IJC
International Journal of Cancer

Timing of births and oral contraceptive use influences ovarian cancer risk

Anna H. Wu [1]*, Celeste Leigh Pearce [1,2]*, Alice W. Lee[3], Chiuchen Tseng[1], Anjali Jotwani[4], Prusha Patel[4] and Malcolm C. Pike[1,4]

[1] Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA
[2] Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI
[3] Department of Health Science, California State University, Fullerton, Fullerton, CA
[4] Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

Cancer Epidemiology

Increasing parity and duration of combined oral contraceptive (COC) use provide substantial protection against ovarian carcinoma (cancer). There are limited data on the impact of the age of the births or age of COC use on reducing ovarian cancer risk. Here, we examined the effects of age at first and last births and age at use of COCs using data from studies conducted in Los Angeles County, California, USA (1,632 cases, 2,340 controls). After adjusting for the number of births, every 5 years that a first birth was delayed reduced the risk of ovarian cancer by 13% (95% CI 5–21%; $p = 0.003$); a first birth after age 35 was associated with a 47% lower risk than a first birth before age 25. COC use before age 35 was associated with greater protection per year of use than COC use at older ages. Considering previously published results as well as the results presented here, increasing parity and a later age at births are both important protective factors against ovarian cancer and the protection extends over 30 or more years from last birth. Current models of the etiology of ovarian cancer do not encompass an effect of late age at births. Our result of an attenuation of the protective effect with COC use after around age 35 needs further investigation as it has not been seen in all studies.

Parity and combined oral contraceptive (COC) use provide substantial protection against ovarian carcinoma (ovarian cancer).[1–9] The protection increases with an increasing number of births and with longer use of COCs,[2,10] and the protection lasts for many decades after the last birth or after stopping use of COCs.[10] There is conflicting literature on the impact of the age of the births on reducing ovarian cancer risk,[3–9] and little data on whether the age at which COCs are used affects the degree of protection.[10] The answer to the question of whether age at births affects ovarian cancer risk

Key words: oral contraceptives, ovarian cancer, parity

Abbreviations: BMI: body mass index; cEPT: continuous combined estrogen-progestin therapy; CI: confidence interval; COC: combined oral contraceptive; CSP: Cancer Surveillance Program; ET: estrogen alone therapy; HGSOC: high grade serous ovarian cancer; HT: hormone therapy; LAC: Los Angeles County; LGSOC: low grade serous ovarian cancer; LNMP: last natural menstrual period; RR: relative risk; SEER: Surveillance, Epidemiology and End Results; sEPT: sequential estrogen-progestin therapy; SES: socio-economic status; USC: University of Southern California

Additional Supporting Information may be found in the online version of this article.

*Anna H. Wu and Celeste Leigh Pearce contributed equally to this work.

Conflicts of interest: All authors declare that they have no potential conflicts of interest.

Disclaimer: The ideas and opinions expressed herein are those of the authors, and endorsement by the State of California, the California Department of Health Services, the National Cancer Institute, or the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred.

Grant sponsor: National Cancer Institute; **Grant numbers:** CA58598, CA17054, **Grant sponsor:** National Cancer Institute Cancer Center Core Grants; **Grant numbers:** P30 CA014089 to the University of Southern California, P30 CA046592 to the University of Michigan, P30 CA008748 to Memorial Sloan Kettering Cancer Center; **Grant sponsor:** National Cancer Institute's Division of Cancer Prevention and Control's Surveillance, Epidemiology and End Results (SEER) Program; **Grant number:** Contract N01CN25403 to USC Cancer Surveillance Program; **Grant sponsor:** California Cancer Research Program; **Grant number:** 2II0200. The collection of incident ovarian cancer cases for this study by the USC Cancer Surveillance Program is also partly supported under subcontract by the California Department of Health.

DOI: 10.1002/ijc.30910

History: Received 31 May 2017; Accepted 10 July 2017; Online 27 July 2017

Correspondence to: Celeste Leigh Pearce, PhD, 1415 Washington Heights, SPH Tower Office #4642, Ann Arbor, MI 48109-2029, E-mail: lpearce@umich.edu; Tel.: 734-764-3835, Fax: 734-764-3192.

What's new?
Parity and combined oral contraceptives (COCs) are associated with a lower risk of ovarian cancer. But might maternal age also play a role? In this study, the authors found that a first birth at a later age provides significant additional protection above that of parity alone. (A first birth after age 35 may provide more than double the protection of a birth before age 25.) COC use before the age of 35 may also be associated with a greater protective benefit than use at older ages, but further investigation is needed.

has the potential of informing on the underlying mechanism through which parity influences risk of ovarian cancer.

Whether age at COC use affects ovarian cancer risk is important from a prevention perspective. Ideally use of COCs for prevention purposes would be done at an earlier age to minimize the impact of the transient increased risk of breast cancer associated with COC use[11] given that the absolute risk of breast cancer among young women is at its lowest level.

In this article, we have investigated the effects of ages at first and last birth and ages at use of COCs on ovarian cancer risk using data from four case-control studies of ovarian cancer conducted in Los Angeles County (LAC), California during the period 1992 through 2008.[1,12] These studies used identical data collection methods including a personal interview with each participant using a life calendar detailing the timing of the exposures of interest, including births and COC use, which affords us the opportunity to look in detail at the timing of these exposures. The results presented here are based on pooling the questionnaire data from the four studies.

Material and Methods

We have previously published details of the methods used in the four studies.[1,12] These studies were approved by the University of Southern California (USC) Institutional Review Board, and written informed consent was obtained from each case and control before her interview.

Case ascertainment

For all studies, newly diagnosed histologically confirmed ovarian cancer cases were identified from the Cancer Surveillance Program (CSP) of the University of Southern California; the CSP is the Surveillance, Epidemiology and End Results (SEER) Registry for LAC. Eligible patients were female residents of LAC of self-reported non-Hispanic white, Hispanic, or African-American race/ethnicity. Cases were eligible for inclusion in the study if they were between 18 and 74 years of age at diagnosis and up to age 79 for cases diagnosed between 2003 and 2008. A total of 3,370 patients met the study criteria. Overall, 15.7% of patients declined to be interviewed, 16.9% had died or were too ill to be interviewed, and 11.4% could not be located or had moved out of LAC. We were thus able to carry out in-person interviews with 1,886, a 63.2% participation rate of the patients approached. The response rate was higher for patients diagnosed with localized cancer (69%) compared with those with more advanced stage (61%). Response rates were highest for those diagnosed under age 60 (70%), intermediate for those ages 60–69 (59%) and lowest for those ages 70+ (47%). In this analysis, we excluded 185 patients who had a previous cancer (other than non-melanoma skin cancer) or had prior bilateral oophorectomy, and a further 69 cases with missing or inconsistent data on one or more of the variables included in the analysis presented here. The final analysis was based on 1,632 cases.

Control ascertainment

Controls were female residents of LAC with at least one intact ovary identified using a well-tested control selection algorithm.[1] Briefly, we initially defined a specified sequence of houses to be visited in the neighborhoods where index cases lived at the time of diagnosis. We then sought to interview the first eligible resident in the sequence. If the first eligible control subject refused to participate, the second eligible one in the sequence was asked, and so on. Letters were left when no one was home, and follow-up was by mail and telephone. Controls were individually matched to cases on neighborhood, race/ethnicity and year of birth ($\pm$5 years). In one study, selection of controls for cases $>$65 years of age was augmented, if necessary, by using lists of female residents of LAC provided by the Health Care Financing Administration, matched to the case on zip code, race/ethnicity and year of birth closest to the case's year of birth. We excluded potential controls who had ever been diagnosed with a cancer (ignoring non-melanoma skin cancer). Overall, 70% of the controls interviewed were the first identified control.

Data collection

In-person interviews were conducted using a standardized questionnaire that included the use of a life calendar. The questionnaire covered events up to 12 months before a case's diagnosis date and a similar reference date for the controls.

The demographic, lifestyle and medical history variables considered in this analysis include age, age at menarche, education, SES (socio-economic status based on census tract of residence),[13] tubal ligation, self-reported physician-diagnosed endometriosis, first-degree family history of ovarian cancer, talc use, current body mass index (BMI, kg m^{-2}), COC use, gravidity, parity, self-reported physician-diagnosed history of infertility not attributable to problems of the partner and tumor histology (from the SEER registry).

Statistical analysis

We used stratified multivariate logistic regression, using the statistical package program STATA 13 (StataCorp, College Station, TX). At the termination of each study, some cases had not been matched to a control and there were some controls whose cases had to be excluded after they completed the interview, because they were ineligible for the current analysis (e.g., not ovarian cancer or did not live in LAC at the time of diagnosis). Although the studies were designed as matched case–control studies, in this report we have used all interviewed cases and controls by adopting a stratified multivariate logistic regression analysis approach with joint stratification for the four studies, three race/ethnicity groups and age groups (<30, 5-year age groups through age 79).

The following risk factors were adjusted for in all (stratified) analyses: first-degree family history of ovarian cancer (mother or sister), history of endometriosis, talc use, tubal ligation and history of infertility; all of which were entered in the logistic regression analysis as categorical binary (Yes/No) variables. Age at menarche (continuous variable) and BMI (continuous variable) were also adjusted for in all analyses. In addition, education (<high school graduate, high school graduate, some further training, college graduate); and five levels of SES were also adjusted for as categorical variables in all analyses.

Age and type of menopause was also adjusted for in all analyses as a categorical variable with categories: premenopausal, hysterectomy (before menopause) at age <40 years and ≥40 years, natural menopause (age at last natural menstrual period—LNMP) at age <45 years, 45−, 50− and 55+. For a woman who started menopausal hormone therapy (HT) while she was still having natural periods and did not have any natural periods after stopping this episode of HT, age at menopause was taken to be the age at which the subject began this episode of HT. If a woman had a natural menstrual period at least 3 months after stopping HT, this episode of use was not considered in defining her age at menopause and not considered to be an episode of HT. If a woman had no natural menstrual periods after stopping COCs (which were started before menopause), her age at menopause was taken as the age at which she last took a COC. The justification for this approach is given in Pike *et al.*[14]

Each episode of HT use was categorized as estrogen alone (ET), sequential estrogen-progestin (sEPT), continuous combined estrogen-progestin (cEPT) or other. ET was defined as use of estrogen alone for ≥20 days per 'month'; sEPT as use of estrogen for ≥20 days per month and number of progestin days ≤60% of number of estrogen days; and cEPT as use of estrogen for ≥20 days per month and number of progestin days the same or greater than number of days of estrogen.

The above factors, taken together, are termed 'the basic factor set' and are adjusted for in all analyses.

Number of births (defined as a pregnancy of >26 weeks, counting from date of last menses) was analyzed categorically (0, 1, 2, 3 and 4+) as well as a continuous variable; age at first birth was analyzed categorically (<20 years, 20−, 25−, 30− and 35+) as well as a continuous variable with these categories scored as 1, 2, 3, 4 and 5; and age at last birth was analyzed categorically (<25 years, 25–29, 30–34, 35–39 and 40+) as well as a continuous variable with these categories scored as 1, 2, 3, 4 and 5. Number of incomplete pregnancies (pregnancy of ≤26 weeks) was analyzed as a continuous variable.

Duration of COC use was analyzed categorically (no use, use for <5 years, 5−, 10− and 15+ years) as well as a continuous variable. We also analyzed the ages at which COCs were used (duration of use at ages <25, 25–34 and 35+ years of age). The estrogen component of COCs was considered high if the dose of ethinyl estradiol was >35 μg or if the dose of mestranol was >70 μg. The progestin component was considered high if the dose was equivalent to 0.30 mg of D,L-norgestrel or higher. This schema was the one used in the two previous papers addressing the issue of COC dose.[1,15] We also had six women who reported use of a progestin-only oral contraceptive and these women were included as COC users.

The histologic type and grade of the ovarian cancers were obtained from the LAC SEER registry. The ovarian cancers were categorized into high (poor/undifferentiated) grade serous ovarian cancer (HGSOC), low grade serous (LGSOC), endometrioid, clear cell, mucinous or not known (including serous of unknown grade).

Odds ratios and corresponding 95% confidence intervals (CIs) were calculated as estimates of the relative risks (RRs), and are presented as RRs. All statistical significance values (*p* values) quoted are two-sided.

Results

There were 1,632 cases and 2,340 controls available for analysis. The race/ethnicity, age, education and income distributions of these cases and controls are shown in Supporting Information Table 1. Similarly, the relative risks for the well-established risk factors of family history of ovarian cancer, history of endometriosis, talc use and BMI are available in Supporting Information Table 2.

Table 1 shows the relative risks for age at first birth and age at last birth fitted separately and together, adjusted for the 'basic factor set' and number of births (continuous) and duration of COC use (continuous at age <35 years and continuous at age ≥35 years—see below). When fitted separately, age at first birth and age at last birth were both highly significantly related to ovarian cancer risk. However, when fitted together, only age at first birth remained significant. Compared to a first birth under age 25, a first birth after age 35 was associated with a 47% reduced risk of ovarian cancer (RR = 0.53, 95% CI 0.32–0.88). Similar results were obtained when we restricted the analysis to cases and controls who had only one birth, and when we restricted the analysis to cases and controls who had two births (data not shown).

The relative risks associated with increasing numbers of births adjusted for the 'basic factor set' and duration of COC

Table 1. Ages at first and last birth and risk of ovarian cancer

Variable	Cases ($n = 1,225$)	Controls ($n = 1,833$)	Fitted separately			Fitted together		
			Adjusted RR[1]	95% CI	*p*	Adjusted RR[1]	95% CI	*p*
Age at first birth (years)								
<20	276	315	1.00			1.00		
20–24	526	650	0.99	0.82–1.19		1.00	0.82–1.22	
25–29	271	489	0.76	0.62–0.93		0.75	0.58–0.98	
30–34	108	248	0.71	0.54–0.93		0.66	0.46–0.94	
35+	44	131	0.57	0.39–0.84		0.53	0.32–0.88	
Per category			0.87	0.82–0.93	<0.001	0.87	0.79–0.95	0.003
Age at last birth (years)								
<25	290	303	1.00			1.00		
25–29	373	521	0.77	0.63–0.95		0.94	0.73–1.21	
30–34	346	569	0.78	0.63–0.97		1.07	0.79–1.45	
35–39	175	335	0.75	0.57–0.97		1.16	0.79–1.69	
40+	41	105	0.53	0.34–0.83		0.84	0.49–1.43	
Per category			0.90	0.83–0.97	0.005	1.01	0.91–1.12	0.88

[1]Stratified analysis (see Methods) and adjusted for the basic factor set (family history of ovarian cancer, history of endometriosis, talc use, tubal ligation, infertility, number of incomplete pregnancies, age at menarche, BMI, education, SES, age and type of menopause, type and duration of menopausal hormone therapy) plus number of births (continuous) and duration of COC use at ages <35 years (continuous) and 35+ yrs (continuous).

Table 2. Births and risk of ovarian cancer

Variable	Cases	Controls	Adjusted RR[1]	95% CI	*p*	Adjusted RR[2]	95% CI	*p*
Births								
0	407	507	1.00			1.00		
1	225	370	0.69	0.55–0.87		1.00	0.74–1.34	
2	444	674	0.67	0.54–0.81		0.89	0.69–1.14	
3	314	416	0.66	0.53–0.84		0.83	0.64–1.07	
4+	242	373	0.40	0.31–0.52		0.48	0.37–0.63	
Per birth			0.86	0.82–0.90	<0.001	0.87	0.83–0.92	<0.001

[1]Stratified analysis (see Methods) and adjusted for the basic factor set (see footnote to Table 1), plus duration of COC use at ages <35 years (continuous) and 35+ yrs (continuous).
[2]As for footnote (1) plus age at first birth category (continuous).

use (continuous at age <35 years and continuous at age ≥35 years—see below) are shown in Table 2. The relative risk associated with a single birth was 31% lower than that associated with nulliparity, much lower than one would expect based on a linear model (on a logistic scale) of reduction in risk with each birth (RR = 0.87). However, when fitted together with the effect of age at first birth, this markedly larger effect of a single birth was eliminated completely. This was due to the much greater average age at first birth among women who only had one birth: 46% of controls who only had one birth had the birth at age 30 or later, while only 14% of controls who had more than one birth had the first birth at age 30 or later.

The relative risks associated with the duration of use of COCs are shown in Table 3. Each 5 years of use was associated with a 28% lower risk of ovarian cancer ($p < 0.001$). There was a 34% reduction in risk associated with 5 years of COC use before age 35, while 5 years of use after age 35 was only associated with a 14% lower risk (*p* for difference in effect, 0.019). There was little difference in the reduction in risk from a fixed duration of COC use before age 25 (0.62, 95% CI 0.52–0.80) and such use at ages 25–34 (0.71, 95% CI 0.60–0.83). The decreased protective effect seen with use after age 35 was consistently seen in all estrogen and progestin 'potency' formulations (data not shown).

Table 4 shows the relative risks for numbers of births and age at first birth by histotype. Although the relative risks show the same relationships with each histotype, the effects are greater for endometrioid and clear cell ovarian cancers, and the effect of age at first birth is weakest and not statistically significant for HGSOC. Table 4 also shows the relative risks for duration of use of COCs overall and by age at use by histotype. The relative risks show approximately the same

Table 3. Oral contraceptive (COC) use and risk of ovarian cancer

Variable	Cases	Controls	Adjusted RR[1]	95% CI	p
COC use (yrs)					
0	707	734	1.00		
>0−	617	826	0.98	0.82–1.15	
5−	172	384	0.57	0.45–0.72	
10−	93	231	0.49	0.37–0.65	
15+	43	165	0.29	0.20–0.43	
Per 5 yrs use			0.72	0.67–0.77	<0.001
Per 5 yrs use					
<35 yrs of age			0.66	0.59–0.73	
35+ yrs of age			0.86	0.73–1.01	
				Difference test	0.019

[1]Stratified analysis (see Methods) and adjusted for the basic factor set (see footnote to Table 1), plus number of births (continuous) and age at first birth category (continuous).

Table 4. Relative risks (95% CIs) for births, age at first birth (per 5 years category) and oral contraceptive (COC) use (5 years of use) and risk of ovarian cancer, by histotype[1]

	No. of cases	Births, per birth[2,3]		Age at first birth[2,3]		COC use[2,4]		COC use <35 yrs[2,4]		COC use 35+ yrs[2,4]	
All women[1]	(n = 1,632)	0.87	(0.83–0.92)	0.87	(0.82–0.93)	0.72	(0.67–0.77)	0.66	(0.59–0.73)	0.86	(0.73–1.01)
HGSOC[2]	(n = 559)	0.89	(0.83–0.96)	0.94	(0.86–1.04)	0.72	(0.64–0.80)	0.67	(0.57–0.79)	0.80	(0.63–1.02)
LGSOC[2]	(n = 207)	0.93	(0.84–1.04)	0.87	(0.75–1.01)	0.69	(0.57–0.83)	0.65	(0.51–0.84)	0.78	(0.51–1.21)
Endometroid	(n = 192)	0.83	(0.74–0.93)	0.82	(0.70–0.95)	0.69	(0.58–0.83)	0.62	(0.49–0.79)	0.88	(0.60–1.29)
Clear Cell	(n = 87)	0.72	(0.58–0.88)	0.74	(0.57–0.96)	0.64	(0.49–0.84)	0.66	(0.46–0.93)	0.61	(0.30–1.25)
Mucinous	(n = 119)	0.82	(0.71–0.96)	0.89	(0.74–1.08)	0.79	(0.64–0.98)	0.73	(0.54–0.97)	0.98	(0.60–1.60)

[1]Numbers do not sum to total due to missing histotype.
[2]Stratified analysis (see Methods) and adjusted for the basic factor set (see footnote to Table 1).
[3]Also adjusted for duration of COC use at ages <35 years (continuous) and 35+ yrs (continuous).
[4]Also adjusted for number of births (continuous) and age at first birth category (continuous).
Abbreviations: HGSOC, high grade serous ovarian cancer; LGSOC, low grade serous ovarian cancer.

relationships with each tumor type, with the possible exception of clear cell ovarian cancers for which COC use in both age groups was equally protective.

The relative risks associated with numbers of births, age at first birth and duration of COC use by age at diagnosis is shown in Table 5. Overall there was a 13% reduction in ovarian cancer risk per birth. The reduction in risk per birth was much stronger at younger ages at diagnosis: a 27% reduction per birth at diagnosis ages <45 years compared to an 8% reduction at diagnosis ages ≥65 years. A similar trend was observed for age at first birth with a 16% reduction at diagnosis ages <45 years compared to a 9% reduction at ages ≥65 years (Table 5). No clear effect of age at diagnosis was seen with the reductions in risk with COC use.

Discussion

Parity and COC use are well-established protective factors for ovarian cancer, but as we move toward a model of personalized prevention it is increasingly important to gain a more in-depth understanding of these and other lifestyle factors associated with risk. In the analysis presented here, the timing of both parity and COC use influence the protection against ovarian cancer afforded by these exposures; a later age at first birth and an earlier age at COC use provide greater benefit.

The reduction in risk we observed with increasing parity, a relative risk of 0.87 per birth, is in good agreement with the results of previous studies.[3–9] We found an overall reduction in relative risk of ovarian cancer of 0.87 per 5 years later age at first birth. One possible explanation for this protective effect of a late first birth that we observed is that the underlying reason for a late age is related to a woman's underlying ovarian cancer risk. We examined the characteristics, including a history of infertility, endometriosis and SES, of the women who had late births and could not find a compelling explanation. If the underlying mechanism of the protective effect of a birth is to reduce cell proliferation one would expect that age at the birth

Table 5. Analysis of births, oral contraceptive (COC) use and age at first birth and risk of ovarian cancer, by age at diagnosis

			RRs and 95% CIs[1]			
Age group	Cases	Controls	Births[2]	Age at 1st birth[3]	COC <35[4]	COC 35+[4]
All ages	1,632	2,340	0.87	0.87	0.66	0.86
			(0.83–0.92)	(0.82–0.93)	(0.59–0.73)	(0.73–1.01)
<45 yrs	217	525	0.73	0.84	0.66	1.03
			(0.61–0.87)	(0.70–1.00)	(0.52–0.84)	(0.52–2.03)
45–54 yrs	470	776	0.86	0.87	0.59	0.77
			(0.78–0.95)	(0.77–0.97)	(0.50–0.70)	(0.56–1.07)
55–64 yrs	511	595	0.89	0.89	0.74	0.82
			(0.82–0.97)	(0.79–1.00)	(0.61–0.90)	(0.62–1.09)
65+ yrs	434	444	0.92	0.91	0.69	0.86
			(0.84–1.00)	(0.78–1.06)	(0.46–1.03)	(0.64–1.14)

[1]Stratified analysis (see Methods) and adjusted for the basic factor set (see footnote to Table 1), plus duration of COC use at ages <35 years (continuous) and 35+ yrs (continuous).
[2]Relative risk (RR) per birth.
[3]RR per 5 years increase in age at first birth (see Table 1).
[4]RR per 5 years of use.

Table 6. Published results on effect of age at first and last births on risk of ovarian cancer[1]

				Independent[2]	
Reference	Study type	Cases	Controls	First Birth	Last Birth
Whittemore et al. (1992)[9]	Case-control	1,363	5,609	0.88[3] (0.80–0.96)	
Adami et al. (1994)[3]	Nested case-control	2,992	14,960	0.89 (0.84–0.94)	
Titus-Ernstoff et al. (2001)[7]	Case-control	563	523	0.88[3] (0.76–1.03)	0.89[3] (0.77–1.03)
Riman et al. (2002)[6]	Case-control	655	3,899	0.97[3] (0.87–1.08)	"No association"
Whiteman et al. (2003)[8]	Case-control	602	723	0.87[3] (0.75–1.01)	0.79[3] (0.69–0.91)
Moorman et al. (2008)[5]	Case-control	713	838	0.87[3,4] (0.77–0.99)	0.81[3,4] (0.73–0.90)
Bevier et al. (2011)[4]	Cohort	17,190	5.7×10^6	0.96[3] (0.94–0.97)	0.90[3] (0.89–0.92)

[1]Excluding hospital-based studies.
[2]Relative risk (RR) per 5 years increase in age at first (last) birth, adjusted for parity (all studies).
[3]RR estimated from the published paper by the method of Greenland and Longnecker.[17]
[4]Combining results from premenopausal and postmenopausal women (see Table 6 of Moorman). These results are only given for invasive and low-malignant potential cases combined, and it is not clear whether the results from first and last births are mutually adjusted. Their results are stated in terms of pregnancies rather than births, but the numbers in their tables are for births.

would have no effect.[16] If a birth results in a reduction of a stem cell pool, an early age at birth should provide greater protection, as is seen in breast cancer.[16] None of these explanations seems to fit with our finding.

Previous studies on the effect of age at first and last births showed associations with late age at both first and last births.[3–9] We also found a reduction in risk with increasing age at last birth—relative risk of 0.90 per 5 years later. Five

of the studies shown in Table 6 also reported on the association of ovarian cancer risk with age at last birth.[4–8] In three of them,[4,5,8] the reduced risk with age at last birth was clearly greater than the reduction in risk with first birth. We found that the effect of age at last birth was eliminated after adjustment for age at first birth (Table 1), but Whiteman *et al.*[8] found the reverse.

Considering the results of all the studies of birth timing shown in Table 6 together with the results we found, we can conclude that a late birth has a clear additional protective effect against ovarian cancer over and above the protective effect of number of births. If a birth results in a reduction of precursor lesions, a late age at birth would provide greater protection, as is seen in endometrial cancer.[18]

We found that the protective effects of parity and late age at first birth diminished with increasing age at diagnosis (Table 5). This reduction in protection with increasing age at diagnosis has been consistently found in previous studies, although these studies expressed this in terms of increased time since first/last birth. Age at diagnosis and time since first/last birth are, of course, positively correlated, and in our data the results were much clearer when expressed in terms of age at birth and age at diagnosis. The attenuation over time is readily explained by models based on ovulatory years; the years pregnant as a proportion of ovulatory years plus time since menopause is reduced with increasing age,[16] but as Adami *et al.*[3] pointed out, the effect of age at births cannot be readily explained on the basis of models of incessant ovulation or ovulatory years.

The important conclusion to be drawn from the results, when all studies are considered together, is that parity and age at births are both important protective factors and that the protection extends over 30 or more years.

We found, as has been repeatedly found before,[10] a clear protective effect of COC use against ovarian cancer. The surprising aspect of our finding is that earlier age at use of COCs is associated with greater protection. We investigated whether this was driven by temporal changes in the doses of COCs, with early age at use potentially being associated with higher dose COCs, but this was not the case. This finding has important implications with respect to risk reduction given that using COCs at a young age as a preventive strategy is appealing given that the absolute risk of breast cancer at a young age is low. Thus, the transient increased risk of breast cancer associated with COC use[11] would be less of a concern.

It is important to note, however, that in The Collaborative Group on Epidemiological Studies of Ovarian Cancer major overview of epidemiological results on ovarian cancer and COC use,[10] no "index of timing of use ... had any material effect" on the reduction in risk of ovarian cancer with COC use, so our finding of an attenuation of protective effect with COC use after around age 35 should be regarded as tentative and needs further investigation in other data sets.

Overall, it appears that the age at births has an effect on the degree of protection afforded by parity. Achieving a better understanding of the effect of births on endometriotic lesions, as the site of origin of endometrioid and clear cell ovarian cancers, and on the fallopian tube as the major site of HGSOC are needed to provide the information needed to develop prevention strategies based on this finding.

Authors contributions

Conception and design: A.H. Wu, C.L. Pearce, M.C. Pike. Development of methodology: A.H. Wu, M.C. Pike. Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.H. Wu, M.C. Pike. Analysis and interpretation of data (*e.g.*, statistical analysis, biostatistics, computational analysis): M.C. Pike, A.W. Lee, C.L. Pearce, A.H. Wu, C.-C. Tseng, A. Jotwani, P. Patel. Writing, review, and/or revision of the manuscript: M.C. Pike, A.W. Lee, C.L. Pearce, A.H. Wu. Administrative, technical, or material support (*i.e.*, reporting or organizing data, constructing databases): A.H. Wu, C.-C. Tseng, M.C. Pike, A. Jotwani, P. Patel. Study supervision: A.H. Wu, M.C. Pike.

Acknowledgements

The authors thank the interviewers and the other members of data collection teams. Most importantly, the authors thank all the study participants for volunteering for these studies.

References

1. Pike MC, Pearce CL, Peters R, et al. Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study. *Fertil Steril* . 2004;82:186–95.
2. Pearce CL, Rossing MA, Lee AW, et al. Combined and interactive effects of environmental and GWAS-identified risk factors in ovarian cancer. *Cancer Epidemiol Biomarkers Prev.* 2013;22:880–90.
3. Adami HO, Hsieh CC, Lambe M, et al. Parity, age at first childbirth, and risk of ovarian cancer. *Lancet* 1994;344:1250–4.
4. Bevier M, Sundquist J, Hemminki K. Does the time interval between first and last birth influence the risk of endometrial and ovarian cancer? *Eur J Cancer* 2011;47:586–91.
5. Moorman PG, Calingaert B, Palmieri RT, et al. Hormonal risk factors for ovarian cancer in premenopausal and postmenopausal women. *Am J Epidemiol* 2008;167:1059–69.
6. Riman T, Dickman PW, Nilsson S, et al. Risk factors for invasive epithelial ovarian cancer: results from a Swedish case-control study. *Am J Epidemiol* . 2002;156:363–73.
7. Titus-Ernstoff L, Perez K, Cramer DW, et al. Menstrual and reproductive factors in relation to ovarian cancer risk. *Br J Cancer* 2001;84:714–21.
8. Whiteman DC, Siskind V, Purdie DM, et al. Timing of pregnancy and the risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prevent Publ Am Assoc Cancer Res Am Soc Prevent Oncol* 2003;12:42–6.
9. Whittemore AS, Harris R, Itnyre J. 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* 1992;136:1184–203.
10. Collaborative Group On Epidemiological Studies Of Ovarian C, Beral V, Doll R, 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* 2008;371:303–14.

11. Collaborative Group on Hormonal Factors in Breast C. 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.
12. Wu AH, Pearce CL, Tseng CC, Pike MC. African Americans and Hispanics remain at lower risk of ovarian cancer than non-Hispanic whites after considering nongenetic risk factors and oophorectomy rates. *Cancer Epidemiol Biomarkers Prev*. 2015;24:1094–100.
13. Yost K, Perkins C, Cohen R, et al. Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. *Cancer Causes Control* 2001;12:703–11.
14. Pike MC, Peters RK, Cozen W, et al. Estrogen-progestin replacement therapy and endometrial cancer. *J Natl Cancer Inst* 1997;89: 1110–6.
15. Schildkraut JM, Calingaert B, Marchbanks PA, et al. Impact of progestin and estrogen potency in oral contraceptives on ovarian cancer risk. *J Natl Cancer Inst* 2002;94:32–8.
16. Pike MC. Age-related factors in cancers of the breast, ovary, and endometrium. *J Chronic Dis* 1987;40(Suppl 2):59S–69S.
17. Greenland S, Longnecker P. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992;135:1301–10.
18. Setiawan VW, Pike MC, Karageorgi S, et al. Age at last birth in relation to risk of endometrial cancer: pooled analysis in the epidemiology of endometrial cancer consortium. *Am J Epidemiol.* 2012;176:269–78.