Paternity and Oral Contraceptive Use in Relation to Ovarian Cancer Risk in Older Women

Valerie McGuire¹, Patricia Hartge², Linda M. Liao³, Rashmi Sinha³, Leslie Bernstein⁴, Alison J. Canchola⁵, Garnet L. Anderson⁶, Marcia L. Stefanick⁷, and Alice S. Whittemore¹

Abstract

Background: Several studies have suggested that the ovarian cancer risk reductions associated with parity and oral contraceptive use are weaker in postmenopausal than premenopausal women, yet little is known about the persistence of these reductions as women age. This question gains importance with the increasing numbers of older women in the population.

Methods: We addressed the question using data from three large U.S. cohort studies involving 310,290 white women aged 50+ years at recruitment, of whom 1,815 developed subsequent incident invasive epithelial ovarian cancer. We used Cox regression, stratified by cohort, to examine age-related trends in the HRs per full-term pregnancy and per year of oral contraceptive use.

Results: The parity-associated risk reductions waned with age (Pwood < 0.001 in HR with increasing age), particularly among women aged 75 years or more, for whom we observed no association with parity. However, we observed no such attenuation in the oral contraceptive–associated risk reductions (P = 0.79 for trend in HR with increasing age).

Conclusion: These findings suggest that prior oral contraceptive use is important for ovarian cancer risk assessment among women of all ages, while the benefits of parity wane as women age.

Impact: This information, if duplicated in other studies, will be useful to preventive counseling and risk prediction, particularly for women at increased ovarian cancer risk due to a personal history of breast cancer or a family history of ovarian cancer.

Introduction

A large and consistent body of evidence indicates that increased parity and duration of oral contraceptive (OC) use are associated with reduced risk of invasive epithelial ovarian cancer (EOC), a malignancy with a 44% 5-year survival rate in the United States (1). Specifically, the data suggest that each full-term pregnancy (FTP) confers a risk reduction of approximately 19% (2), and risks among women with three or more years of OC use are 30% to 50% lower than those of women with little or no use (2, 3).

The available data also suggest that these associations are weaker in postmenopausal than premenopausal women (4–7). However, this observation is based largely on women aged less than 65 years, and little is known about the long-term effects of pregnancy and OC use among women as they age. This question has important clinical and public health significance, as more than 80% of all EOCs now occur after the age of 50 years (8), and this age group represents an increasing proportion of women in developed countries. Thus, the burden of this highly fatal cancer will continue to grow as population distributions of women become more heavily skewed toward older ages, and accurate assessment of women’s risks is critical for the development of cost-effective preventive strategies.

Here, we assess the existence and extent of age-related trends in the effects of parity and OC use in older women using data from three large U.S. cohort studies involving 310,290 white women aged 50 years or more at recruitment, of whom 1,815 developed subsequent incident invasive EOC. The three studies were the NIH-AARP Diet and Health Study (hereafter called the AARP study), the California Teachers Study (CTS), and the Women’s Health Initiative (WHI).

Materials and Methods

Study population

The AARP study, established in 1995 to 1996, included 339,669 male and 222,732 female AARP members ages 50 to 71 years and residing in eight regions; California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania, and the metropolitan areas of Atlanta and Detroit. The CTS, established in 1995 to 1996, included 133,479 female California public school professionals (active or retired) ages 22 years or more at recruitment. The WHI, established in 1993 to 1998 and comprising longitudinal data from a randomized intervention trial and an observational study, includes 161,808 postmenopausal women ages 50 to 79 years, as identified by 40 U.S. study sites. Details about the studies’ designs and characteristics have been described elsewhere (9–11).
Participants were potentially eligible for the current analysis if at recruitment they reported that they were white, ages 50 years or more, without prior invasive or noninvasive ovarian cancer diagnosis, and without prior bilateral oophorectomy. A total of 318,709 participants met these criteria (155,636 from AARP, 50,772 from CTS, and 110,407 from the WHI trial and observational cohorts). Of these, 310,290 (154,045 from AARP, 47,365 from CTS, and 108,880 from WHI) provided complete information on parity and duration of OC use and were included in the analysis. Among the 108,880 eligible WHI subjects, 45,939 (42%) were trial participants. Of these, 16,208 participated in the Hormone Replacement Therapy (HRT) Trial and the remaining 29,731 participated in one or both of the two diet trials (Diet Modification Trial and Calcium and Vitamin D Trial). Among the 16,208 HRT Trial participants, 10,373 also participated one or both of the two dietary trials. We focused on parity and OC use because the three cohorts lacked comparable information on other covariates associated with ovarian cancer (e.g., tubal ligation, prior hysterectomy without bilateral oophorectomy, and duration of menopausal hormone therapy).

### Ovarian cancer ascertainment

The AARP and CTS investigators identified incident ovarian cancer cases via linkages with cancer registries in the studies' recruitment areas, while the WHI investigators did so using questionnaires mailed semiannually during active intervention for clinical trial participants and annually otherwise. All three studies monitored participants' vital statuses using questionnaires mailed semiannually during active intervention for clinical trial participants and annually otherwise. Table 1 presents selected characteristics of the three cohorts and the distributions of their eligible participants according to the year of birth, age at recruitment, parity, and years of OC use. Participants contributed, on average, 10.5 person-years at risk (PYR) using Cox proportional hazards regression models stratified by cohort, with age as the underlying time variable. Each participant’s time-at-risk was left truncated at the age she completed her baseline questionnaire and right censored at her age at first occurrence of the following events: last contact, death from any cause; diagnosis of any ovarian cancer (in situ, low malignant potential, invasive epithelial, nonepithelial); bilateral oophorectomy subsequent to baseline questionnaire; and, for AARP and CTS, departure from the cohort catchment area (total US-SEER region for AARP and California for CTS).

All regressions included parity (categorized as categorical or as ordinal variable), years of oral contraceptive use, (categorized as categorical or as continuous variable), and year of birth (categorized as continuous variable). We lacked data on recency of OC use. We used likelihood ratio statistics to evaluate age-related trends in the HRs per FTP and per 5 years of OC use. For example, we tested the null hypothesis of no age-related trend in parity-specific HRs by comparing the likelihood of the basic model that includes parity as ordinal variable (adjusted for OC use and birth year as continuous variables) with that of an expanded model that also includes terms for the product of parity and an ordinal variable for the three age-at-risk categories 50–64, 65–74, and 75+ years. We also used likelihood ratio statistics to evaluate age-related heterogeneity in EOC histology and cohort-heterogeneity in age-specific HRs for parity and OC use. Analyses were implemented using SAS Statistical Software 9.4 (SAS Institute, Cary, NC). All tests of statistical significance are two sided.

This research was approved by the Institutional Review Boards at the three study sites and at Stanford University School of Medicine (Stanford, CA).

### Results

Table 1 presents selected characteristics of the three cohorts and the distributions of their eligible participants according to the year of birth, age at recruitment, parity, and years of OC use. Participants contributed, on average, 10.5 person-years at risk (PYR).
Table 3 shows EOC HRs corresponding to parity and OC use for women aged less than 75 years, with increasing parity for women aged less than 75 years, with 75–84 and 85+ age groups (data not shown).

Table 3: Parity and OC use in relation to invasive EOC incidence by age at risk

<table>
<thead>
<tr>
<th>Age (years) at risk</th>
<th>50–64</th>
<th>65–74</th>
<th>75+</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>209,428.3 116 55.39 1.00 (ref)</td>
<td>194,582.2 154 79.14 1.00 (ref)</td>
<td>82,103.5 34 41.41 0.88 (0.83–0.93)</td>
</tr>
<tr>
<td>3–4</td>
<td>523,357.8 206 39.36 0.93 (0.75–1.16)</td>
<td>485,899.1 234 46.16 0.84 (0.69–1.02)</td>
<td>242,262.1 153 59.34 0.99 (0.88–1.00)</td>
</tr>
<tr>
<td>5+</td>
<td>391,359.8 173 44.21 0.69 (0.54–0.89)</td>
<td>587,899.6 367 62.43 0.74 (0.61–0.89)</td>
<td>224,262.6 161 74.02 0.98 (0.72–1.32)</td>
</tr>
<tr>
<td>Trend per FTP</td>
<td>82,103.5 34 41.41 0.38 (0.22–0.63)</td>
<td>194,164.4 135 69.53 0.56 (0.43–0.73)</td>
<td>75,274.3 69 91.66 0.92 (0.62–1.36)</td>
</tr>
<tr>
<td>Trend per 5 years of use</td>
<td>0.88 (0.83–0.93)</td>
<td>0.91 (0.88–0.95)</td>
<td>1.00 (0.95–1.06)</td>
</tr>
</tbody>
</table>

Years of OC use

| 0                   |       |       |     |
| <1                  | 508,337.6 248 48.79 1.00 (ref) | 963,115.4 650 67.49 1.00 (ref) | 478,316.4 346 72.34 1.00 (ref) |
| 1–4                 | 302,470.8 125 41.33 0.85 (0.68–1.06) | 208,348.1 116 55.68 0.87 (0.71–1.06) | 41,104.1 19 46.23 0.65 (0.41–1.03) |
| 5–9                 | 225,398.2 94 41.70 0.86 (0.67–1.09) | 151,149.4 76 50.28 0.80 (0.63–1.02) | 28,862.5 16 55.44 0.77 (0.46–1.27) |
| 10+                 | 170,002.8 62 55.39 0.75 (0.55–0.97) | 139,932.4 48 79.14 0.53 (0.39–0.71) | 30,889.0 15 74.30 0.70 (0.42–1.18) |
| Trend per 5 years of use | 0.88 (0.80–0.98) | 0.82 (0.74–0.91) | 0.85 (0.71–1.02) |

Abbreviation: CI, confidence interval.

aCIR, crude incidence rate (# EOCs per 100,000 PYRs).

bHR, hazard ratio from Cox regression with baseline hazard stratified by cohort. Parity HRs are adjusted for birth year and OC use, and OC HRs are adjusted for birth year and parity.

cLikelihood ratio χ² test of hypothesis that risk per FTP does not vary with age at risk.

dLikelihood ratio χ² test of hypothesis that risk per 5 years of OC use does not vary with age at risk.
Discussion

We used data from Caucasian participants of three large prospective cohort studies to examine how the risk reductions associated with parity and OC use change as women age. We found age-related differences in the protective effects of parity, with significantly reduced parity-associated HRs among women less than 75 years, but no effect at later ages. In contrast, we did not find evidence that the risk reductions associated with OC use wane with age among older women.

Interpreting these findings and their implications for the etiology and pathogenesis of EOC is challenging. As the lag between last exposure and age at risk is likely to be greater for pregnancy than for OC use (which may end only at menopause), the observed lack of age-related trend in the effects of OC use could reflect its recency relative to that of pregnancy. Another issue is that the HR associated with OC use may be attenuated among women aged 50 to 60 years by their use of menopausal hormone therapy, which is positively correlated with OC use (13).

The observed temporal waning of the effects of pregnancy is consistent with the hypothesis that anovulation reduces a woman’s ovarian cancer risk by reducing her burden of mutated epithelial cells at risk of conversion to malignancy. These mutations may reflect some ovariolytic consequence (such as rupture of the ovarian epithelium or cellular exposure to follicular fluid or to hormonal fluctuations). The long-term benefits of anovulation (i.e., reducing the burden of premalignant cells) may be attenuated by the occurrence of additional somatic mutations occurring as part of normal ovarian tissue aging (14, 15). The attenuation may be greater for pregnancy than OC use because pregnancies occurred in the more distant past. Alternatively, the attenuation may be more obvious for pregnancy than OC use because a year of pregnancy-induced anovulation confers a greater risk reduction at all ages than one due to OC use, possibly due to transient hormonal changes during pregnancy that induce apoptosis of existing premalignant cells (16).

The current combined analysis of large prospective cohorts has several advantages. Unlike retrospective case–control studies comparing prior OC use as recalled by EOC cases with those of disease-free controls, the cohort design ascertains reproductive history at cohort entry relatively soon after menopause and before the onset of disease, and thus avoids potential long-term recall bias. However, the combined analysis of large cohorts has weaknesses. In this study, for example, the questionnaire data were too limited to allow evaluation of such factors as recency of anovulatory exposures to age at risk. Another limitation is the sparsity of OC users who subsequently developed EOC at ages 75+ years (n = 50). These limitations emphasize the need for replication of the current observations in other large cohorts of older women.

In summary, the current data suggest that the protective effects of OC use persist for decades after the menopause, while the protection afforded by increased parity wanes in older women, particularly those aged 75 years and more. This information, if duplicated in other studies, will be useful to preventive counseling and risk prediction, particularly for women at elevated ovarian cancer risk due to a personal history of breast cancer or a family history of ovarian cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: V. McGuire, P. Hartge, R. Sinha, M.L. Stefanick, A.S. Whittemore

Development of methodology: V. McGuire, A.S. Whittemore

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P. Hartge, L.M. Liao, R. Sinha, L. Bernstein, G.L. Anderson, M.L. Stefanick

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): V. McGuire, G.L. Anderson, A.S. Whittemore

Writing, review, and/or revision of the manuscript: V. McGuire, P. Hartge, L.M. Liao, R. Sinha, L. Bernstein, A.J. Canchola, G.L. Anderson, M.L. Stefanick, A.S. Whittemore

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. Bernstein, A.J. Canchola, M.L. Stefanick

Study supervision: L. Bernstein, A.S. Whittemore

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