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

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## 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 US cohort studies involving 310,290 white women aged 50+ years at recruitment, of whom 1815 developed subsequent incident invasive epithelial ovarian cancer. We used Cox regression, stratified by cohort, to examine age-related trends in the hazard ratios per full-term pregnancy and per year of oral contraceptive use.

**Results—**The parity-associated risk reductions waned with age ($P < 0.001$ for trend in hazard ratio 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 hazard ratio 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.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

No potential conflicts of interest were disclosed.

**Keywords**

age trends; oral contraceptive use; ovarian cancer; parity

## 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% five-year survival rate in the US (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 30–50% 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 longer-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 age 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 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 US cohort studies involving 310,290 white women aged 50 years or more at recruitment, of whom 1815 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 1995–96, included 339,669 male and 222,732 female AARP members aged 50–71 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 1995–96, included 133,479 female California public school professionals (active or retired) aged 22 years or more at recruitment. The WHI, established in 1993–98 and comprising longitudinal data from a randomized intervention trial and an observational study, includes 161,808 postmenopausal women aged 50–79 years, as identified by 40 US 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, aged 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 in 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 semi-annually during active intervention for clinical trial participants and annually otherwise. All three studies monitored participants' vital statuses using the U.S. Social Security Administration Death Master File or the National Death Index. The present analysis includes invasive EOC's diagnosed by December 31, 2006 (AARP), December 31, 2011 (CTS) and August 19, 2009 (WHI). EOC histology was available from the cancer registries for the AARP Study and CTS. In the WHI, all reported ovarian cancers were documented with medical records and pathology reports obtained at each clinic site and centrally reviewed and coded according to SEER standards (12).

## Statistical methods

We performed left-truncated, right-censored survival analyses 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 (coded as categorical or as ordinal variable), years of oral contraceptive use, (coded as categorical or as continuous variable) and year of birth (coded as continuous variable). We lacked data on recency of OC use. We used likelihood ratio statistics to evaluate age-related trends in the hazard-ratios (HRs) per full-term pregnancy 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 hazard ratios 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.

## RESULTS

Table 1 presents selected characteristics of the three cohorts, and the distributions of their eligible participants according to year of birth, age at recruitment, parity and years of OC use. Participants contributed, on average, 10.5 person-years at risk (PYRs) with overall standard deviation (SD) given by 3.3 PYRs. Corresponding cohort-specific values were 9.8 (SD = 2.2) for AARP, 13.0 (SD = 4.7) for CTS and 10.3 (SD = 3.3) for WHI, during which a total of 1815 EOCs were diagnosed. The crude incidence rates (CIRs) are higher than the US SEER rates for white women of similar ages, a difference that reflects the requirement here that time at risk of ovarian cancer be contributed only by participants with at least one intact ovary. (We checked this assertion by applying the SEER rates to the person-years at risk contributed by an expanded AARP cohort supplemented by women who reported a prior bilateral oophorectomy, and found that the expected number of cases was similar to the number observed in the cohort.) As expected, the CIRs decreased with increasing year of birth, increasing number of FTPs, increasing years of OC use, and decreasing age at recruitment.

Table 2 shows that most EOCs were classified as serous cancers (49.7% serous, versus 22.1% non-serous and 28.2% other/unspecified EOCs cancers). The proportion of serous EOCs among those of known histology did not vary significantly with age at risk ($\chi^2_2=3.19$, $P = 0.20$) for test of heterogeneity among the three age groups (data not shown).

Table 3 shows EOC hazard ratios corresponding to parity and OC duration, for three age-at-risk categories: 50–64, 65–74 and 75+ years. The table shows clear patterns of decreasing EOC risk with increasing parity for women aged less than 75 years, with statistically significant risk reductions of 12% per full-term pregnancy (FTP) among women aged < 65 years, and 8% per FTP among women aged 65–74 years. However these patterns are not evident among women aged 75+ years. Indeed there is no decrease in the EOC hazard ratio with increasing FTPs (P < 0.001 for interaction between parity and age at risk).

In contrast, the lower EOC risk associated with duration of OC use did not vary with attained age (P = 0.79 for interaction). The risk reductions per five years of OC use ranged from 12% to 18% in the three age groups, with no evidence for differences among the attained age groups, and with an overall reduction of 14% (95% confidence interval: 8–20%) among all ages combined. Indeed, even in the highest age group, despite the relatively few person-years contributed by women with a history of OC use, we nevertheless observed a statistically significant risk reduction among OC users relative to nonusers, with only 50 ovarian cancer cases observed among users compared to 72.4 cases expected (P < 0.004). Overall, increasing duration of OC use was associated with decreasing risk: a model involving four duration categories provided better fit (P = 0.01) than one involving just two

categories (use for less than or more than one year). These findings were similar when we restricted analysis to serous and to nonserous EOCs (data not shown). Restriction of analysis to EOC cases with specific nonserous histologies was precluded by the sparsity of these cases, as seen in Table 2. Finally, we found no evidence for inter-cohort heterogeneity in the hazard ratios associated with parity (nulliparous vs. parous; P = 0.39) or duration of OC use (less than one year vs. one or more years; P = 0.71).

## 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 hazard ratios 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. Since 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 50–60 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 ovulatory 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 present combined analysis of large prospective cohorts has several advantages. Unlike retrospective case-control studies comparing prior oral contraceptive 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 the present study, for example, the questionnaire data was 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 of 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.

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## ABBREVIATIONS

| | |
|---|---|
| **AARP** | American Association of Retired Persons |
| **CI** | confidence interval |
| **CIR** | crude incidence rate |
| **CTS** | California Teachers Study |
| **EOC** | epithelial ovarian cancer |
| **FTP** | full-term pregnancy |
| **HR** | hazard ratio |
| **NIH** | National Institutes of Health |
| **OC** | oral contraceptive |
| **PYRs** | person-years |
| **WHI** | Women's Health Initiative |

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**Table 1**

Distribution of Participants, Person-years at Risk (PYR) and Invasive Epithelial Ovarian Cancers (EOCs), by Study Site

| | | AARP | | | | CTS | | | | WHI | | | | Total | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | PYRs | EOCs | CIR[b] | N | PYRs | EOCs | CIR | N | PYRs | EOCs | CIR | N | PYRs | EOCs | CIR |
| All participants | | 154,045 | 1,508,720 | 836 | 55.4 | 47,365 | 617,526 | 380 | 61.5 | 108,880 | 1,120,878 | 599 | 53.4 | 310,290 | 3,247,124 | 1815 | 55.9 |
| Year of birth | <1930 | 44,444 | 427,330 | 305 | 71.4 | 17,614 | 204,446 | 171 | 83.6 | 40,341 | 394,481 | 227 | 57.5 | 102,399 | 1,026,261 | 703 | 68.5 |
| | 1930–39 | 80,326 | 789,177 | 406 | 51.5 | 15,102 | 207,323 | 125 | 60.3 | 47,158 | 494,275 | 285 | 57.7 | 142,586 | 1,490,773 | 816 | 54.7 |
| | 1940+ | 29,275 | 292,213 | 125 | 42.8 | 14,649 | 205,757 | 84 | 40.8 | 21,381 | 232,122 | 87 | 37.5 | 65,305 | 730,090 | 296 | 40.5 |
| Age (yrs) at recruitment | 50–64 | 100,651 | 995,395 | 473 | 47.5 | 28,384 | 394,815 | 192 | 48.6 | 61,277 | 651,837 | 323 | 49.6 | 190,312 | 2,042,047 | 988 | 48.4 |
| | 65–74 | 53,394 | 513,325 | 363 | 70.7 | 11,448 | 149,893 | 131 | 87.4 | 40,456 | 404,786 | 232 | 57.3 | 105,298 | 1,068,004 | 726 | 68.0 |
| | 75+ | -- | -- | -- | | 7,533 | 72,818 | 57 | 78.3 | 7,147 | 64,255 | 44 | 68.5 | 14,680 | 137,073 | 101 | 73.7 |
| Number of FTPs[a] | 0 | 23,838 | 233,185 | 162 | 69.5 | 9,775 | 125,271 | 92 | 73.4 | 12,369 | 127,660 | 77 | 60.3 | 45,982 | 486,116 | 331 | 68.1 |
| | 1–2 | 56,154 | 552,485 | 318 | 57.6 | 21,675 | 282,897 | 172 | 60.8 | 35,900 | 370,582 | 215 | 58.0 | 113,729 | 1,205,964 | 717 | 59.5 |
| | 3–4 | 57,500 | 562,992 | 292 | 51.9 | 13,895 | 182,942 | 108 | 59.0 | 44,318 | 457,568 | 230 | 50.3 | 115,713 | 1,203,502 | 630 | 52.4 |
| | 5+ | 16,553 | 160,058 | 64 | 40.0 | 2,020 | 26,416 | 8 | 30.3 | 16,293 | 165,068 | 77 | 46.7 | 34,866 | 351,542 | 149 | 42.4 |
| Yrs OC use | <1 | 91,827 | 896,198 | 566 | 63.2 | 26,193 | 324,358 | 252 | 77.7 | 72,027 | 729,214 | 426 | 58.4 | 190,047 | 1,949,770 | 1244 | 63.8 |
| | 1–4 | 27,529 | 270,681 | 131 | 48.4 | 8,170 | 113,004 | 56 | 49.6 | 15,821 | 168,234 | 73 | 43.4 | 51,520 | 551,920 | 260 | 47.1 |
| | 5–9 | 19,536 | 192,573 | 89 | 46.2 | 7,085 | 98,058 | 39 | 39.8 | 10,752 | 114,780 | 58 | 50.5 | 37,373 | 405,410 | 186 | 45.9 |
| | 10+ | 15,153 | 149,268 | 50 | 33.5 | 5,917 | 82,106 | 33 | 40.2 | 10,280 | 108,650 | 42 | 38.7 | 31,350 | 340,024 | 125 | 36.8 |

[a] FTP = full-term pregnancy

[b] CIR = crude incidence rate (# EOCs per 100,000 PYRs)

**Table 2**

Distribution of epithelial ovarian cancer (EOC) cases according to histological subtype, by cohort

| | AARP N=836 | | CTS n-380 | | WHI N=599 | | Total N=1815 | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| All cases | 836 | 46.0 | 380 | 21.3 | 599 | 33.0 | 1815 | 100.0 |
| Serous | 436 | 52.2 | 169 | 44.5 | 297 | 49.6 | 902 | 49.7 |
| Endometrioid | 67 | 8.0 | 44 | 11.6 | 59 | 9.9 | 170 | 9.4 |
| Mucinous | 36 | 4.3 | 13 | 3.4 | 21 | 3.5 | 70 | 3.9 |
| Clear Cell | 26 | 3.1 | 20 | 5.3 | 30 | 5.0 | 76 | 4.2 |
| Undifferentiated/Unclassified | 271 | 32.4 | 134 | 35.2 | 192 | 32.0 | 597 | 32.8 |

**Table 3**

Parity and Oral Contraceptive (OC) Use in Relation to Invasive Epithelial Ovarian Cancer (EOCs) Incidence, by Age at Risk

| | Age (years) at Risk | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 50 – 64 | | | | | 65 – 74 | | | | | 75 + | | | | |
| | PYRs[a] | EOCs | CIR[a] | HR[b] | 95% CI | PYRs | EOCs | CIR | HR | 95% CI | PYRs | EOCs | CIR | HR | 95% CI |
| FTP[c] | | | -- | -- | -- | | | -- | -- | -- | | | -- | -- | -- |
| 0 | 209428.3 | 116 | 55.39 | 1.00 | REF | 194582.2 | 154 | 79.14 | 1.00 | REF | 82104.3 | 61 | 74.30 | 1.00 | REF |
| 1–2 | 523337.8 | 206 | 39.36 | 0.93 | 0.75–1.16 | 485899.1 | 234 | 48.16 | 0.84 | 0.69–1.02 | 196728.6 | 100 | 50.83 | 1.01 | 0.75–1.37 |
| 3–4 | 391339.8 | 173 | 44.21 | 0.69 | 0.54–0.89 | 587899.6 | 367 | 62.43 | 0.74 | 0.61–0.89 | 224262.1 | 166 | 74.02 | 0.98 | 0.72–1.32 |
| 5+ | 82103.5 | 34 | 41.41 | 0.38 | 0.22–0.63 | 194164.4 | 135 | 69.53 | 0.56 | 0.43–0.73 | 75274.3 | 69 | 91.66 | 0.92 | 0.62–1.36 |
| Trend per FTP | | | | 0.88 | 0.83–0.93 | | | | 0.91 | 0.88–0.95 | | | | 1.00 | 0.95–1.06 |
| | | | | | | $P_{interaction} = <0.001$ [d] | | | | | | | | | |
| Yrs OC Use | | | | | | | | | | | | | | | |
| <1 | 508337.6 | 248 | 48.79 | 1.00 | REF | 963115.4 | 650 | 67.49 | 1.00 | REF | 478316.4 | 346 | 72.34 | 1.00 | REF |
| 1–4 | 302470.8 | 125 | 41.33 | 0.85 | 0.68–1.06 | 208348.1 | 116 | 55.68 | 0.87 | 0.71–1.06 | 41101.4 | 19 | 46.23 | 0.65 | 0.41–1.03 |
| 5–9 | 225398.2 | 94 | 41.70 | 0.86 | 0.67–1.09 | 151149.4 | 76 | 50.28 | 0.80 | 0.63–1.02 | 28862.5 | 16 | 55.44 | 0.77 | 0.46–1.27 |
| 10+ | 170002.8 | 62 | 55.39 | 0.73 | 0.55–0.97 | 139932.4 | 48 | 79.14 | 0.53 | 0.39–0.71 | 30089.0 | 15 | 74.30 | 0.70 | 0.42–1.18 |
| Trend per 5 yrs use | | | | 0.88 | 0.80–0.98 | | | | 0.82 | 0.74–0.91 | | | | 0.85 | 0.71–1.02 |
| | | | | | | $P_{interaction} = 0.79$[e] | | | | | | | | | |

[a] PYRs = person-years at risk; CIR = crude incidence rate (# EOCs per 100,000 PRYs)

[b] HR = 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

[c] FTP = full-term pregnancy

[d] likelihood ratio $\chi^2_2$ test of hypothesis that risk per FTP does not vary with age at risk

[e] likelihood ratio $\chi^2_2$ test of hypothesis that risk per 5 years of OC use does not vary with age at risk