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Reproductive Factors of Ovarian and Endometrial Cancer Risk in a High Fertility Population in Mexico

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ABSTRACT

A case-control study was carried out in Mexico City during 1995–1997 among women with epithelial ovarian cancer (84 cases) and endometrial cancer (85 cases). The control group consisted of 668 healthy women, matched according to age categories. In a multivariate analysis, the reproductive risk factors for ovarian and endometrial cancer are similar. The risk of ovarian cancer was inversely related to the number of full-term pregnancies; the odds ratio (OR) was 0.17 and the 95% confidence interval (CI) was 0.05–0.54 when comparing nulliparous women *versus* those with more than seven pregnancies. For endometrial cancer, a similar association was observed (OR, 0.11; 95% CI, 0.04–0.34). The use of oral contraceptive hormones was inversely associated with both ovarian (OR, 0.36; 95% CI, 0.15–0.83) and endometrial cancer risk (OR, 0.36; 95% CI, 0.14–0.90). In women with a history of more than 8.7 years without ovulation, the risk of ovarian cancer decreased four times (OR, 0.23; 95% CI, 0.10–0.50), and that of endometrial cancer decreased more than five times (OR, 0.17; 95% CI, 0.08–0.35). These two neoplasms are clearly typified as hormone dependent, and it is possible to establish that "ovulation" and "exfoliative" mechanisms jointly determine the level of risk for both ovarian and endometrial cancer.

INTRODUCTION

OC[2] and EC have the highest incidence and mortality rate in the industrialized world. It is estimated that in 1993, OC caused 123,000 deaths and EC caused 64,000 deaths worldwide (1), and that OC is the sixth most common form of neoplasm in women, registering 162,000 (2) cases per year, whereas EC ranks eighth with 140,000 cases (2). In Mexico, these cancers have increased during recent years. In 1996, with 2000 cases, OC was the ninth among all types of tumors (2.4% of the total), and EC was fifth, with 3710 cases (3).

Several studies assessing risk factors for these pathologies have reported consistent results in regard to pregnancies (4–7). The observation that OC is more prevalent among nulliparous women has served as a basis for the hypothesis that repeated ovulatory activity might lead to a carcinogenic effect on the epithelium of the ovary (8). As for EC, it has been suggested that during delivery, epithelial cells, including those undergoing malignant transformation, are removed by a simple mechanical exfoliative effect (9). In countries such as Mexico, OC and EC, as well as other types of neoplasms in women, are an ever-increasing threat that may be explained, among other reasons, by increased life expectancy, a reduction in fertility or birth rate, and the fact that breastfeeding is becoming less common. The present study of a sample of Mexican women evaluates the reproductive factors and their relationship with OC and EC, establishing the similarities and differences between them.

MATERIALS AND METHODS

A case-control study was carried out from August 1995 to June 1997. The cases were patients of the Instituto Mexicano del Seguro Social "Dr. Luis Castelazo Ayala" Gynaecology and Obstetrics Hospital, where >75% of the women in the metropolitan area of Mexico City in whom there is clinical suspicion of these conditions are directed for diagnostic confirmation and treatment of gynecological neoplasms.

Cases. A group of 84 cases of ovarian epithelial neoplasm and a group of 85 cases of endometrial adenocarcinoma were selected. Included in the study were women from the gynecological oncology service who, when undergoing radiological imaging, ultrasound, or tomography, showed clinical suspicion of ovarian or endometrial cancer that was later confirmed with a biopsy-positive result. All cases were incident and had received no treatment for the condition prior to the study. The response rate in the case group was 100%.

Controls. A control group of 668 women was obtained according to age by frequency matching in five-year categories (± 2.5 years) in a ratio of four to each case. These women were outpatients receiving primary care, in the same source area as the cases. The main reasons for the selected controls visiting the outpatient clinic were gastrointestinal upsets (34%), acute respiratory infections (22%), and skin diseases (19%), among others. The response rate was 93% (of 718 eligible controls; 50 declined to participate).

Data Collection. In both cases and controls, information was collected by a standard questionnaire on risk factors and clinical histopathological records designed especially for the study. The questionnaire collected information on demographic data, gynecological and obstetrical history, consumption of oral contraceptives, and anthropometric measurements. Interviews were carried out by two standardized interviewers with experience in epidemiological studies. The histogenetic classification proposed by the WHO was used (10).

Statistical Analyses. Crude and adjusted analyses were carried out by means of unconditional polytomic logistic regression (11), using the STATA 5.0 statistical package.[3] OR with 95% CI were estimated. The final logistic models were established with the incorporating significant variables resulting from the bivariate analysis as well as other relevant biological variables.

To build the index of anovulation, a modification of the methods described by Casagrande *et al.* (12) and Risch *et al.* (13) was used, taking into account 9 months for each full-term pregnancy plus 6 months for each breast-fed child. To this figure, the number of months during which hormones were consumed within the period from the onset of menses until menopause (if still menstruating, the date of diagnosis and/or interview was used) was added. We estimated physical activity energy output expressed in METS (metabolic unit spent) according to METS/hour/week (14) and categorized it as an ongoing variable in tertiles. The body build index was established according to age groups following Sorensen's suggestion (15); body mass index was calculated using a kg/m^2 formula (16).

RESULTS

Seventy-one % of the OC cases were detected at an advanced stage (III-IV), with undifferentiated grade tumors (38%). On the other hand, 80% of the EC cases were detected at an early stage (I-II), with well-differentiated grade tumors (56.47%).

There were no age differences between the cases and the controls, reflecting a successful age-frequency matching. The average scholastic level and age at menarche were similar in cases and controls. The

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[2] The abbreviations used are: OC, ovarian cancer; EC, endometrial cancer; OR, odds ratio; CI, confidence interval.

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proportion of women with at least one pregnancy in the study group was very high, 80.9% for OC and 74.1% for EC. Statistically significant differences in the number of pregnancies between women with EC (3.5 pregnancies) and the controls (4.6 pregnancies, $P = 0.006$) were observed. The mean age of the last pregnancy was significantly higher among the controls (26.7 years) than among OC cases (23.7 years, $P = 0.04$) or EC cases (22.2 years, $P = 0.002$). The average time of contraceptive hormones use was 7 months greater in the controls than in EC cases (5.1 months, $P = 0.05$). Average length of anovulation was lower in EC cases (50.3 months, $P = 0.002$) compared with the control group (71 months). The body mass index was greater among women with EC than among the control group ($P = 0.002$). The prevalence of diabetes mellitus in the control group was 5.4%, whereas among OC cases, it was 10.7%, and 22.3% in EC cases. Hypertension prevalence was 19.6% in the control group, 25% among OC cases, and 36.4% in the EC group (Table 1). In multivariate analyses, an inverse association between pregnancy and OC and EC risk was observed. In women with a history of seven or more full-term pregnancies, the risk of OC was five times lower (OR, 0.17; 95% CI, 0.05–0.54) and in that of EC, was nine times lower (OR, 0.11; 95% CI, 0.04–0.34) when compared with women who have never had a full-term pregnancy. The number of pregnancies showed a statistical significant trend ($P < 0.001$).

Age at the onset of menstruation and of menopause were not related to risk of OC or EC (Table 2). The number of deliveries was inversely related to the risk of both cancers, with a statistical significant trend. After the fourth delivery, the risk of OC decreased 3-fold (OR, 0.32; 95% CI, 0.12–0.81), and the risk of EC decreased 6-fold (OR, 0.16; 95% CI, 0.06–0.40).

The number of miscarriages was not associated with either OC (OR, 0.61; 95% CI, 0.30–1.2) or EC risk (OR, 1.1; 95% CI, 0.59–2.1; Table 3). Age at first delivery was not associated with OC risk (OR, 1.6; 95% CI, 0.74–3.6); however, in the case of EC, the risk was twice as great when first delivery was at a later age (OR, 2.4; 95% CI, 1.1–5.3). The age at last delivery does not show a statistically significant relationship with OC (OR, 0.87; 95% CI, 0.40–1.8). The age at last delivery was inversely associated with EC risk (OR, 0.69; 95% CI, 0.29–1.6; trend $P = 0.02$; Table 4).

Breastfeeding was inversely related to the risk of both OC and EC. In OC, a 4-fold protective effect was found after the first month of breastfeeding (OR, 0.24; 95% CI, 0.10–0.57), although we did not observe a statistically significant trend ($P = 0.11$). In EC, the protective effect was 2.3 times greater after the first month of breastfeeding (OR, 0.42; 95% CI, 0.19–0.91), with a statistically significant trend ($P < 0.001$) when compared with women who had never breastfed.

The length of anovulation was strongly inverse associated with OC risk (OR, 0.23; 95% CI, 0.10–0.50), and a clear statistically significant trend was observed ($P < 0.001$). A similar relationship was observed with EC risk (OR, 0.17; 95% CI, 0.08–0.35; trend $P < 0.001$) when comparing women in the highest quartile to those in the lowest (Table 5).

In the case of OC, the use of oral contraceptives reduced the risk 2.7 times compared with women who have never used them (OR, 0.36; 95% CI, 0.15–0.83); a similar effect was observed with EC risk (OR, 0.36; 95% CI, 0.14–0.90; Table 6). The use of an intrauterine device showed no relationship with OC risk, but for EC there was a statistically significant inverse association (OR, 0.42; 95% CI, 0.19–0.95). Hormone replacement therapy was not related to the risk of OC or EC. As for the state of menopause, the risk of OC is 4-fold among women with natural menopause (OR, 3.6; 95% CI, 1.5–8.9). In women whose

Table 1 *Distribution of selected factors among cases and controls, Mexico 1995–1997*

	Controls ($n = 668$)	Ovary cases ($n = 84$)	Endometrium cases ($n = 85$)
Age (yr)[a]	54.6	52.8	57.1
Education (completed yr)[a]	5.7	6.7	4.9
Age at menarche (yr)[a]	13.1	13.2	13.4
No. of full-term pregnancies[a]	4.6	3.9	3.5[b]
Age at first delivery (yr)[a]	18.4	16.8	16.5
No. of deliveries[a]	4.0	3.5	3.0[b]
Age at last delivery[a] (yr)	26.7	23.7[b]	22.2[b]
Total time of lactation[a] (mo)	34.3	29.2	27.6
No. of children breastfeeding[a]	2.7	2.4	2.2
Contraceptive use[a] (mo)	12.3	8.4	5.1
Age at menopause[a] (yr)	47.6	46.4	47.9
Anovulatory index[a] (mo)	71.0	58.7	50.3[b]
Quetelet index[a] (Kg/cm^2)	27.6	26.7	29.6[b]
History of pregnancy (%)	87.2	80.9	74.1
Contraceptive use (%)	29.1	15.4	15.1
Diabetes mellitus (%)	5.4	10.7	22.3
Hypertension (%)	19.6	25.0	36.4
Current smoking (%)	15.9	10.7	15.3
Physical activity (%)	15.8	15.4	4.7

[a] Mean.
[b] Student t test: $P < 0.05$, with respect to controls.

Table 2 *Pregnancy, age at menarche, and menopause in OC and EC, Mexico 1995–1997*

	Cases	Controls	OR[a]	95% CI	Test for trend
Age at menarche[b] (yr)					
Ovary					
≤10	9	117	1.0		
11–13	40	287	1.8	0.78–4.5	
≥14	35	264	2.2	0.93–5.4	
					$P = 0.24$
Endometrium					
9–10	12	117	1.0		
11–13	35	287	0.99	0.46–2.1	
14–20	38	264	1.1	0.50–2.4	
					$P = 0.62$
Full-term pregnancies[c]					
Ovary					
Never	16	85	1.0		
Ever	68	583	0.46	0.22–0.96	
Endometrium					
Never	22	85	1.0		
Ever	63	583	0.25	0.12–0.49	
No. of full-term pregnancies[c]					
Ovary					
0	16	85	1.0		
1–2	19	135	0.55	0.23–1.3	
3–4	21	159	0.46	0.20–1.0	
5–6	14	103	0.43	0.17–1.1	
≥7	14	186	0.17	0.05–0.54	
					$P = 0.02$
Endometrium					
0	22	85	1.0		
1–2	19	135	0.41	0.18–0.91	
3–4	15	159	0.19	0.08–0.44	
5–6	13	103	0.20	0.08–0.52	
≥7	16	186	0.11	0.04–0.34	
					$P < 0.001$
Age at menopause[d] (yr)					
Ovary					
≤40	7	32	1.0		
41–45	8	61	0.51	0.14–1.7	
46–50	15	88	0.97	0.33–2.8	
≥51	19	117	0.94	0.33–2.6	
					$P = 0.25$
Endometrium					
≤40	7	32	1.0		
41–45	13	61	1.1	0.34–3.7	
46–50	16	88	1.0	0.34–3.3	
≥51	22	117	1.2	0.42–3.6	
					$P = 0.50$

[a] Multivariate polytomous model OR.
[b] Adjusted by age, anovulatory index, smoking, diabetes mellitus, hypertension, physical activity, menopausal status, and body build index.
[c] Adjusted by age, hormonal use, breastfeeding, smoking, diabetes mellitus, hypertension, physical activity, menopausal status, and body build index.
[d] Adjusted by age, anovulatory index, smoking, diabetes mellitus, hypertension, physical activity, and body build index.

Table 3 *Parity and abortions in ovarian and endometrial cancer, Mexico 1995–1997*

	Cases	Controls	OR[a]	95% CI	Test for trend
Parity					
Ovary					
0	20	97	1.0		
1–2	17	153	0.44	0.19–1.0	
3–4	23	175	0.48	0.22–1.0	
≥5	24	243	0.32	0.12–0.81	
					$P = 0.04$
Endometrium					
0	25	97	1.0		
1–2	22	153	0.41	0.19–0.86	
3–4	14	175	0.15	0.06–0.36	
≥5	24	243	0.16	0.06–0.40	
					$P < 0.001$
No. of miscarriages					
Ovary					
0	62	452	1.0		
1	10	118	0.61	0.30–1.2	
≥2	12	98	0.90	0.44–1.8	
					$P = 0.21$
Endometrium					
0	58	452	1.0		
1	16	118	1.1	0.59–2.1	
≥2	11	98	0.86	0.39–1.8	
					$P = 0.15$

[a] Multivariate polytomous model OR adjusted by age, hormonal use, breastfeeding, smoking, diabetes mellitus, hypertension, physical activity, menopausal status, and body build index.

menopause was other than natural, the risk of OC was attenuated (OR, 2.3; 95% CI, 0.92–5.7). In the case of EC, the risk is five times greater for women with natural menopause as compared with premenopausal women (OR, 4.7; 95% CI, 1.7–12.8), and the relationship with surgical menopause was not statistically significant (OR, 2.3; 95% CI, 0.82–6.5).

In relation to some other nonreproductive factors, particularly diabetes, hypertension, and obesity, all insulin resistance-related factors, we did not observe any relationship with OC risk. However, the presence of diabetes, hypertension, and obesity were all positively related to EC risk (OR, 3.6 and 95% CI, 1.7–7.5; OR, 1.8 and 95% CI, 1.1–3.2; and OR, 1.9 and 95% CI, 1.1–3.6, respectively).

DISCUSSION

The results observed in this low-risk population are consistent with those found in high-risk populations and support the etiological hypotheses of "ovulation" and "exfoliation" mechanisms for OC and EC, respectively (8, 9, 17, 18).

Full-term pregnancy and parity are the factors associated with ovarian cancer, which are the best documented. The results of meta-analyses of case-control studies carried out in the United States and Europe report a risk reduction in women with at least one full-term pregnancy, with a clear lineal relationship according to the number of pregnancies (19, 20). This protective effect against OC has been also reported in other follow-up (21, 22) and mortality (23) studies. For EC, the relationship with pregnancy appears to be the same. Our results are consistent with previous studies showing a strong inverse relationship between full-term pregnancies and EC risk (4, 24, 25).

Parity is associated with a protective effect against OC because it includes a cascade of endocrine factors relating to hormone production (pregnancy record and breastfeeding). Studies carried out in China, the United States, and Sweden (26–28) have found that the number of children significantly reduces the risk of OC. In our investigation, parity was shown to be strongly inversely related to OC risk. A similar relationship was observed for EC risk, and these results are consistent with previous reports (4, 25).

Pregnancies that are not carried to term appear to be inversely related to the risk of OC. Pooled analyses carried out in Europe and the United States report a slight decrease in risk; however, because they distinguish between spontaneous and induced abortions, the results are not comparable (19, 20). The relationship between abortion and EC is even more inconsistent; several investigations show no association (4, 5, 24, 25). In our study, there was no association with the number of abortions, probably because the number of women with cancer and a history of abortion is small.

The age at first and last delivery is the most frequently studied and the most controversial characteristic. In the case of OC, several studies show little or even no association (19, 26, 29, 30), whereas others indicate an inverse effect with first delivery at a later age (7, 28). The results of this variable are inconsistent in the case of EC; some studies show a slight relationship, whereas others show no evidence of an effect (5, 24, 31). In different studies, the relationship of OC with the last birth at a later age show no relationship (7, 21, 32), whereas in the case of EC, a consistently inverse relationship (5, 24, 31) is associated with this variable.

The majority of studies on breastfeeding and its relationship with OC show an inverse effect. Breastfeeding induces a partial inhibition of ovulation and increases the secretion of follicle-stimulating and luteinizing hormones, leading to conflicting hypotheses. Among women with a history of breastfeeding, risk of OC is lower compared with those who never breastfed their children; this association is inversely proportionate to the number of months of lactation (19, 32–34). Breastfeeding is related to the number of births and pregnancies and, together with other factors, to a shorter ovulation span. Because of the fact that estrogen levels are low during breastfeeding, it has been suggested that this ought to reduce the risk of EC. Nevertheless, results obtained in different countries are inconsistent and fail to show an association (6, 35), although recent investigations have found a protective effect at an early age (36).

The relationship between the age at menarche and OC is controversial. Some case-control studies have found a 4-fold risk (26) when menses begin at an early age, whereas others with summary OR techniques have found this relationship to be weak or nonexistent (19). Moreover, longitudinal studies indicate no association between OC and menarche at an early age (21, 22). In EC, the relationship is clearer, and the results are consistent, although there are reports that

Table 4 *Age at first and last delivery, Mexico 1995–1997*

	Cases	Controls	OR[a]	95% CI	Test for trend
Age at first delivery					
Ovary					
≤20 years	26	286	1.0		
21–25 years	22	269	1.4	0.74–2.9	
≥26 years	15	224	1.6	0.74–3.6	
					$P = 0.27$
Endometrium					
≤20 years	22	286	1.0		
21–25 years	19	269	1.2	0.56–2.6	
≥26 years	19	224	2.4	1.1–5.3	
					$P = 0.03$
Age at last delivery					
Ovary					
≤25 years	36	223	1.0		
26–35 years	28	274	0.65	0.34–1.2	
≥36 years	20	171	0.87	0.40–1.8	
					$P = 0.15$
Endometrium					
≤25 years	33	223	1.0		
26–35 years	37	274	0.95	0.50–1.8	
≥36 years	15	171	0.69	0.29–1.6	
					$P = 0.02$

[a] Multivariate polytomous model OR adjusted by age, anovulatory index, smoking, diabetes mellitus, hypertension, physical activity, menopausal status, and body build index.

Table 5 *Breastfeeding and anovulation in OC and EC, Mexico 1995–1997*

	Cases	Controls	OR[a]	95% CI	Test for trend
Breastfeeding[b]					
Ovary					
Never	38	172	1.0		
Ever	46	496	0.31	0.18–0.53	
Endometrium					
Never	33	172	1.0		
Ever	52	496	0.34	0.19–0.58	
Total time of breastfeeding[b] (mo)					
Ovary					
0	38	172	1.0		
1–12	10	141	0.24	0.10–0.57	
13–24	14	155	0.29	0.13–0.61	
≥25	22	200	0.36	0.19–0.69	
					$P = 0.11$
Endometrium					
0	33	172	1.0		
1–12	14	141	0.42	0.19–0.91	
13–24	14	155	0.28	0.13–0.63	
≥25	24	200	0.33	0.17–0.65	
					$P < 0.001$
No. of children breastfeeding[b]					
Ovary					
0	39	230	1.0		
1–2	13	151	0.42	0.19–0.92	
3–5	20	164	0.69	0.37–1.29	
≥6	12	123	0.50	0.23–1.06	
					$P = 0.17$
Endometrium					
0	40	230	1.0		
1–2	14	151	0.58	0.28–1.2	
3–5	17	164	0.48	0.24–0.94	
≥6	14	123	0.48	0.24–1.0	
					$P = 0.02$
Anovulatory index[c] (mo)					
Ovary					
≤26	28	159	1.0		
27–59	21	152	0.45	0.22–0.91	
60–104	21	180	0.49	0.25–0.97	
≥105	14	177	0.23	0.10–0.50	
					$P < 0.001$
Endometrium					
≤26	34	159	1.0		
27–59	17	152	0.25	0.12–0.53	
60–104	19	180	0.22	0.11–0.46	
≥105	15	177	0.17	0.08–0.35	
					$P < 0.001$

[a] Multivariate polytomous model OR.
[b] Adjusted by age, hormonal use, number of pregnancies, smoking, diabetes mellitus, hypertension, physical activity, menopausal status, and body build index.
[c] Adjusted by age, smoking, diabetes mellitus, hypertension, physical activity, menopausal status, and body build index.

find no association (25). Other case-control studies show that the risk increases 2-fold when menarche is at a later age (4), and prospective studies indicate the opposite, *i.e.*, that there is a reduction in risk when this takes place at a later age (24). In our study, no association was found between the age at menarche and OC or EC.

The relationship between the onset of menopause at a later age and OC is one of the most researched, with no conclusive results. Pooled analyses in Europe (37) indicate a significant increase (OR, 1.9), whereas in Asia, case-control studies show no relationship (26, 29), as do pooled analyses in the United States (19). Nor have follow up studies in Europe and America managed to establish a relationship between menopause at a later age and OC (21, 22). Evaluation of the relationship between this variable, late onset of menopause, and EC shows no association in some case-control studies (4), whereas other more recent case-control (25) and follow-up (24) studies show a 5 and 87% increased risk, respectively.

The protective effect of combined oral contraceptives is one of the most consistent findings of the study of OC. Research in different countries has found an important reduction in risk, proportionate to the increase and length of consumption of these products (19, 32, 33, 38–42). Our results match these findings; we discovered a strong association between oral contraceptive use and OC risk reduction. The use of oral contraceptives has been consistently associated with an almost 50% reduction in the risk of EC, and furthermore, a dose-response gradient has been observed (43). The protective effect of these hormone compounds persists, even after their use has been interrupted for up to 15 years (42–45). Hormone replacement therapy has not been associated with OC in any consistent manner. Some studies report no relationship (19, 30), others report a slightly positive relationship among certain histological subtypes (endometriod; Ref. 33), and cohort studies reveal an increased in the risk of fatal OC, according to the length of time during which replacement therapy is used (46). In a meta-analysis carried out in the United States by Grady *et al.* (47), it was conclusively shown that hormone replacement therapy is an important risk factor in the development of cancer of the endometrium. Our results show no association, probably due to the fact that prevalence of hormone replacement therapy among the study group was very low, which prevents its evaluation.

The time span of ovulation is the result of different contributing endocrinological factors. As such, more than as an individual function of each of its components, it is related with an increase of OC (26, 29, 48, 49) and EC risk (24) in proportion to the number of years during which a woman ovulates.

In our study, a clear endocrine protective factor for both types of neoplasms was found. Our results are consistent with those of previous studies and support currently accepted hypotheses that typify OC and EC as hormone-dependent conditions. In the case of OC, the ovulation hypothesis indicates that any factor that suppresses this function has a protective effect. In EC, the reduction of risk is

Table 6 *Menopausal status and oral hormone use in OC and EC, Mexico 1995–1997*

	Cases	Controls	OR[a]	95% CI	Test for trend
Oral contraceptives use[b] (mo)					
Ovary					
0	71	473	1.0		
1–12	6	78	0.56	0.22–1.3	
≥13	7	117	0.36	0.15–0.83	
					$P = 0.01$
Endometrium					
0	72	473	1.0		
1–12	6	78	0.51	0.18–1.4	
≥13	7	117	0.36	0.14–0.90	
					$P = 0.01$
Use of intrauterine device[c]					
Ovary					
No	61	465	1.0		
Yes	23	203	0.87	0.46–1.6	
Endometrium					
No	75	465	1.0		
Yes	10	203	0.42	0.19–0.95	
Replacement hormone therapy[c]					
Ovary					
No	79	630	1.0		
Yes	5	38	1.0	0.36–2.7	
Endometrium					
No	79	630	1.0		
Yes	6	38	0.92	0.32–2.6	
Menopausal status[d]					
Ovary					
Premenopausal	17	225	1.0		
Surgical postmenopausal	18	145	2.3	0.92–5.7	
Natural postmenopausal	49	298	3.6	1.5–8.9	
Endometrium					
Premenopausal	13	225	1.0		
Surgical postmenopausal	14	145	2.3	0.82–6.5	
Natural postmenopausal	58	298	4.7	1.7–12.8	

[a] Multivariate polytomous model OR.
[b] Adjusted by age, number of pregnancies, breastfeeding, smoking, diabetes mellitus, hypertension, physical activity, menopausal status, and body build index.
[c] Adjusted by age, anovulatory index, smoking, diabetes mellitus, hypertension, physical activity, menopausal status, and body build index.
[d] Adjusted by age, anovulatory index, smoking, diabetes mellitus, hypertension, physical activity, and body build index.

explained by: (*a*) the exfoliation hypothesis, *i.e.*, the removal of epithelial cells from the endometrium during each delivery; and (*b*) the decrease in endogenic estrogens, as during breastfeeding. These mechanisms, and perhaps others yet to be accounted for, determine the level of risk for both OC and EC.

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