated nonprofits have been offered an accommodation under which they are supposed to be absolved from involvement in covering contraception, but their employees and family members must still receive that coverage through the insurance company [8]. However, there are serious questions, and a complete dearth of information, about whether and how plans are complying.

Despite these gaps in the reach of the federal guarantee, the findings of this study bode well for the health and well-being of women, couples and families. Government bodies and private-sector experts have long recognized contraceptive services as a vital and effective component of preventive health care, and an extensive body of research shows that contraceptive use helps women avoid unintended pregnancy and improve birth spacing, resulting in substantial health, social and economic benefits [10–12]. By guaranteeing that women have coverage for a wide range of contraceptive choices without cost sharing, the federal requirement may help them overcome financial barriers to choosing a contraceptive method they will be able to use consistently and effectively, thus increasing their likelihood of avoiding unplanned pregnancies.

# References

- [1] Public Health Service Act, sec. 2713.
- [2] Sonfield A, Gold RB, Frost JJ, Darroch JE. U.S. insurance coverage of contraceptives and the impact of contraceptive coverage mandates, 2002. Perspect Sex Reprod Health 2004;36 (2):72–9.

- [3] Finer LB, Sonfield A, Jones RK. Changes in out-ofpocket payments for contraception by privately insured women during implementation of the federal contraceptive coverage requirement. Contraception 2014;89 (2):97–102.
- [4] IMS Institute for Healthcare Informatics. Medicine use and shifting costs of healthcare, a review of the use of medicines in the United States in 2013. Parsippany, NJ: IMS Institute for Healthcare Informatics; 2014 [Available from: http://www.plannedparenthoodadvocate.org/2014/ IIHI\_US\_Use\_of\_Meds\_for\_2013.pdf. Accessed September 3, 2014].
- [5] Liang S-Y, Grossman D, Phillips K. Women's current out-of-pocket expenditures and dispensing patterns for oral contraceptives. Contraception 2011;83(6):528–36.
- [6] Kaiser Family Foundation, Health Research and Educational Trust. Employer health benefits: 2014 annual survey; 2014 [Available from: http://kff.org/report-section/ehbs-2014-section-thirteengrandfathered-health-plans/. Accessed September 10, 2014].
- [7] Employee Benefits Security Administration and Department of Labor. FAQs about Affordable Care Act implementation part XII; 2013 [Available from: http://www.dol.gov/ebsa/faqs/faq-aca12.html. Accessed September 3, 2014].
- [8] Department of the Treasury, Department ofLabor, Department of Health and Human Services. Coverage of certain preventive services under the Affordable Care Act: final rules. Fed Regist 2013;78(127):39870– 99 [Available from: http://www.gpo.gov/fdsys/pkg/FR-2013-07-02/pdf/ 2013-15866.pdf. Accessed September 3, 2014].

- [9] Sonfield A. Implementing the federal contraceptive coverage guarantee: progress and prospects. Guttmacher Policy Rev 2013;16(4):8–12.
- [10] Guttmacher Institute. Testimony of Guttmacher Institute, submitted to the Committee on Preventive Services for Women, Institute of Medicine, 2011, [Available from: http://www.guttmacher.org/pubs/ CPSW-testimony.pdf. Accessed September 3, 2014].
- [11] Kavanaugh ML, Anderson RM. Contraception and beyond: the health benefits of services provided at family planning centers. New York: Guttmacher Institute; 2013 [Available from: http://www.guttmacher. org/pubs/health-benefits.pdf. Accessed September 3, 2014].
- [12] Sonfield A, Hasstedt K, Kavanaugh ML, Anderson RM. The social and economic benefits of women's ability to determine whether and when to have children. New York: Guttmacher Institute; 2013 [Available from: www.guttmacher.org/pubs/social-economicbenefits.pdf. Accessed September 3, 2014].

# 512a APPENDIX CC

#### **ORIGINAL RESEARCH ARTICLE**

# CHANGES IN OUT-OF-POCKET COSTS FOR HORMONAL IUDS AFTER IMPLEMENTATION OF THE AFFORDABLE CARE ACT: AN ANALYSIS OF INSURANCE BENEFIT INQUIRIES

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## Abstract

**Background**: The Affordable Care Act (ACA) requires that privately insured women can obtain contraceptive services and supplies without cost sharing. This may substantially affect women who prefer an intrauterine device (IUD), a long-acting reversible contraceptive, because of high upfront costs that they would otherwise face. However, imperfect enforcement of and exceptions to this provision could limit its effect. Study design: We analyzed administrative data for 417,221 women whose physicians queried their insurance plans from January 2012 to March 2014 to determine whether each woman had insurance coverage for a hormonal IUD and the extent of that coverage.

**Results**: In January 2012, 58% of women would have incurred out-of-pocket costs for an IUD, compared to only 13% of women in March 2014. Differentials by age and region virtually dissolved over the period studied, which suggests that the ACA reduced inequality among insured women.

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**Conclusions**: Our findings suggest that the cost of hormonal IUDs fell to US\$0 for most insured women following the implementation of the ACA.

**Implications**: Financial barriers to one of the most effective methods of contraception fell substantially following the ACA. If more women interested in this method can access it, this may contribute to a decline in unintended pregnancies in the United States.

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# *Keywords: Contraception; Healthcare reform; Out-of-pocket costs; IUD; LARC; Insurance*

#### **1. Introduction**

In the United States, 43 million women are at risk of unintended pregnancy, and 39 million of them (90%) use contraception [1,2]. Some 30 million (78% of contraceptors) use a method more effective than condoms, and 4 million (10%) use an intrauterine device (IUD), while fewer than a half million use another long-acting reversible method [1,3]. Fewer than 1% of women who use IUDs will become pregnant within a year, in contrast to 18% of women who use condoms to prevent pregnancy, and 9% of women who use the pill [4].

Women who would otherwise prefer the IUD face barriers that can lead them to use less effective contraceptives; these include high upfront costs that can exceed a thousand dollars [5–11]. Greater uptake of the IUD and the implant preceded fewer births in Colorado and fewer abortions in Iowa, and in St. Louis, teenagers provided these methods at no-cost exhibited rates of pregnancy, birth and abortion far lower than the national average [8,12,13].

Insurance mandates may help women to access the contraceptive of their choice. In 1993, 32% of insurers covered the IUD [14]. By 2002, in part because insurance mandates came into effect in many states, this increased to

94% [14]. However, when an insurance company covers a contraceptive, a woman may still incur costs for example, women may incur copayments for the prescription and visits to a doctor's office or clinic.

A provision of the Affordable Care Act (ACA) requires that patients do not face out-of-pocket costs for contraceptive services and supplies at in-network providers. This provision matters particularly in the context of the high upfront costs of an IUD. This ACA mandate phased in starting in August 2012, and it took effect for many health insurance plans in January 2013. This may improve the ability of millions of women to afford safe and effective contraception [15].

The ACA can affect insurers exempt from state mandates, whereas states lacked authority over self-funded employer plans. However, other exceptions may limit the effect of the ACA's contraceptive coverage mandate. These include grandfathered insurance plans and the contraceptive exclusion. Grandfathered plans are those that came into being no later than March 2010 and have not seen substantial benefit changes since then [16]. The contraceptive exclusion exempts certain religious employers from the ACA's contraceptive coverage provision. As such, even if insurance companies adhere perfectly to the law, some women covered by private insurance may still have to pay the full cost of the IUD and other contraceptives.

Women interested in an IUD may face a higher financial burden if their insurance plan requires out-of-pocket costs. In addition to the cost of the device itself and the initial doctor's visit, women may also face costs to insert and remove their IUD [5–7,10,17]. In 2002, a year after the hormonal IUD came on the market (complementing the nonhormonal copper IUD, which had been available in the United States since 1988), 94% of insurers covered IUDs, but cost sharing continued to make the IUD unaffordable for many women interested in it [8,9,14].

To understand the impact of the ACA's contraceptive coverage provision on IUD cost sharing, we would need to know what costs women faced before and after the ACA. Unfortunately, the extant literature on IUD cost sharing after the ACA went into effect is limited. One analysis estimated that full coverage increased from 45% to 62% after the ACA, based on data from 165 privately insured women [18]. Data from the National Survey of Family Growth (NSFG), the available representative survev of best women's contraceptive behavior, do not indicate when women obtained their IUDs or how much they paid. Even if the NSFG asked women how much they paid, this information would not provide us the percentage of women seeking an IUD who faced out-of-pocket costs: if cost inhibits IUD uptake, the extant data will under-represent women with higher costs [8–10]. All surveys that measure cost based on women who obtained IUDs share this limitation, as do claims data. Finally, none of these surveys address the effect of the contraceptive exclusion, which exempts certain religious employers from providing full coverage.

To help address these limitations, we analyzed data on insurance inquiries; these show what an insured woman would have paid if she had chosen to obtain an IUD, between January 2012 and March 2014, a period covering the introduction of the ACA's contraceptive coverage provision and its initial implementation for many plans.

## 2. Materials and methods

### 2.1. Data

Bayer HealthCare, the manufacturer of the Mirena® and Skyla® IUDs, used by some 3 of 4 million American IUD users [3] offers a voluntary "benefit inquiry" service to healthcare providers to determine the type and extent of a patient's insurance coverage for an IUD and whether the patient's insurance company requires cost sharing. Bayer utilizes an outside benefits-verification contractor and does not obtain the data directly. Within a few days after a healthcare provider's inquiry, typewritten reports with a narrative summary of coverage are faxed by the contractor to healthcare providers, and details of each benefit inquiry are recorded in the contractor's database<sup>1</sup>. Though healthcare providers can pursue this information independently, they may elect to use this free service to reduce their administrative caseload.

The dataset we obtained contained 444,316 women whose physicians inquired about a Mirena or Skyla IUD between January 2012 and March 2014. Of these, we excluded 27,095 women from the analysis because they were minors (4,577, in order to focus on adults who were likely to have their own insurance), they had no insurance  $(11,363)^2$ , a woman's insurer would not reveal benefit information to a third party (10,382), women or their healthcare providers did not completely fill out the form (763), or the healthcare provider canceled the inquiry (10). The resulting number of cases we analyzed was 417,221.

The analysis period includes time both before and after the ACA's key provision regarding contraceptive coverage took effect, which allowed us to study its impact. We hypothesized that there would be a sharp decline in the percentage of women subject to cost sharing in the first quarter of 2013, since patients with existing coverage typically sign up for new plans or renew their insurance at the beginning of a calendar year, and January 2013 was the first new year after the implementation of the ACA's contraceptive coverage provision.

<sup>&</sup>lt;sup>1</sup> The data record whether patients were subject to cost sharing, and if so, what the copayment or coinsurance rate was and not what providers charge.

<sup>&</sup>lt;sup>2</sup> This could arise if, for example, a woman's coverage is not yet active or is no longer active, but the data do not record this. Because our goal was an analysis of insured women's IUD benefits, we excluded these women.
## 2.2. Methods

We analyzed changes between January 2012 and March 2014 in the percentage of women who would have had outof-pocket costs for a hormonal IUD. The ACA's contraceptive coverage provision came into effect in August 2012, but did not affect most women until January 2013, as most employer-based insurance plans are typically renewed on January 1.

For 2013 onward (n=231,086), we assessed how these results were affected when taking into account two additional factors that affect cost sharing: copayment for insertion and cost sharing owing to a deductible (data not available in 2012). This may affect our results as, for example, women whose insurers covered the cost of the device might not have interpreted the ACA mandate to apply to services as well as supplies.

We estimated trends for all women by month in whether a woman's insurance coverage required cost sharing. We also estimated trends by quarter for age and region subgroups to examine inequality in coverage before, and after, the ACA came into effect.

In an analysis of a very large dataset, trivial fluctuations can reach statistical significance. It is therefore inappropriate to compare p-values, as, for example, a trivial decline of 0.01%, which might only reflect random fluctuations, may be described as "statistically" significant [19]. Therefore, we highlight the substantive size of change over time<sup>3</sup>.

In order to understand how much women who still have costs would be required to pay, we also computed cost estimates at the median and 90th percentiles. A woman's outof-pocket cost is the sum of a fixed copayment and the product of the IUD's price and her coinsurance rate.

<sup>&</sup>lt;sup>3</sup> Results of logistic regressions, which compare each month to January 2013 or each quarter to the first quarter of 2013, are available from the authors upon request.

Unfortunately, we do not know the price that a healthcare provider would charge a patient for the IUD. Therefore, for the 13% of women subject to coinsurance, we multiplied their coinsurance rate by the most recent published estimates for Mirena's wholesale price, US\$844 [7]. This strategy understates the actual cost because patients may also be required to pay for an initial visit to their healthcare provider and for the device's insertion.

Finally, the dataset indicates whether a woman's coverage was subject to the contraceptive exclusion for religious employers, and we use this to estimate the percentage of women without coverage who would have had coverage if not for this exclusion.

#### 2.3. Sensitivity analyses

Of the women in our data, 50,804 have multiple insurers. We do not know their insurers' names or why they have duplicative coverage. We suspect, for example, that some may have private insurance from their employer, as well as secondary insurance from Medicaid or their spouse's employer. In our main analysis, we assumed that women with multiple insurers can choose which insurer to use. They may not have this choice, however<sup>4</sup>. Therefore, we performed a sensitivity analysis in which we assume that a woman with duplicative coverage must use whichever insurer offers the worst coverage.

#### Fig. 1.

Percentage of women who would have had out-of-pocket costs for a hormonal IUD, by month. Note: The lighter line begins in

<sup>&</sup>lt;sup>4</sup> We speculate, for example, that a woman's employer's insurance may be her *primary* insurer in some cases, and she may also have insurance from her spouse's employer; she may have to use her employer's insurer even if her spouse's insurer offers a lower copay. Alternatively, a woman's primary insurer may cover the IUD but may require a copayment; if she has Medicaid, then, Medicaid should cover the copayment.

# January 2013 because the 2012 data do not contain insertion copayments and deductible applicability.

\* \* \*

#### 3. Results

The black line in Fig. 1 shows the decreasing percentage of women who faced out-of-pocket costs for a hormonal IUD (and at least some cost for its insertion) over the 27 months between January 2012 and March 2014. In January 2012, out-of-pocket costs were required of 58% of insured patients; by March 2014, this number dropped to 13%. The percentage of women who faced out-of-pocket costs did not decrease during the first half of 2012; we first observe decreases toward the end of 2012, as the ACA's contraceptive coverage requirement first took effect for patients signing up for new health plans. Coverage increased substantially at the end of 2012, when many patients' annual plans were renewed and the ACA took effect for those without grandfathered plans; the percent with out-of-pocket costs declined 3 percentage points in December 2012, from 52% to 49%, and 21 points in January 2013, from 49% to 28%. Over the next 15 months, from February 2013 through March 2014, the percentage of women who faced out-of-pocket costs fell to 13%, or by 1 percentage point per month.

We analyzed whether a woman's insurer required a copayment for the device's insertion or otherwise required cost sharing due to a deductible from 2013 onwards (as these data were not available for 2012). The results did not substantively differ from the trend described above for full coverage. The gray line in Fig. 1 shows that 16% rather than 13% of women faced out-of-pocket costs for both the device and its insertion. These estimates of change over time may be conservative, however, as the percentage of women with insurers who required them to share in the cost of the device's insertion might have been higher in 2012 than in 2013.

Figs. 2 and 3 show trends in IUD coverage by age and region, respectively. Before the implementation of the ACA provision, young and Northeastern women experienced higher levels of coverage than other women; after implementation, differences by age and region narrowed sharply.

#### Fig. 2

#### In each age group: percentage of women who would have had out-of-pocket costs for a hormonal IUD, by quarter.

\* \* \*

In Q1 2012, 49% and 63%, respectively, of women aged 18–24 and 40–49 years would have had to pay out of pocket, a 14-point difference (Fig. 2). In Q1 2013, less than a third of this gap remained (4 points, 24% versus 28%); differences by age nearly dissolved by the end of the analysis period. Similarly, in Q1 2012, 53% and 61–64%, respectively, of women in the Northeast and elsewhere would have had to pay something out of pocket (Fig. 3). In Q1 2013, four fifths of this gap remained, and after another year, differences by region nearly dissolved (to 0–3 points). Differences by region dissolved as much as differences by age but less rapidly.

Table 1 reports the percentage of women with full coverage for a hormonal IUD (and at least partial coverage for its insertion), with partial coverage for the IUD or without coverage, by quarter, between Q1 2012 and Q1 2014. The table indicates that very few women in these data had no coverage at all. Thus, most of the increase in full coverage appears to be driven by insurance companies moving from partial to full coverage.

#### Fig. 3

#### In each region: percentage of women would have had out-ofpocket costs for a hormonal IUD, by quarter.

\* \* \*

Table 1 also reports that the percentage of women in these data affected by the contraceptive exclusion for religious employers varies from 0.4% to 2.2% in the five quarters between January 2013 and January 2014. Dividing the percentage without coverage due to the contraceptive exclusion by the percentage of women with no coverage shows, however, that these 0.4–2.2% of women who sought an IUD amount to 8.8–37.9% of women who sought an IUD and had no coverage; this may suggest that a nontrivial portion of women with interest in an IUD but without any coverage worked for a religious employer that denies contraceptive coverage. Considering the wide variation in these numbers, however, they should be interpreted with caution.

Table 2 reports cost estimates for the IUD itself at the median and 90th percentiles. The 90th percentile declines to \$169 in the first quarter of 2013 and to \$15 in the first quarter of 2014, from \$844 in the first three quarters of 2012. Median estimates are much smaller, at \$20 in the first half of 2012, and fall to \$0 in Q4 2012, as by then fewer than half of women (49.9%) faced out-of-pocket costs for the IUD itself.

In a sensitivity analysis, we examined the percentage of women who faced out-of-pocket costs for obtaining an IUD under the assumption that women with multiple insurers for example, backed up by Medicaid — could not rely on the insurance with the lowest out-of-pocket cost available to them. In this scenario, 20% of women would have had outof-pocket costs for the IUD and insertion in March 2014, compared to 16% as shown in Fig. 1. In both coverage scenarios, 58–59% faced out-of-pocket costs in January 2012, so this sensitivity analysis corroborates the overall analysis.

#### 4. Discussion

Following implementation of the ACA, we observed a substantial decline in the percentage of women having to pay out of pocket for a hormonal IUD and the elimination of cost disparities by age and region. Potential for further decline remains, as 13% of women still did not have complete coverage as of March 2014.

Some of the decrease in women who face costs could follow from other causes aside from the ACA. However, we note the complete absence of any trend prior to the point in time at which the ACA's provisions came into effect.

Either the ACA reduces differences between the North-east and other regions or the characteristics of the healthcare providers who use the benefit inquiry service differ in the Northeast. If so, then these findings may reflect a convergence in coverage not by region but by unobserved socioeconomic characteristics. We cannot identify effects by individual characteristics such as income or race, but trends by region suggest that IUD coverage increased substantially under ACA throughout the United States.

To address the representativeness of the benefit inquiry data, we compared the available demographics — age and geographic region — to U.S. Census data and the NSFG. With regard to age, the women in the benefit inquiry data do not differ significantly from all women of reproductive age. With regard to geography, the comparisons indicate that the benefit inquiry data overrepresent women in the Northeast and underrepresent women in the West, although women in the West are more likely to have an IUD in the NSFG and in a recent Centers for Disease Control and Prevention analysis of services provided to teenagers in Title X clinics [3,20]; this may reflect differences by region in the use of the benefit inquiry service.

#### Table 1

# Percentage of women with different levels of coverage for a hormonal IUD and percentage affected by the contraceptive exclusion for religious employers, by quarter

\* \* \*

We note several limitations of our approach. A key limitation is that we rely upon both the manufacturer of the hormonal IUDs and the manufacturer's benefits-verification contractor for the data's authenticity and accuracy. We also cannot determine how many of the 13% of women who remain without complete coverage in March 2014 do so because of imperfect adherence to the ACA requirement or because they have a grandfathered insurance plan. Evidence of imperfect adherence leads advocates like the National Women's Law Center to publish advice to women faced with costs in spite of the federal mandate [21-23]. Also, as previously noted, these data do not represent all women seeking Mirena or Skyla, nor do we know the percentage of these women who actually went on to obtain an IUD or the number of IUDs sold. Finally, we expect but cannot confirm that these data predominantly represent women with private insurance, as a doctor familiar with the public insurance plans within his or her state would likely know a publicly insured woman's coverage. While we note these limitations, our findings corroborate similar results from other studies that analyze other contraceptives [17,18].

#### Table 2

# Median and 90th percentile cost estimates for a hormonal IUD, by quarter

\* \* \*

Earlier studies reported that most women with private insurance had at least partial coverage [10,14,17,18,24], but these studies could have underestimated the number of women with no coverage because they analyzed women who obtained an IUD, and women who discovered that their insurance did not cover an IUD might not obtain one. In contrast to these earlier studies, our results are not biased by this limitation.

Noticeable gaps in the percentage of women who are covered and not subject to cost sharing, between women by region and women by age, dissolved after the ACA took effect. This convergence suggests that the ACA reduced inequality among insured women. Were race or income available in these data, it would have been interesting to test

## whether race or income inequality in coverage declined over time. We believe that this is worth further study.

Our study also contributes the first nonanecdotal estimates of the extent to which the contraceptive exclusion for religious employers inhibits women's access to the contraceptive of their choice. We interpret these results with caution, however, given the between-quarter fluctuations in the percentage of women denied IUD coverage due to the exclusion. We might expect that as the share of women without coverage declines, the proportion of uncovered women subject to the religious exclusion would increase, but we observe the opposite, with a higher proportion of women without coverage affected by the religious exclusion in the first quarter of 2013 than in the first quarter of 2014.

Between 2006 and 2010, unintended pregnancy rates declined in all but 2 of the 41 states for which data are available [25]. This decline corresponded with a national increase in long-acting reversible contraceptive (LARC) use, predominantly of the IUD, from 3.7% in 2007 to 8.5% in 2009 [26]. As noted earlier, IUD use has since risen further, reaching 10% in 2011–2013 [3], and prior research shows that eliminating costs can lead to increased LARC use, which in turn can contribute to lower pregnancy, abortion and birth rates [8,9,12]. Other factors may also contribute to the decline in unintended pregnancy. However, if the ACA leads to additional uptake, this may contribute to continued declines in unintended pregnancy.

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References

- [1] Daniels K, Daugherty J, Jones J. Current Contraceptive Status Among Women Aged 15–44: United States, 2011– 2013. NCHS Data Brief; 20141–8.
- [2] Contraceptive Use in the United States. at http://www.guttmacher.org/ pubs/fb\_contr\_use.html#2.
- [3] Kavanaugh M, Jerman J, Finer L. Changes in use of longacting reversible contraceptive methods among United States women. Obstet Gynecol 2015;83:2009–12.
- [4] Trussell J. Contraceptive failure in the United States. Contraception 2011;83:397–404.
- [5] Trussell J, Lalla A, Doan Q, Reyes E. Cost effectiveness of contraceptives in the United States. Contraception 2009;79(1):5–4 [at http://www. sciencedirect.com/science/article/pii/S0010782408004101].
- [6] Trussell J. Update on the cost-effectiveness of contraceptives in the United States. Contraception 2010;82:391.
- [7] Trussell J. Update on and correction to the cost effectiveness of contraceptives in the United States. Contraception 2012;85:218.
- [8] Ricketts S, Klingler G, Schwalberg R. Game change in Colorado: widespread use of long-acting reversible contraceptives and rapid decline in births among young, low-income women. Perspect Sex Reprod Health 2014;46:125–32.
- [9] Postlethwaite D, Trussell J, Zoolakis A, Shabear R, Petitti D. A comparison of contraceptive procurement pre- and postbenefit change. Contraception 2007;76:360–5.
- [10] Gariepy A, Simon E, Patel D. The impact of out-of-pocket expense on IUD utilization among women with private insurance. Contraception 2011;84(6):39–42 [at http://www.sciencedirect.com/science/article/pii/ S001078241100432X].

- [11] Secura GM, Madden T, McNicholas C, Mullersman J, Buckel CM, Zhao Q, et al. Provision of no-cost, long-acting contraception and teenage pregnancy. N Engl J Med 2014;371:1316–23.
- [12] Biggs MA, Rocca CH, Brindis CD, Hirsch H, Grossman D. Did increasing use of highly effective contraception contribute to declining abortions in Iowa? Contraception 2015;91:167–73.
- [13] Peipert JF, Madden T, Allsworth JE, Secura GM. Preventing unintended pregnancies by providing no-cost contraception. Obstet Gynecol 2012;120:1291–7.
- [14] Sonfield A, Gold RB, Frost JJ, Darroch JE. U.S. insurance coverage of contraceptives and the impact of contraceptive coverage mandates, 2002. Perspect Sex Reprod Health 2004;36:72–9.
- [15] Sonfeld A. Implementing the federal contraceptive coverage guaran-tee: progress and prospects. Guttmacher, Policy Rev. 16; 2013.
- [16] Marketplace options for grandfathered health insurance plans. HealthCare.gov at https://www.healthcare.gov/health-care-law-protections/grandfathered-plans/.
- [17] Finer LB, Sonfield A, Jones RK. Changes in out-of-pocket payments for contraception by privately insured women during implementation of the federal contraceptive coverage requirement. Contraception 2014;89:97–02.
- [18] Sonfield A, Tapales A, Jones RK, Finer LB. Impact of the federal contraceptive coverage guarantee on out-of-pocket payments for contraceptives: 2014 update. Contraception 2015;91:44–8.
- [19] Lin M, Lucas HC, Shmueli G. Research commentary too big to fail: large samples and the p-value problem. Inf Syst Res 2013;24:906–17.
- [20] Vital Signs: Trends in Use of Long-Acting Reversible Contraception Among Teens Aged 15–19 Years Seeking Contraceptive Services — United States, 2005–2013. at http://www.cdc.gov/mmwr/preview/mmwrhtml/ mm64e0407a1.htm?s\_cid=mm64e0407a1\_e.

- [21] State of Women's Coverage: Health Plan Violations of the Affordable Care Act. National Women's Law Center; 2015 [at http://www.nwlc. org/stateofcoverage].
- [22] National Women's Law Center. Getting the Coverage You Deserve: What to Do If You Are Charged a Co-Payment, Deductible, or Co-Insurance for a Preventive Service. (National Women's Law Center); 2014.
- [23] Sobel Laurie, Salganicoff A, Kurani N. Coverage of Contraceptive Services: A Review of Health Insurance Plans in Five States. at http:// kff.org/privateinsurance/report/coverage-of-contraceptive-services-areview-of-health-insurance-plans-in-five-states/2015.
- [24] Dusetzina SB, Dalton VK, Chernew ME, Pace LE, Bowden G, Fendrick AM. Cost of contraceptive methods to privately insured women in the United States. Womens Health Issues 2013;23:e69–71.
- [25] Kost K. Unintended Pregnancy Rates at the State Level: Estimates for 2010 and Trends Since 2002. at http://www.guttmacher.org/pubs/StateUP10.pdf? utm\_source=Master+ List&utm\_campaign=e5cff5fe20-State\_Unintended\_Pregnancy\_2010&utmmedium=email&ut m term=0 9ac83dc920-e5cff5fe20-2442939492015.
- [26] Finer LB, Jerman J, Kavanaugh ML. Changes in use of longacting contraceptive methods in the United States, 2007– 2009. Fertil Steril 2012;98:893–7.

## **APPENDIX DD**

WOMEN'S HEALTH By Nora V. Becker and Daniel Polsky

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# WOMEN SAW LARGE DECREASE IN OUT-OF-POCKET SPENDING FOR CONTRACEPTIVES AFTER ACA MANDATE REMOVED COST SHARING

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**ABSTRACT** The Affordable Care Act mandates that private health insurance plans cover prescription contraceptives with no consumer cost sharing. The positive financial impact of this new provision on consumers who purchase contraceptives could be substantial, but it has not yet been estimated. Using a large administrative claims data set from a national insurer, we estimated out-of-pocket spending before and after the mandate. We found that mean and median per prescription out-of-pocket expenses have decreased for almost all reversible contraceptive methods on the market. The average percentages of out-of-pocket spending for oral contraceptive pill prescriptions and intrauterine device insertions by women using those methods both dropped by 20 percentage points after implementation of the ACA mandate. We estimated average out-of-pocket savings per contraceptive user to be \$248 for the intrauterine device and \$255 annually for the oral contraceptive pill. Our results suggest that the mandate has led to large reductions in total out-of-pocket spending on contraceptives and that these price changes are likely to be salient for women with private health insurance.

Contraceptives are among the most widely used medical services in the United States, and 99 percent of sexually active women have used at least one type of contraceptive in their lifetime.<sup>1</sup> Contraceptives are much less costly than maternal deliveries for insurers and patients, and their use has been shown to result in net savings to insurers.<sup>2</sup>

Contraceptive use also has important effects on families and the economy. Studies of the effects of legalization of the contraceptive pill in the 1960s and 1970s found that increased access to contraception was associated with lower rates of subsequent entry into poverty, higher rates of laborforce participation and entry into professional school, and higher wages for women.<sup>3-6</sup> These economic gains also affect subsequent generations: The children of women with increased access to contraception have higher rates of college completion and higher incomes, compared to children whose mothers did not have access to family planning.<sup>7</sup>

A variety of contraceptive products are currently available to women in the United States. Some—like the oral contraceptive pill—are relatively inexpensive but must be purchased monthly. Others can be very expensive but require only a one-time purchase for months or years of contraceptive coverage. These methods of long-act-ing reversible contraceptives (sometimes called LARCs) are the intrauterine device (IUD) and the subdermal implant. Both are much more effective than oral contraceptives, but before the ACA they could require a one-time out-of-pocket payment of several hundred dollars.

This high up-front cost may have deterred some women from using long-acting reversible contraception methods. A recent study of women enrolled in private health insurance who ex-pressed interest in an IUD found that women with a lower out-of-pocket spending requirement for the device and insertion procedure were significantly more likely to receive an IUD than women who faced higher out-of-pocket expenses.<sup>8</sup>

The Affordable Care Act (ACA) includes a mandate that "preventive services"—a category of services that includes both prescription contraceptives and their related medical services—be covered with no consumer cost sharing. This mandate went into effect August 1, 2012. It required that insurance plans come into compliance at the beginning of the subsequent plan year, which for many women was January 1, 2013. The mandate includes all contraceptive methods approved by the Food and Drug Administration (FDA), including female sterilization and prescription emergency contraception, but it excludes over-the-counter emergency contraception and abortifacients.<sup>9</sup> The mandate does not require that insurance companies cover every brand of prescription contraceptive on the market.

The ACA mandate applies nationally to all private health insurance plans, including those offered in the health insurance Marketplaces and by employers. The only exceptions are grand-fathered plans and those offered by employers that receive an exemption for religious reasons. Grandfathered plans are health plans that have not substantially changed their cost-sharing requirements since March 2010, the month when the ACA became law. These plans are gradually being phased out of the employersponsored health insurance marketplace but still covered 36 percent of insured workers as of 2013.<sup>10</sup> This means that a significant subset of women are still enrolled in plans that are not yet subject to the ACA's mandate of zero cost sharing for contraception.

The inclusion of prescription contraceptive coverage in the ACA's mandate has drawn a large amount of political attention. Much of the debate surrounding the mandate has focused on either the effect of the mandate on employers' religious freedom or the potential impact of the mandate on women's health.<sup>11-12</sup> Its financial impacts on women as consumers have attracted far less attention. However, one recent survey of several hundred privately insured women found that the average out-of-pocket price for the pill had dropped from \$14.35 per month in 2012 to \$6.48 in 2014.<sup>13</sup>

Our aim was to systematically quantify declines in out-ofpocket spending between 2012 and 2013 for all available reversible prescription contraceptive methods. This will allow an understanding of relative changes in price across methods, particularly between the pill and long-acting reversible contraception methods. We also put these spending changes into their financial context for women as consumers by examining how these price declines affect both their total out-of-pocket spending on health care and the proportion of that spending that is spent on prescription contraceptives.

#### **Study Data And Methods**

We used a 10 percent sample of the Clinfor-matics<sup>TM</sup> Data Mart from Optum Insight, a claims database from a large national insurer, to calculate monthly out-of-pocket spending between January 2008 and June 2013 for the eight categories of prescription contraceptives listed in Exhibit 1. Our sample consisted of 17.6 million month-level observations for 790,895 women ages 13-45 who were enrolled in private health insurance for at least one month during this period. The mean and median lengths of insurance enrollment were

22.3 and 17.0 months, respectively. The data set included women in all fifty states and the District of Columbia.

### **EXHIBIT 1**

# Characteristics Of Prescription Contraceptives And Consumers' Out-Of-Pocket Expenses

\* \* \*

# THE INCLUSION OF PRESCRIPTION CONTRACEPTIVE COVERAGE IN THE ACA'S MANDATE HAS DRAWN A LARGE AMOUNT OF POLITICAL ATTENTION.

**ESTIMATING AVERAGE OUT-OF-POCKET SPENDING** Per claim out-of-pocket spending was calculated using pharmacy claims for contraceptive methods delivered in a pharmacy, such as oral contraceptives, the contraceptive patch and ring, and diaphragms and cervical caps. Contraceptive methods delivered in a physician office (IUDs, implants, and injections) were identified in the medical claims data using Current Procedural Terminology, Fourth Edition (CPT-4); level 2 Healthcare Common Procedure Coding System (HCPCS); and International Classification of Diseases, Ninth Revision (ICD-9), procedural and diagnostic codes. We estimated out-ofpocket spending for these three methods by aggregating all patient cost sharing for the encounter during which the method or device was delivered, because procedural costs associated with these methods are billed separately from the cost of the device itself.

For all contraceptive methods, we report the six-month mean or median per claim out-of-pocket expense. For shortterm products such as the pill, the patch, and the ring, this calculation is not equivalent to the per month out-of-pocket expense because many women receive two to three months of contraceptive supplies when they fill their prescriptions. Our cost estimates are therefore not comparable with monthly estimates reported previously in the survey literature.

Before the ACA mandate, contraceptives were subject to yearly deductibles and out-of-pocket limits. The average costs per method therefore declined predictably over the course of a given year as some women used up their deductibles or hit their out-of-pocket spending limits and incurred lower out-of-pocket expenses for their method of contraception. To remove the influence of deductibles and out-of-pocket limits from our estimates, in some of our analyses we regressed pre-August 2012 out-of-pocket expenses on a set of monthly dummies and then plotted the residual variation in out-of-pocket spending.<sup>14</sup>

**ESTIMATING CHANGES IN TOTAL OUT-OF-POCKT SPENDING** To estimate the share of out-of-pocket spending for prescription contraceptives, we focused on users of the pill and women who had new IUD insertions, since the pill and the IUD are the two most commonly used reversible prescription contraceptive methods in the United States.<sup>15</sup> To minimize selection bias, we limited our spending analysis to women who were continuously enrolled in insurance from January 2012 to June 2013. We then compared spending patterns among pill users and women who received IUD insertions in the pre period (January-June 2012) to patterns in the post period (January-June 2013).

We defined *pill users* as women who had at least one claim for an oral contraceptive pill in both the pre and post periods. We included spending in both periods for pill users. We defined *IUD users* as women who had an IUD inserted in either the pre or the post period. We included spending for IUD users only in the period in which they received their IUD.

For each woman, we summed her out-of-pocket spending on either pills or IUD insertion and divided that value by her total out-of-pocket spending during that period. Using these percentages and the mean and median total out-of-pocket spending values for these users, we then estimated the mean and median implied savings on pills and IUD insertions per woman attributable to the ACA mandate.

Implied savings were calculated by multiplying the mean (or median) total spending by the mean (or median) percentage of spending spent on that method for each period and then subtracting the 2013 estimate from the 2012 estimate. This calculation took into account the possibility that total average out-of-pocket spending might have changed during this time period. For pill users, this value was then multiplied by two to estimate total yearly spending.

All costs are presented in inflation-adjusted 2013 dollars. Analyses were performed using Stata/MP, version 13.

**LIMITATIONS** There were a number of important limitations to our study. Claims for emergency contraception and diaphragms or cervical caps were infrequent in our data, so we recommend caution when interpreting estimates for these methods. Additionally, we did not include cost sharing for physician appointments or costs of IUD or implant removals in our estimates, which resulted in a conservative estimate of out-of-pocket spending.

For contraceptive methods obtained in a physician office and reported in medical claims (the IUD, implant, and injection), we calculated expenses per encounter. If a woman received another expensive service at the same encounter for instance, if an IUD or implant was inserted immediately after maternal delivery—it is possible that we erroneously included the costs of those procedures in some of our totals. We therefore report both means and medians in our results. We also conducted a sensitivity analysis in which we excluded the top 1 percent of expenses for each of these methods. This lowered the estimated mean expenses slightly but had almost no effect on the estimated median expenses. Finally, our implied savings estimates assumed that in the absence of the mandate, out-of-pocket expenses for consumers would have stayed the same as they were in the period January-June 2012. This could be an unrealistic assumption in particular for IUDs, which demonstrated a dynamic average monthly out-of-pocket price prior to the mandate's implementation. Because of this limitation, the savings estimates should be interpreted as short-term changes in out-of-pocket spending only and should not be used for long-term estimates of out-of-pocket spending reductions.

#### **Study Results**

Adjusted mean per claim out-of-pocket spending declined for both the pill and the IUD after implementation of the ACA mandate (Exhibit 2). The average adjusted out-ofpocket expense for a pill prescription fell from \$33.58 in June 2012 to \$19.84 in June 2013, and the out-of-pocket expense for an IUD insertion fell from \$293.28 to \$145.24.

#### \$255

#### Per year

# The average user of the pill saved \$254.91 per year after the ACA mandate took effect.

To better examine the change in costs for all contraceptive methods, we report the unadjusted six-month mean and median per claim out-of-pocket spending for each prescription contraceptive method in the pre and post periods (Exhibit 3). At baseline in 2012, the method that was most expensive up front was the implant, with a mean expense of \$320.31, followed by the IUD, at \$262.38. The methods with the lowest per claim expense were the pill (\$32.74), emergency contraceptives (\$26.16), and diaphragms or cervical caps (\$34.48).

However, out-of-pocket spending for short-term methods compared to that of long-term methods must be considered in the context of the length of time the methods are used. Short-term methods such as the pill must be purchased

repeatedly over time, while the out-of-pocket expense for long-term methods such as IUDs is a one-time expense. In the long run, long-acting reversible contraception methods such as the IUD or implant have been shown to be less costly than repeatedly purchasing a short-term method such as the pill for an equivalent length of time.<sup>16</sup>

We observed large decreases in the mean out-of-pocket expenses of most methods following implementation of the mandate (Exhibit 3).

#### EXHIBIT 2

Trend In Mean Adjusted Per Claim Out-Of-Pocket Expenses For Oral Contraceptive Pill Prescription Fills And Intrauterine Device (IUD) Insertions, 2008-13

\* \* \*

#### EXHIBIT 3

# Mean And Median Per Prescription Out-Of-Pocket Expenses For Prescription Contraceptive Methods Before And After Implementation Of The Affordable Care Act Mandate, 2012 And 2013

\* \* \*

From June 2012 to June 2013 the mean out-of-pocket expense for the pill declined by 38 percent, and the mean out-of-pocket expense for an IUD declined by 68 percent. We also found decreases in spending for emergency contraception (93 percent), diaphragms or cervical caps (84 percent), the implant (72 percent), and the injection (68 percent). In contrast, spending for the ring and the patch declined only 2 percent and 3 percent, respectively, over this period.

Median out-of-pocket per prescription spending fell to zero for almost all prescription contraceptive methods following implementation of the ACA mandate. This suggests that while some women were still paying large amounts out of pocket for their contraception, the majority of women were paying nothing by June 2013. The ring and the patch were the exceptions: Their mean and median out-of-pocket expenses remained similar during this time period.

To assess the relative magnitude of these out-of-pocket spending changes for contraceptive users, we examined total mean and median out-of-pocket spending and the percentage of that spending spent on contraceptives for pill users and women who received IUD insertions (Exhibit 4). Because the mandate was implemented mid-2012, we compared spending percentages in the first six months of 2012 with those in the first six months of 2013. For women who were enrolled in insurance continuously and had at least one claim for oral contraceptive pills in both periods, the mean and median percentages of out-of-pocket spending spent on the pill dropped from 44.0 percent and 36.0 percent to 22.4 percent and 0.0 percent, respectively. For women who received an IUD during the same periods, the mean and median out-of-pocket spending percentages in the period they received their IUD dropped from 30.3 percent and 13.2 percent to 11.3 percent and 0.0 percent, respectively.

We used these values to estimate the per woman savings on yearly oral contraceptive pill costs for pill users and on IUD insertions for women receiving IUDs. We estimated that the average pill user saved \$254.91 per year, and the median pill user saved \$204.65 per year (Exhibit 4). The mean and median savings on IUD insertions were estimated to be \$248.30 and \$107.95, respectively, per woman.

#### Discussion

Out-of-pocket expenses used in this study for the period before the implementation of the ACA mandate were roughly equivalent to those in other available data.<sup>16-17</sup> However, we found substantial drops in both the mean and the median outof-pocket spending for most contraceptive methods after the mandate's implementation. Median spending for almost all contraceptive methods fell to zero within ten months of implementation, and mean spending dropped by large percentages (38-93 percent, depending on the method). Mean out-of-pocket spending remained above zero for two reasons: Not all brands are required to be covered with zero cost sharing, and a subset of women in the data were enrolled in grandfathered plans that were not yet subject to the mandate.

Before the mandate's implementation, out-of-pocket for contraceptives for women using them expenses represented a significant portion (30-44 percent) of these women's total out-of-pocket health care spending. This is a finding that, to our knowledge, has not been previously reported. It is likely that contraceptives are a significant proportion of total health spending because contraceptive users tend to be young women with few serious health issues. For these women, obtaining contraceptives is likely their primary reason for visiting a health care provider and paying out-of-pocket amounts. Because contraceptives represented a large portion of their health care spending before the mandate, the price reductions caused by the ACA are likely to be salient for these women.

A recent industry report estimated that the ACA mandate saved women \$483 million in out-of-pocket spending on the pill in 2013.<sup>18</sup> Our findings suggest that reductions in out-ofpocket expenditures on contraceptives in 2013 were in fact much higher, as demonstrated using a quick back-of-theenvelope calculation. The most recent estimates suggest that there are 6.88 million privately insured pill users in the United States.' Multiplying this by our conservative median estimate of \$204.65 peryear yields an estimate of \$1.4 billion per year in out-of-pocket savings on the pill alone.

#### EXHIBIT 4

# Out-Of-Pocket Spending On Prescription Birth Control By Oral Contraceptive Pill Users And Women Receiving Intrauterine Devices (IUDs), 2012 And 2013

\* \* \*

#### **Policy Implications**

Our findings suggest that the ACA mandate will likely significantly reduce the out-of-pocket expenditures of contraceptive users, in some cases to nothing. But it is still too early to predict the final impact of the mandate on health care use and spending, or the mandate's impact on other health and socioeconomic outcomes for women.

Economic theory and empirical evidence suggest that decreasing out-of-pocket contraception expenses to consumers will result in increased use.<sup>19-20</sup> An increase in the use of contraceptives could have long-ranging impacts upon women's health and the economy, potentially lowering fertility rates and increasing economic opportunities for women and their families.<sup>4-6, 21</sup>

The ACA mandate also changes the relative prices of different contraceptive methods. Because long-acting reversible contraceptive methods are more costly up front, it is possible that removing financial barriers to all methods might induce women to choose long-acting reversible contraceptive methods at higher rates.

The CHOICE Project, a recent prospective cohort study of 9,256 women ages 14-45, offered participants their choice of contraceptive at no cost after they received counseling and education about all available methods.22'23 With the barriers of cost, knowledge, and access removed, 75 percent of participants chose a long-acting reversible contraception method. Participants who chose such methods had higher rates of continuing to use their device and of satisfaction at twelve and twenty-four months of follow-up. In addition, their rates of pregnancies, births, and abortions in the twenty-

four-month follow-up period were much lower than national rates during the same period.

Some policy makers and media outlets have raised concerns that no-cost contraceptives, or increased use of more effective contraceptives, might increase risky sexual behavior. However, the CHOICE Project found no evidence of increased sexual risk taking among the study cohort.

The CHOICE Project enrolled only women who were interested in starting a new contraceptive method and specifically counseled participants about the relative effectiveness of long-acting reversible contraception methods compared to more short-term methods. In contrast, the ACA mandate lowered the out-of-pocket expense for contraceptives for all women in private health plans, many of whom might be uninterested in changing their current contraceptive method.

# IT IS STILL TOO EARLY TO PREDICT THE FINAL IMPACT OF THE MANDATE ON HEALTH CARE USE AND SPENDING, OR ON OTHER HEALTH AND SOCIOECONOMIC OUTCOMES FOR WOMEN.

Furthermore, the ACA mandate does not directly change providers' behavior or affect consumers' knowledge about contraceptives, although some providers may take it upon themselves to educate their patients about the mandate. In some cases, women may not even be aware that their coverage has changed. A recent study of young adults' experiences in shopping for health insurance on HealthCare.gov found that many were unaware that well-women visits and contraception were included as preventive services with no cost sharing.<sup>24</sup>

The impact of the ACA mandate on contraceptive utilization will therefore depend on how sensitive consumers are to out-of-pocket expenses for contraceptives and how many women were dissuaded from using contraceptive by products that expense before the mandate's implementation." Very few studies have estimated the responsiveness of consumers to the out-of-pocket expense of contraceptives in the United States, and no study has estimated it for the population of privately insured women affected by the ACA mandate. Future work will need to measure whether these spending changes result in increased use of contraceptives or changes in the choice of contraceptive methods.

Lastly, insurance companies are required to cover all contraceptive methods with no consumer cost sharing in plans that are not grandfathered, but they are not required to cover all brands. The large national insurer that provided our data appeared to be interpreting this broadly, as out-of-pocket spending for the patch and the vaginal ring did not follow the same pattern as spending for other methods. Mean and median out-of-pocket expenses for the patch and vaginal ring remained very similar to premandate levels.

These findings are consistent with results from several recent studies suggesting that not all insurers are fully complying with the mandate.<sup>26, 27</sup> In response to these reports, the Departments of Labor, Health and Human Services, and the Treasury jointly issued new guidelines May 11, 2015, clarifying the requirements of the mandate. These guidelines specify that insurers must cover with no cost sharing at least one of the eighteen FDA-approved contraceptive methods, including methods such as the patch and the ring.<sup>28</sup> Insurers can use cost sharing to direct consumers to lower-cost methods within a category, as long as at least one method within each category is covered with zero cost sharing.

With this new clarification from the administration of President Barack Obama, we expect that the pattern of outof-pocket expenses for the patch and the ring among the

population we studied will soon resemble that of other methods.

# Conclusion

We found the ACA-mandated removal of consumer cost sharing for prescription contraceptives in nongrandfathered insurance plans resulted in large reductions in out-of-pocket spending on contraceptives. A woman who uses oral contraceptive pills or the IUD, the two most commonly used reversible prescription contraceptive methods, has the potential to save several hundreds of dollars each year. This represents a significant portion of the average total out-ofpocket medical spending in this population. The impact of these reductions in out-of-pocket expenditures on the use of contraceptives, fertility, and women's health will depend on the price sensitivity of privately insured women for prescription contraceptives.

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#### NOTES

- 1 Daniels K, Mosher WD, Jones J. Contraceptive methods women have ever used: United States, 1982-2010. Nati Health Stat Report. 2013;(62): 1-15.
- 2 Foster DG, Rostovtseva DP, Brindis CD, Biggs MA, Hulett D, Darney PD. Cost savings from the provision of specific methods of contraception in a publicly funded program. Am J Public Health. 2009;99(3):446-51.
- **3** Bailey MJ, Hershbein B, Miller AR. The opt-in revolution? Contraception and the gender gap in wages

[Internet]. Cambridge (MA): National Bureau of Economic Research; 2012 Mar [cited 2015 May 15]. (NBER Working Paper No. 17922). Available from: http://www.nber.org/papers/w17922.pdf

- **4** Goldin C, Katz LF. The power of the pill: oral contraceptives and women's career and marriage decisions. J Polit Econ. 2002;110(4):730-70.
- **5** Browne SP, LaLumia S. The effects of contraception on female poverty. J Policy Anal Manage. 2014;33(3): 602-22.
- 6 Ananat EO, Hungerman DM. The power of the pill for the next generation [Internet]. Cambridge (MA): National Bureau of Economic Research; 2007 Sep [cited 2015 May 15]. (NBER Working Paper No. 13402). Available from: http:// www.nber.org/papers/w13402.pdf
- 7 Bailey MJ. Fifty years of family planning: new evidence on the long-run effects of increasing access to contraception [Internet]. Cambridge (MA): National Bureau of Economic Research; 2013 Oct [cited 2015 May 15]. (NBER Working Paper No. 19493). Available from: http://www.nber.org/papers/w19493.pdf
- 8 Gariepy AM, Simon EJ, Patel DA, Creinin MD, Schwarz EB. The impact of out-of-pocket expense on IUD utilization among women with private insurance. Contraception. 2011; 84(6):e39-42.
- 9 Kraemer J. The ACA's contraception coverage mandate: Constitutional limits on exempting employers. Health Affairs Blog [blog on the Internet]. 2014 Mar 20 [cited 2015 May 15]. Available from: http:// healthaffairs.org/blog/2014/03/20/ the-acascontraception-coverage-mandate-constitutional-limitson-exempting-employers/

- 10 Henry J. Kaiser Family Foundation, Health Research and Educational Trust. Employer health benefits: 2013 annual survey [Internet]. Menlo Park (CA): KFF; 2013 Sep [cited 2015 Jun 8]. Available from: http://kff.org/private-insurance/ report/2013-employerhealth-benefits/
- 11 Annas GJ, Ruger TW, Ruger JP. Money, sex, and religion: the Supreme Court's ACA sequel. N Engl J Med. 2014;371(9):862-6.
- 12 Gossett DR, Kiley JW, Hammond C. Contraception is a fundamental primary care service. JAMA. 2013; 309(19):1997-8.
- **13** Sonfield A, Tapales A, Jones RK, Finer LB. Impact of the federal contraceptive coverage guarantee on out-of-pocket payments for contraceptives: 2014 update. Contraception. 2014;91(1):44-8.
- 14 Lovell MC. Seasonal adjustment of economic time series and multiple regression analysis. J Am Stat Assoc. 1963;58(304):993-1010.
- 15 Jones J, Mosher W, Daniels K. Current contraceptive use in the United States, 2006-2010, and changes in patterns of use since 1995. Nati Health Stat Report. 2012; (60):1-25.
- 16 Trussell J, Lana AM, Doan QV, Reyes E, Pinto L, Gricar J. Cost effectiveness of contraceptives in the United States. Contraception. 2009;79(1): 5-14.
- 17 Center for American Progress. The high costs of birth control: it's not as affordable as you think [Internet]. Washington (DC): The Center; 2012 Feb 15 [cited 2015 May 18]. (Fact Sheet). Available from: https://www .americanprogress.org/issues/
  women/news/2012/02/15/11054/ the-high-costs-of-birth-control/

- 18 IMS Institute for Healthcare Informatics. Medicine use and shifting costs of healthcare: a review of the use of medicines in the United States in 2013 [Internet]. Parsippany (NJ): IMS; 2014 Apr [cited 2015 May 18]. Available from: http://www .imshealth.com/cds/imshealth/ Global/Content/Corporate/IMS %20Health%20Institute/Reports/ Secure/IIHI\_US\_Use\_of Meds\_ for\_2013.pdf
- **19** Pauly MV. The economics of moral hazard: comment. Am Econ Rev. 1968;58(3):531-7.
- **20** Manning WG, Newhouse JP, Duan N, Keeler EB, Leibowitz A, Marquis MS. Health insurance and the demand for medical care: evidence from a randomized experiment. Am Econ Rev. 1987;77(3):251-77.
- **21** Bailey MJ. "Momma's got the pill": how Anthony Comstock and Griswold v. Connecticut shaped US childbearing. Am Econ Rev. 2010;100(1): 98-129.
- 22 Secura GM, Madden T, McNicholas C, Mullersman J, Buckel CM, Zhao Q, et al. Provision of no-cost, longacting contraception and teenage pregnancy. N Engl J Med. 2014; 371(14):1316-23.
- **23** McNicholas C, Madden T, Secura G, Peipert JF. The Contraceptive CHOICE Project round up: what we did and what we learned. Clin Obstet Gynecol. 2014;57(4):635-43.
- 24 Wong CA, Asch DA, Vinoya CM, Ford CA, Baker T, Town R, et al. The experience of young adults on HealthCare.gov: suggestions for improvement. Ann Intern Med. 2014; 161(3):231-2.
- **25** Pauly MV, Held PJ. Benign moral hazard and the costeffectiveness analysis of insurance coverage. J Health Econ. 1990;9(4):447-61.

- 26 Sobel L, Salganicoff A, Kurani N. Coverage of contraceptive services: a review of health insurance plans in five states [Internet]. Menlo Park (CA): Henry J. Kaiser Family Foundation; 2015 Apr 16 [cited 2015 May 26]. Available from: http://kff .org/privateinsurance/report/ coverage-of-contraceptive-services-areview-of-health-insurance-plans-in-five-states/
- 27 National Women's Law Center. State of birth control coverage: health plan violations of the Affordable Care Act [Internet]. Washington (DC): NWLC; 2015 Apr [cited 2015 Jun 18]. Available from: http://www .nwlc.org/resource/state-birth-control-coverage-healthplan-violations-affordable-care-act
- 28 Departments of Labor, Health and Human Services, and the Treasury. FAQs about Affordable Care Act implementation (part XXVI) [Internet]. Washington (DC): HHS; 2015 May 11 [cited 2015 May 26]. Available from: http://www.cms.gov/ CCIIO/Resources/Fact-Sheets-and-FAQs/Downloads/aca implementation faqs26.pdf