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ORIGINAL PAPER

Reproductive factors, adiposity, breastfeeding and their associations with ovarian cancer in an Asian cohort

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Abstract
Purpose The aim of this study was to assess associations of breastfeeding, adiposity and reproductive risk factors with ovarian cancer risk in a Singaporean population. In addition to the main analysis, interaction effects of parity on other risk factors were examined.
Methods A retrospective cohort consisting of 28,201 women with 107 incident ovarian cancers in up to 17 years of follow-up from the Singapore Breast Cancer Screening Project (1994–1997) was studied. Hazard ratios (HRs) for risk factors were estimated using Cox proportional hazards models.
Results Body mass index and breastfeeding were found to have no statistical significant association with ovarian cancer risk. Gravidity was inversely associated with ovarian cancer risk [each pregnancy, adjusted HR 0.89, 95 % confidence interval (CI) 0.81, 0.97], while results for parity were very similar (per delivery, HR 0.89, 95 % CI 0.81, 0.98). Each additional year of ovulatory period was found to increase ovarian cancer risk by 2 % (HR 1.02, 95 % CI 1.00, 1.04). Each year increase in total duration of oral contraceptive use reduced ovarian cancer risk by 6 % (HR 0.94, 95 % CI 0.85, 1.02).
Conclusions Parity, gravidity and shorter ovulatory period were associated with lower ovarian cancer risk. Breastfeeding and body mass index were not associated with ovarian cancer risk, while increased duration of oral contraceptive use resulted in borderline risk reduction. No significant evidence was found to suggest that parity had an interaction effect on any risk factor.

Keywords Asian · Breastfeeding · Obesity · Ovarian cancer · Reproductive factors · Risk factors

Ovarian cancer ranks globally as the second most frequent gynecological malignancy and accounts for 4.2 % of cancer-related mortality in females [1, 2]. Despite a substantial number of studies on ovarian cancer available in the literature, the epidemiology of ovarian cancer among Asian women is less studied. This study, which was conducted in Singapore, a multi-ethnic Asian city-state of 5.4 million people comprising 74 % Chinese, 13 % Malays and 9 % Indians, and where ovarian cancer is the leading cause of mortality from gynecological malignancies and the fifth most common cancer in females [3], aims to contribute to this domain.

Ninety percent of ovarian cancers arise from the ovarian epithelium [1]. Studies have shown that reproductive factors such as parity and oral contraceptive use are associated with lower ovarian cancer risk. Other reproductive factors such as age of menarche and age of menopause are found to have weaker associations, but results for them are inconsistent [4–7]. This inconsistency extends to conclusions about obesity as a risk factor, even though two meta-analyses concluded similarly that obese (but not overweight) women are at a higher risk than women with normal body mass index (BMI) [8, 9].

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In 2013, Bodelon et al. [10], motivated by studies showing different ovarian cancer associations of BMI and oral contraceptive use by parity status [11, 12], investigated whether parity had a modifying effect on these two ovarian cancer risk factors, among others. Although the American study, which had a study population comprising of mostly non-Hispanic white women (90.8 %), did not find sufficient evidence to conclude that the associations of the other risk factors with ovarian cancer differed by parity status, it would be meaningful to validate this result with an Asian cohort.

Further, the effect of breastfeeding on ovarian cancer risk is uncertain. Breastfeeding usually results in suppressed ovulation cycles and reduced gonadotropins levels [13]. This suggests that breastfeeding should have an inverse association with ovarian cancer. However, evidence for breastfeeding and its association with ovarian cancer risk has not been consistent among individual studies [4, 14–16]. Nonetheless, a recent meta-analysis by Luan et al. [17] supports the hypothesis that ever breastfeeding and a longer duration of breastfeeding are both associated with lower risk of ovarian cancer.

In this ancillary study, we analyzed associations of reproductive factors, obesity and breastfeeding with ovarian cancer risk in a prospective breast cancer cohort study conducted on women living in a multi-ethnic Asian city-state. Additionally, risk factor associations for serous histological subtype of ovarian cancer were examined.

Methods

Study population

Subjects from this study were from the Singapore Breast Cancer Screening Project (SBCSP), which was a population-based mammography screening project conducted between October 1994 and February 1997 described in detail by Chay et al. [18]. The cohort consisted of 28,234 women aged 50–64 at the point of recruitment. Women who participated in the mammography project answered a detailed questionnaire on reproductive factors, as well as breastfeeding and oral contraceptive use.

Outcome ascertainment

In 2012, data from these women were matched with the Singapore Cancer Registry (SCR) to identify incident epithelial ovarian cancers (henceforth referred to as ovarian cancers in short) and histological subtypes from the date of recruitment until 30 December 2011. Mortality and dates of deaths were obtained from the Registry of Births and Deaths. The SCR obtains data from notifications by the medical profession, pathology records, hospital records and other sources following verification. About 10 % of all cancer cases were ascertained by pathologists in laboratories. Such cases were not notified by physicians but were subsequently registered by the registry staff [3]. Histology of the ovarian cancer cases was classified based on International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes, in the following way [19]: serous (ICD-O-3 codes 8441, 8442, 8460, 8461, 8462 and 9014), mucinous (8470, 8471, 8472, 8480, 8481, 8482, 8490 and 9015), endometrioid (8380, 8381, 8560 and 8570), clear cell (8310 and 8313) and others. Given the small size of Singapore and its relatively advanced economic and social development, the SCR is believed to be complete in cancer notifications [3] and the Registry of Births and Death is also believed to be comprehensive.

Participants were censored at the occurrence of ovarian cancer, death or at the end of the study (30 December 2011). Thirty-three women were excluded from the study: 24 women were diagnosed with ovarian cancer prior to study entry, while nine women had data collection errors resulting in non-credible age at recruitment or follow-up time. A total of 28,201 women were included in the analysis.

Exposure and covariate assessment

Information on sociodemographics, health behaviors, menstrual and reproductive factors, and exogenous hormone use (non-specific estrogen–progestin composition) were obtained at recruitment in 1994–1996. Data collected included age, race, smoking status, educational level, housing status, self-reported height and weight, and family history of breast cancers. BMI was calculated as weight in kilograms divided by the height in meters squared. The BMI range used in this study was based on internationally accepted Asian BMI cutoffs [20]. Information on reproductive factors collected included age of menarche, age of menopause, total reproductive period for postmenopausal women (defined as the period between age of menarche and age of menopause), total ovulatory period (in years) for postmenopausal women [estimated by, total reproductive period − (number of deliveries × 10/12 + total duration of oral contraceptive use)], ever pregnant, number of pregnancies, ever delivered, number of deliveries, and history of oral contraceptive use and total duration of oral contraceptive use (in years).

Participants in the study were also asked whether every child was breastfed, and if so, the duration of breastfeeding for each child. The total duration of breastfeeding was calculated as the sum of all individual breastfeeding duration across all deliveries for which there was available information. The average duration of breastfeeding was

calculated as the total duration of breastfeeding divided by the total number of deliveries.

Statistical analyses

Cohort characteristics were first summarized using descriptive statistics. In bivariate analyses, each unadjusted association with the outcome was evaluated by Pearson's Chi-squared test for categorical variables or Student's *t* test for continuous variables. Cox proportional hazards regression models were used on each risk factor to estimate the hazard ratios (HRs) and their 95 % confidence intervals (CIs), with person-years as the underlying timescale and occurrence of ovarian cancer as the failure event. The models were tested for the proportionality of hazards assumption. Specifically, stratified Cox models were used for multivariate analyses where covariates for statistical adjustment were identified a priori. All models were adjusted for age (continuous), housing type (1–3 room flat, ≥4 room flat, private or landed property, others), and family history of breast cancer. BMI status (underweight, normal, overweight, obese) and smoking status (never smoked, ever smoked), having failed the proportional hazards test, were included into the models as stratifying variables. Race (Chinese, Malay, Indian, others) was also included as a stratifying variable given strong differences in ovarian cancer incidence by race. Further adjustments by significant exposures in univariate analyses were performed. This set of hazard ratios are presented as supplementary material (Table S1) due to concerns of multicollinearity and sample size. Education was not included in the list of adjustment covariates due to its considerable correlation with housing.

Histological analyses were restricted to serous cases only due to limited sample size. Further, parity as an effect modifier for reproductive factors, breastfeeding, BMI and oral contraceptive use was examined. To accomplish this, likelihood ratio tests compared each adjusted model plus a parity term to the same model with additional, respective risk factor–parity interaction term(s). Linear trends were tested by including appropriate ordinal variables into each model and evaluated by the Wald test. All p values calculated were two-tailed, and significance was set at $p < 0.05$. All statistical analyses were performed using STATA statistical software, version 11.0 (StataCorp LP, College Station, Texas) and R, version 3.0.1.

Results

At the time of censoring, this cohort had a total follow-up of 450,000 person-years (with an average of 17 years per person), during which there were 107 diagnosed cases of ovarian cancer. Of these cases of ovarian cancer, 48 were of the serous subtype, 9 were mucinous, 14 were endometrioid, 14 were clear cell and 22 were of other subtypes. The 28,201 women in this study had a mean age at entry of 57.4 years [standard deviation (SD) = 4.22], were predominantly of Chinese ethnicity (84.2 %), and at the time of recruitment, most had no formal education (61.2 %), were married (79.9 %), lived in four or more room flats (45.9 %), were not working (68.0 %), were overweight (42.4 %), never smoked in their lives (93.8 %) and had no family history of breast cancer (97.0 %) (Table 1).

Most of the women in the study reported an age of menarche of 15 years old or below (72.6 %) and among the postmenopausal women in the study (89.5 %), an age of menopause of 50 years old or above (59.2 %). More than half of the women (74.1 %) had a total reproductive period (defined as age of menopause—age of menarche) between 30 and 39 years. The majority of the women (92.8 %) were parous at the time of recruitment, and the mean number of babies the women gave birth to was 4. Oral contraceptive use was infrequent, with 62.0 % of the women reported never using them. However, a substantial number of them who did use oral contraceptives had used them for a total duration of more than 1 year (23.3 % of the cohort). The majority of women in this cohort breastfed their children (69.3 %), with an average breastfeeding duration of 4.47 (SD = 6.88) months per child, and a mean total breastfeeding duration of 1.88 years (SD = 3.29) (Table 2).

The 15-year absolute risk of developing ovarian cancer for women in this study was 24.9 cases per 100,000 person-years. Chinese women had higher absolute risks (27.2 per 100,000 person-years) than Malay women (13.2 per 100,000 person-years), Indian women (14.9 per 100,000 person-years) and women of other ethnicities (9.4 per 100,000 person-years). Younger women aged 50–59 in this study had an absolute risk of 25.3 per 100,000 person-years, which is higher than the absolute risk of older women age 60–67 by 1.1 per 100,000 person-years.

Table 2 contains crude and adjusted hazard ratios for each identified risk factor. Given the adjusted models produced very similar results to the unadjusted ones, subsequent results presented below are from the adjusted models (unless otherwise stated).

Risk factors

Reproductive period

Age of menarche, age of menopause and total reproductive period were not associated with ovarian cancer risk both before and after adjustments (Table 2). Total ovulatory period, however, was found to be significantly positively associated with ovarian cancer risk. Women in the study

Table 1 Characteristics of women in the SBCSP, 1994–1997

Variable	No ovarian cancer	Ovarian cancer							Univariate cox model	
		Serous	Mucinous	Endometrioid	Clear cell	Others	Total	*p* value[a]		
	28,094 (99.62 %)	48 (0.17 %)	9 (0.03 %)	14 (0.05 %)	14 (0.05 %)	22 (0.05 %)	107 (0.38 %)		HR	95 % CI
Age at entry, mean (SD)								0.310		
	57.4 (4.22)	56.7 (3.68)	55.7 (4.82)	56.1 (4.64)	56.9 (3.83)	59.0 (4.39)	57 (4.14)		0.98	0.94, 1.03
Race, *n* (%)								0.183		
Chinese	23,645 (84.2)	43 (89.6)	9 (100)	12 (85.7)	14 (100)	20 (90.9)	98 (91.6)		1	Ref
Malay	1,583 (5.6)	1 (2.1)	0 (0)	2 (14.3)	0 (0)	0 (0)	3 (2.8)		0.47	0.15, 1.48
Indian	1,393 (5.0)	3 (6.3)	0 (0)	0 (0)	0 (0)	1 (4.6)	4 (3.7)		0.7	0.26, 1.90
Others	1,472 (5.2)	1 (2.1)	0 (0)	0 (0)	0 (0)	1 (4.6)	2 (1.9)		0.33	0.08, 1.35
Education level, *n* (%)								0.440		
No formal	17,190 (61.2)	28 (58.3)	6 (66.7)	6 (42.9)	8 (57.1)	10 (45.5)	58 (54.2)		1	Ref
Primary	5,229 (18.6)	10 (20.8)	2 (22.2)	5 (35.7)	2 (14.3)	6 (27.3)	25 (23.4)		1.39	0.87, 2.22
Secondary/diploma	5,009 (17.8)	10 (20.8)	1 (11.1)	3 (21.4)	3 (21.4)	5 (22.7)	22 (20.6)		1.27	0.77, 2.07
Tertiary and higher	665 (2.4)	0 (0.0)	0 (0)	0 (0)	1 (7.1)	1 (4.6)	2 (1.9)		0.87	0.21, 3.56
Marital status, *n* (%)								0.008		
Single	1,195 (4.3)	5 (10.4)	1 (11.1)	0 (0)	2 (14.3)	3 (13.6)	11 (10.3)		1	Ref
Married	22,440 (79.9)	37 (77.1)	7 (77.8)	11 (78.6)	10 (71.4)	17 (77.3)	82 (76.6)		0.4	0.21, 0.75
Divorced/widowed/separated	4,458 (15.9)	6 (12.5)	1 (11.1)	3 (21.4)	2 (14.3)	2 (9.1)	14 (13.1)		0.35	0.16, 0.78
Housing type, *n* (%)								0.091		
HDB (1–3 rooms)	10,951 (39.0)	24 (50.0)	2 (22.2)	8 (57.1)	5 (35.7)	8 (36.4)	47 (43.9)		1	Ref
HDB (≥4 rooms)	12,889 (45.9)	16 (33.3)	7 (77.8)	5 (35.7)	7 (50.0)	8 (36.4)	43 (40.2)		0.77	0.51, 1.17
Private/landed	3,739 (13.3)	7 (14.6)	0 (0)	0 (0)	1 (7.1)	4 (18.2)	12 (11.2)		0.74	0.39, 1.39
Others	514 (1.8)	1 (2.1)	0 (0)	1 (7.1)	1 (7.1)	2 (9.1)	5 (4.7)		2.23	0.89, 5.61
Occupational status, *n* (%)								0.034		
Working	8,993 (32.0)	26 (54.2)	4 (44.4)	6 (42.9)	3 (21.4)	6 (27.3)	45 (42.1)		1	Ref
Not working	19,100 (68.0)	22 (45.8)	5 (55.6)	8 (57.1)	11 (78.6)	16 (72.7)	62 (57.9)		0.66	0.45, 0.97
BMI status, *n* (%)								0.142		
Underweight (<18.0)	1,281 (4.6)	4 (8.3)	2 (22.2)	3 (21.4)	2 (14.3)	7 (31.8)	6 (5.6)		1.47	0.61, 3.56
Normal (18.5–22.9)	8,656 (30.8)	14 (29.2)	0 (0)	0 (0)	1 (7.1)	1 (4.6)	28 (26.2)		1	Ref
Overweight (23.0–27.4)	11,905 (42.4)	25 (52.1)	5 (55.6)	8 (57.1)	8 (57.1)	10 (45.5)	56 (52.3)		1.46	0.93, 2.30
Obese (≥27.5)	6,251 (22.3)	5 (10.4)	2 (22.2)	3 (21.4)	3 (21.4)	4 (18.2)	17 (15.9)		0.86	0.47, 1.57
Smoking status, *n* (%)								0.392		
Never smoked	26,350 (93.8)	46 (95.8)	9 (100)	14 (100)	14 (100)	20 (90.9)	103 (96.3)		1	Ref
Ever smoked	1,743 (6.2)	2 (4.2)	0 (0)	0 (0)	0 (0)	2 (9.1)	4 (3.7)		0.62	0.23, 1.68
Family history of breast cancer[b], *n* (%)								0.857		

Table 1 continued

Variable	No ovarian cancer	Ovarian cancer						Univariate cox model	
		Serous	Mucinous	Endometrioid	Clear cell	Others	Total	*p* value[a]	HR	95 % CI
	28,094 (99.62 %)	48 (0.17 %)	9 (0.03 %)	14 (0.05 %)	14 (0.05 %)	22 (0.05 %)	107 (0.38 %)			
No	27,258 (97.0)	47 (97.9)	9 (100)	14 (100)	13 (92.9)	20 (90.9)	103 (96.3)		1	Ref
Yes	835 (3.0)	1 (2.1)	0 (0)	0 (0)	1 (7.1)	2 (9.1)	4 (3.7)		1.26	0.46, 3.41
Tumor stage (AJCC 6th edition)										
I		4 (8.3)	3 (33.3)	8 (57.1)	5 (35.7)	6 (27.3)	26 (24.3)			
II		3 (6.3)	0 (0)	4 (28.6)	3 (21.4)	4 (18.2)	14 (13.1)			
III		22 (45.8)	2 (22.2)	1 (7.1)	0 (0)	4 (18.2)	29 (27.1)			
IV		14 (29.2)	2 (22.2)	0 (0)	3 (21.4)	4 (18.2)	23 (21.5)			
Unknown		5 (10.4)	2 (22.2)	1 (7.1)	3 (21.4)	4 (18.2)	15 (14.0)			

CI confidence interval, *HR* hazard ratio, *SD* standard deviation

[a] Chi-square test and *t* test for discrete and continuous variables, respectively, on "No Ovarian Cancer" and "Total Ovarian Cancer"

[b] Defined as breast cancer incidence in first- or second-degree female relatives

whose total ovulatory period was more than or equal to 35 years had about twice the risk of developing ovarian cancer compared to those whose ovulatory period was less than 25 years (adjusted HR 2.23, 95 % CI 1.25, 3.97). Each additional year of total ovulatory period resulted in a 2 % increase in ovarian cancer risk (HR 1.02, 95 % CI 1.00, 1.04).

Gravidity

Being ever pregnant reduced overall ovarian cancer risk by 45 % (HR 0.55, 95 % CI 0.31, 0.97). Women who were pregnant at least once, but not more than three times, had 44 % lower risk than nulligravida women (HR 0.56, 95 % CI 0.30, 1.05). Similarly, women who were pregnant more than three times had 47 % lower risk than nulliparous women (HR 0.53, 95 % CI 0.29, 0.97). Each pregnancy was associated with 11 % reduction in ovarian cancer risk (HR 0.89, 95 % CI 0.81, 0.97).

Parity

Parity was similarly associated with ovarian cancer risk due to its high correlation with gravidity. Parous women had 40 % lower ovarian cancer risk than nulliparous women (HR 0.60, 95 % CI 0.34, 1.09). Parous women who gave birth to not more than three children had 36 % lower risk than nulliparous women (HR 0.64, 95 % CI 0.35, 1.16). Likewise, women who gave birth to more than three children had 45 % lower risk than nulliparous women (HR 0.55, 95 % CI 0.30, 1.03). Overall, there was a 10 % reduction in ovarian cancer risk for every child delivered (HR 0.90, 95 % CI 0.81, 1.00).

Oral contraceptives

Women who used oral contraceptives had 15 % lower risk in ovarian cancer, although this result was not statistically significant (HR 0.85, 95 % CI 0.57, 1.27). The inverse association between longer duration of oral contraceptive use and ovarian cancer risk was borderline significant (HR 0.94 per year, 95 % CI 0.85, 1.02).

Hormone therapy

There was no significant association between history of reproductive hormone therapy and ovarian cancer risk (HR 0.62, 95 % CI 0.32, 1.20).

Breastfeeding

There was no association between ever breastfeeding and risk of ovarian cancer (adjusted HR 0.97, 95 % CI 0.63,

Table 2 Ovarian cancer risk factors for women in the SBCSP, 1994–1997

Variable	No ovarian cancer 28,094 (99.62 %)	Ovarian cancer 107 (0.38 %)	Person-years	Crude HR	95 % CI	Adjusted HR[a]	95 % CI
Age of menarche, *n* (%)							
<14	9,848 (35.1)	36 (33.6)	156,681	1	Ref	1	Ref
14–15	10,538 (37.5)	44 (41.1)	167,129	1.15	0.74, 1.78	1.09	0.70, 1.70
≥16	7,695 (27.4)	27 (25.2)	121,907	0.96	0.59, 1.59	0.90	0.53, 1.50
Trend				0.99	$p = 0.94$	0.95	$p = 0.71$
Age of menarche, mean (SD)							
	14.42 (1.90)	14.4 (1.96)		1	0.90, 1.10	0.98	0.88, 1.09
Age of menopause[b], *n* (%)							
<45	2,892 (11.5)	11 (11.7)	45,515	0.98	0.52, 1.87	0.99	0.52, 1.89
45–49	7,359 (29.3)	25 (26.6)	116,336	0.87	0.55, 1.40	0.88	0.55, 1.40
≥50	14,896 (59.2)	58 (61.7)	235,957	1	Ref	1	Ref
Trend				1.05	$p = 0.94$	1.04	$p = 0.78$
Age of menopause, mean (SD)							
	49.4 (4.52)	49.5 (4.45)		1.01	0.96, 1.05	1.01	0.96, 1.05
Menopause status, *n* (%)							
Postmenopausal	25,147 (89.5)	94 (87.9)	397,808	1	Ref	1	Ref
Premenopausal	2,946 (10.5)	13 (12.2)	48,087	1.15	0.64, 2.05	1.05	0.56, 1.96
Total reproductive period in years[b,c], *n* (%)							
<30	2,984 (11.9)	12 (12.8)	46,861	1	Ref	1	Ref
30–39	18,629 (74.1)	67 (71.3)	295,391	0.89	0.48, 1.64	0.87	0.47, 1.62
≥40	3,534 (14.1)	15 (16.0)	55,557	1.05	0.49, 2.25	1.07	0.50, 2.30
Trend				1.04	$p = 0.85$	1.05	$p = 0.81$
Total reproductive period in years, mean (SD)							
	34.9 (4.75)	35.1 (4.93)		1.01	0.97, 1.05	1.01	0.97, 1.06
Total ovulatory period in years[b,d], *n* (%)							
<25	8,317 (33.1)	20 (21.3)	131,152	1	Ref	1	Ref
25–34	11,804 (46.9)	46 (48.9)	186,474	1.62	0.96, 2.74	1.59	0.94, 2.70
≥35	5,026 (20.0)	28 (29.8)	80,182	2.29	1.29, 4.07	2.23	1.25, 3.97
Trend				1.51	$p < 0.01$	1.49	$p = 0.01$
Total ovulatory period in years, mean (SD)							
	25.4 (12.2)	28.2 (10.9)		1.02	1.00, 1.04	1.02	1.00, 1.04
Ever pregnant, *n* (%)							
No	2,033 (7.2)	14 (13.1)	32,502	1	Ref	1	Ref
Yes	26,060 (92.8)	93 (86.9)	413,393	0.52	0.30, 0.91	0.55	0.31, 0.97
No. of pregnancies, *n* (%)							
0	2,033 (7.2)	14 (13.1)	32,502	1	Ref	1	Ref
1–3	9,177 (32.7)	36 (33.6)	147,435	0.57	0.31, 1.05	0.56	0.30, 1.05
> 3	16,883 (60.1)	57 (53.3)	265,958	0.50	0.28, 0.89	0.53	0.29, 0.97
Trend				0.60	$p < 0.01$	0.79	$p = 0.11$
No. of pregnancies, mean (SD)							
	4.34 (2.57)	3.54 (2.34)		0.88	0.81, 0.95	0.89	0.81, 0.97
Ever gave birth, *n* (%)							
No	2,211 (7.9)	14 (13.1)	35,265	1	Ref	1	Ref
Yes	25,882 (92.1)	93 (86.9)	410,630	0.57	0.32, 1.00	0.60	0.34, 1.06
No. of deliveries, *n* (%)							
0	2,211 (7.9)	14 (13.1)	35,265	1	Ref	1	Ref
1–3	12,056 (42.9)	49 (45.8)	193,627	0.64	0.35, 1.15	0.64	0.35, 1.16
> 3	13,826 (49.2)	44 (41.1)	217,003	0.51	0.28, 0.93	0.55	0.30, 1.03
Trend				0.67	$p = 0.01$	0.77	$p = 0.10$
No. of deliveries, mean (SD)							
	3.77 (2.31)	3.13 (2.08)		0.88	0.80, 0.96	0.89	0.81, 0.98

Table 2 continued

Variable	No ovarian cancer 28,094 (99.62 %)	Ovarian cancer 107 (0.38 %)	Person-years	Crude HR	95 % CI	Adjusted HR[a]	95 % CI
Ever OC use, *n* (%)							
No	17,423 (62.0)	70 (65.4)	275,863	1	Ref	1	Ref
Yes	10,670 (38.0)	37 (34.6)	170,032	0.86	0.58, 1.28	0.85	0.57, 1.27
Total duration of OC use in years, *n* (%)							
Never	17,440 (62.1)	70 (65.4)	276,142	1	Ref	1	Ref
≤ 1	4,113 (14.6)	20 (18.7)	94,508	1.09	0.69, 1.70	1.16	0.70, 1.92
> 1	6,539 (23.3)	17 (15.9)	75,229	0.58	0.31, 1.09	0.65	0.38, 1.10
Trend				0.83	$p = 0.17$	0.84	$p = 0.17$
Total duration of OC use in years, mean (SD)							
	1.29 (2.86)	0.88 (2.55)		0.93	0.85, 1.02	0.94	0.85, 1.02
Hormone therapy							
No	24,350 (86.7)	97 (90.7)	385,556	1	Ref	1	Ref
Yes	3,743 (13.3)	10 (9.4)	60,339	0.66	0.34, 1.26	0.62	0.32, 1.20
Total duration of hormone therapy in years[e], mean (SD)							
	0.41 (1.77)	0.17 (0.86)		0.85	0.68, 1.06	0.83	0.66, 1.05
Ever breastfed[d], *n* (%)							
No	7,955 (30.7)	31 (33.3)	126,410	1	Ref	1	Ref
Yes	17,927 (69.3)	62 (66.7)	284,220	0.89	0.58, 1.37	0.97	0.63, 1.51
Breastfeeding duration in years[e], *n* (%)							
Never	8,818 (34.1)	31 (33.3)	140,483	1	Ref	1	Ref
≤ 1	7,850 (30.3)	29 (31.2)	125,813	1.04	0.63, 1.73	1.09	0.66, 1.81
> 1	9,214 (35.6)	33 (35.5)	144,334	1.04	0.63, 1.69	1.20	0.72, 2.01
Trend				1.02	$p = 0.89$	1.10	$p = 0.48$
Breastfeeding duration in years[e], mean (SD)							
	1.88 (3.29)	1.75 (3.19)		0.99	0.93, 1.06	1.01	0.95, 1.09
Average breastfeeding duration in months[e,f], mean (SD)							
	4.47 (6.88)	4.70 (7.63)		1.01	0.98, 1.03	1.02	0.99, 1.05
BMI status, *n* (%)							
Underweight (<18.0)	1,281 (4.6)	6 (5.6)	20,119	1.47	0.61, 3.56	1.96	0.64, 5.97
Normal (18.5–22.9)	8,656 (30.8)	28 (26.2)	138,417	1	Ref	1	Ref
Overweight (23.0–27.4)	11,905 (42.4)	56 (52.3)	189,462	1.46	0.93, 2.30	1.34	0.69, 2.58
Obese (≥27.5)	6,251 (22.3)	17 (15.9)	97,898	0.86	0.47, 1.57	0.55	0.19, 1.55
Trend				0.95	$p = 0.67$	0.80	$p = 0.22$
BMI (continuous)							
	24.7 (4.19)	24.6 (3.66)		0.99	0.95, 1.04	1.01	0.96, 1.06
Family history of breast cancer[g]							
No	27,258 (97.0)	103 (96.3)	432,513	1	Ref	1	Ref
Yes	835 (3.0)	4 (3.7)	13,382	1.26	0.46, 3.41	1.25	0.46, 3.41

CI confidence interval, *HR* hazard ratio, *OC* oral contraceptive, *SD* standard deviation

[a] Stratified Cox models are used. Adjusted for age (continuous), housing type (1–3 room flat, ≥4 room flat, private or landed property, others) and family history of breast cancer. Stratified by race (Chinese, Malay, Indian, others), BMI status (underweight, normal, overweight, obese) and smoking status (never smoked, ever smoked)

[b] Only among postmenopausal women

[c] Defined as age of menopause—age of menarche

[d] Defined as (total reproductive period − number of deliveries × 10/12 − total duration of OC use)

[e] Only among parous women who had one or more deliveries

[f] Defined as total breastfeeding duration divided by total number of deliveries

[g] Defined as breast cancer incidence in first- or second-degree female relatives

1.51). Null effects for both total duration of breastfeeding and average duration of breastfeeding per child were observed.

Body mass index and family history of breast cancer

In overall, higher BMI was not associated with increased ovarian cancer risk (HR 1.01, 95 % CI 0.96, 1.06). BMI categories were also not statistically associated with ovarian cancer risk before and after adjustments (Table 2). Women with family history of breast cancer had an overall higher ovarian cancer risk, but this association was not statistically significant (HR 1.25, 95 % CI 0.46, 3.41).

Interaction with parity status

There was no evidence (data not shown) that parity had a modifying effect on BMI (P-heterogeneity = 0.97) or reproductive risk factors (P-heterogeneity, age of menarche = 0.86; age of menopause = 0.36; menopause status = 0.78; reproductive period = 0.35; ovulatory period = 0.39; ever oral contraceptive use = 0.46; ever hormone therapy use = 0.68) to ovarian cancer risk.

Serous ovarian cancer

Women who had total ovulatory period longer than 35 years were associated with higher risk of serous ovarian cancer (HR 2.69, 95 % CI 1.12, 6.43). Each year increase in total ovulatory period increased serous ovarian cancer risk by 3 % (HR 1.03, 95 % CI 1.00, 1.06). No other significant associations were detected (Table 3).

Discussion

In summary, gravidity and parity were found to be inversely associated with ovarian cancer risk in this study. Women who had longer ovulatory periods had a higher risk of ovarian cancer. In contrast, women who had longer reproductive periods were not at a higher risk. Risk reduction brought by an increased duration of oral contraceptive use was borderline significant. No association between breastfeeding and ovarian cancer risk was found.

There are several hypotheses about the etiology of ovarian epithelial tumors. The "Incessant Ovulation" theory postulates that the ovarian epithelium is traumatized by ovulation and requires repair. This process of continuous damage and repair increases the likelihood of errors during cellular replication, leading to the development of ovarian epithelial tumors [21]. The "Gonadotropins" theory postulates that high levels of circulating gonadotropins increase estrogenic stimulation to the ovarian epithelium, which can then lead to malignant transformation [22]. Gonadotropins (follicle-stimulating hormone and luteinizing hormone), which stimulate ovarian functions via the regulation of oogenesis and biosynthesis of steroid hormones in the ovary [23], are released in a surge prior to each onset of ovulation [24] during each menstrual cycle in a coordinated fashion. Finally, Risch has suggested that progesterone, a hormone produced by the corpus luteum in the luteal phase of a regular menstruation cycle and maintained at high levels by the placenta during pregnancy, has a protective role against ovarian cancer [25].

The first two hypotheses imply that women with high lifetime ovulation cycles have increased ovarian cancer risk [26, 27]. Studies have supported this with evidence that reducing lifetime ovulation cycles—whether through increased parity or the use of oral contraceptives—reduces epithelial ovarian cancer risk [7, 28]. The third hypothesis is supported by studies that have generally found parity to have a protective association with risk of ovarian cancer [4, 29]. However, some studies have shown similar risk reduction for low-progestin and high-progestin dosage oral contraceptive pills [30], which does not support this hypothesis.

This study found a strong positive association between total ovulatory period and ovarian cancer risk, which is a result consistent with literature [31, 32]. A similar association was not found between reproduction period and ovarian cancer risk. In this case, the number of ovulations was better correlated with ovarian cancer risk than the length of the reproductive period.

The finding that parity and gravidity were inversely related to ovarian cancer risk is consistent with the literature as well [10, 33]. During pregnancy, high levels of progesterone maintained by the corpus luteum and the placenta (after 8 weeks post-implantation) cause anovulation. In addition, progesterone and other hormones suppress production of the gonadotropins [34] during pregnancy.

Oral contraceptives generally prevent pregnancies in two ways: low-progestin dosage contraceptives rely on the thickening of the cervical mucus to prevent sperm entry through the cervix, while high-progestin dosage contraceptives inhibit ovulations completely by suppressing the release of gonadotropin-releasing hormones and consequently the levels of gonadotropins (in addition to thickening cervical mucus) [35]. In our study, oral contraceptive use was found to be slightly protective against developing ovarian cancer. Unfortunately, we could not ascertain which type of oral contraceptive pills were used by women in this cohort. The association between oral contraceptive consumption and ovarian cancer risk has been previously examined. Most studies, including a collaborative reanalysis of data from 45 epidemiological studies in 21 countries

Table 3 Serous ovarian cancer risk factors for women in the SBCSP, 1994–1997

Variable	Person-years	Serous ovarian cancer		
		Cases (%)	HR[a]	95 % CI
Age of menarche, *n* (%)				
<14		17 (35.4)	1	Ref
14–15		20 (41.7)	1.08	0.56, 2.08
≥16		11 (22.9)	0.81	0.37, 1.77
Trend			0.91	$p = 0.64$
Age of menarche, mean (SD)				
		14.3 (1.9)	0.96	0.82, 1.12
Age of menopause[b], *n* (%)				
<45	45,515	6 (13.6)	1.04	0.43, 2.52
45–49	116,336	9 (20.5)	0.61	0.29, 1.28
≥50	235,957	29 (65.9)	1	Ref
Trend			1.12	$p = 0.61$
Age of menopause, mean (SD)				
		49.6 (4.4)	1.02	0.95, 1.09
Menopause status, *n* (%)				
Postmenopausal	397,808	44 (91.7)	1	Ref
Premenopausal	48,087	4 (8.3)	0.60	0.20, 1.75
Total reproductive period in years[b,c], *n* (%)				
<30	46,861	6 (13.6)	1	Ref
30–39	295,391	32 (72.7)	0.83	0.35, 1.99
≥40	55,557	6 (13.6)	0.89	0.29, 2.76
Trend			0.94	$p = 0.85$
Total reproductive period in years, mean (SD)				
		35.2 (5.1)	1.02	0.95, 1.08
Total ovulatory period in years[b,d], *n* (%)				
<25	131,152	8 (18.2)	1	Ref
25–34	186,474	22 (50.0)	1.91	0.85, 4.29
≥35	80,182	14 (31.8)	2.69	1.12, 6.43
Trend			1.61	$p = 0.02$
Total ovulatory period in years, mean (SD)				
		29.3 (9.2)	1.03	1.00, 1.06
Ever pregnant, *n* (%)				
No	32,502	5 (10.4)	1	Ref
Yes	413,393	43 (89.6)	0.80	0.31, 2.04
No. of pregnancies, *n* (%)				
0	32,502	5 (10.4)	1	Ref
1–3	147,435	14 (29.2)	0.65	0.23, 1.82
> 3	265,958	29 (60.4)	0.92	0.35, 2.43
Trend			1.11	$p = 0.67$
No. of pregnancies, mean (SD)				
		3.94 (2.37)	0.99	0.86, 1.13
Ever gave birth, *n* (%)				
No	35,265	5 (10.4)	1	Ref
Yes	410,630	43 (89.6)	0.87	0.34, 2.23
No. of deliveries, *n* (%)				
0	35,265	5 (10.4)	1	Ref
1–3	193,627	22 (45.8)	0.85	0.32, 2.27
> 3	217,003	21 (43.8)	0.90	0.33, 2.46
Trend			0.99	$p = 0.95$
No. of deliveries, mean (SD)				
		3.31 (1.97)	0.97	0.84, 1.13

Table 3 continued

Variable	Person-years	Serous ovarian cancer		
		Cases (%)	HR[a]	95 % CI
Ever OC use, *n* (%)				
No	275,863	30 (62.5)	1	Ref
Yes	170,032	18 (37.5)	0.99	0.55, 1.79
Total duration of OC use in years, *n* (%)				
Never	276,142	30 (62.5)	1	Ref
≤ 1	94,508	16 (33.3)	1.65	0.84, 3.26
> 1	75,229	2 (4.2)	0.55	0.23, 1.34
Trend			0.85	$p = 0.39$
Total duration of OC use in years, mean (SD)				
		0.51 (1.21)	0.83	0.67, 1.02
Hormone therapy				
No	385,556	43 (89.6)	1	Ref
Yes	60,339	5 (10.4)	0.67	0.26, 1.73
Total duration of hormone therapy in years[e], mean (SD)				
		0.10 (0.58)	0.69	0.39, 1.21
Ever breastfed[d], *n* (%)				
No	126,410	14 (32.6)	1	Ref
Yes	284,220	29 (67.4)	1.07	0.56, 2.04
Breastfeeding duration in years[e], *n* (%)				
Never	140,483	14 (32.6)	1	Ref
≤ 1	125,813	13 (30.2)	1.11	0.52, 2.36
> 1	144,334	16 (37.2)	1.45	0.68, 3.09
Trend			1.21	$p = 0.34$
Breastfeeding duration in years[e], mean (SD)				
		1.95 (3.82)	1.05	0.96, 1.15
Average breastfeeding duration in months[e,f], mean (SD)				
		5.15 (9.27)	1.03	0.99, 1.07
BMI status, *n* (%)				
Underweight (<18.0)	138,417	14 (29.2)	1.96	0.64, 5.97
Normal (18.5–22.9)	20,119	4 (8.3)	1	Ref
Overweight (23.0–27.4)	189,462	25 (52.1)	1.34	0.69, 2.58
Obese ($\geq$27.5)	97,898	5 (10.4)	0.55	0.19, 1.55
Trend			0.80	$p = 0.22$
BMI (continuous)				
		24.4 (4.17)	0.99	0.92, 1.06
Family history of breast cancer[g]				
No	432,513	47 (97.9)	1	Ref
Yes	13,382	1 (2.1)	0.64	0.09, 4.63

CI confidence interval, *HR* hazard ratio, *OC* oral contraceptive, *SD* standard deviation

[a] Stratified Cox models were used. Adjusted for age (continuous), housing type (1–3 room flat, $\geq$4 room flat, private or landed property, others) and family history of breast cancer. Stratified by race (Chinese, Malay, Indian, others), BMI status (underweight, normal, overweight, obese) and smoking status (never smoked, ever smoked)

[b] Only among postmenopausal women

[c] Defined as age of menopause—age of menarche

[d] Defined as (total reproductive period − number of deliveries × 10/12 − total duration of OC use)

[e] Only among parous women who had one or more deliveries

[f] Defined as total breastfeeding duration divided by total number of deliveries

[g] Defined as breast cancer incidence in first- or second-degree female relatives

[7], indicated an inverse relationship between contraceptive use and ovarian cancer. Results from this study are consistent with these findings.

Breastfeeding elevates levels of prolactin which similarly inhibits the pulsatile secretion of gonadotropin-releasing hormones (and hence gonadotropins), resulting in anovulation. However, a recent study found that circulating prolactin levels may be associated with higher risk of ovarian cancer [36]. The data from this study did not suggest any strong association between breastfeeding and ovarian cancer risk. Inconsistent results of breastfeeding as a risk factor in the literature may be due to the opposing effects of anovulation and prolactin on ovarian cancer risk. In addition, misclassification of breastfeeding history may be frequent [37]: Breastfeeding histories are commonly assessed retrospectively, and the length of recall varies widely among studies. In this study, the mean age of entry into the SBCSP was 57 years old and the mean age of first delivery was 24 years old. Recall of this length may be a substantial source of error. Furthermore, frequency and amount of lactation that occurred during each breastfeeding period were unknown; ovulation may restart at indeterminate times when breastfeeding, and is dependent among others on these factors [38]. These potential sources of error could have biased our estimate toward the null.

The absence of an association between BMI and ovarian cancer risk in this study is not unexpected. Individual cohort studies such as Mink et al.'s [39] examination on the Iowa Women's Health Study Cohort and a Swedish study in 1994 [40] have shown similar results. Evidence from a systematic review by Purdie et al. [41] in 2001 supports a small-to-moderate positive relationship between high BMI and ovarian cancer risk. However, the studies that Purdie et al. presented adopted different BMI cutoffs for comparisons and did not adjust for a uniform set of confounders, which might have influenced the results of their meta-analysis.

A recent study by Bodelon et al. [10] in 2013 provided suggestive evidence that the relative effects of BMI on ovarian cancer risk differ by parity. However, no evidence of this modifying effect (P-heterogeneity $= 0.97$) was found in this study. In addition, the data from this study did not show significant interaction between parity and each of the other risk factors, though this may be attributed to low statistical power arising from small numbers in the nulliparous group.

Studies on three major cohorts, namely the US Nurses' Health Study (NHS) I and II cohorts [42], the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort [43] and the National Institutes of Health (NIH)-AARP cohort [44], investigated differences in risk factor associations by histological subtypes. All three studies had similar results, with serous ovarian cancer being positively associated with length of ovulatory period, and negatively associated with duration of oral contraceptive use. Parity was negatively correlated with serous ovarian cancer risk, although this association was statistically significant only in the EPIC cohort study. Estimates from this study are consistent with these results.

Overall, associations found in this study are similar to those reported in predominantly Caucasian populations. The dissimilarities, such as the null findings of age of menarche, age of menopause and breastfeeding as risk factors in this study, might be a consequence of ethnicity differences, although a meta-analysis is needed to ascertain such a claim. This difference in risk factor associations might also be attributed to the dissimilarity in ovarian tumor characteristics (especially histology) between typical Asian and non-Asian populations. For instance, clear cell and endometrioid tumors are more commonly observed in Asian populations than in non-Asian populations.

Strengths of this study include a relatively large cohort size, the ability to exclude women with ovarian cancer prior to study entry, and a long average follow-up time. Furthermore, registration of cancer is fairly complete. Limitations of this study include the possibility that cancer outcome data are incomplete from women who have left Singapore either temporarily or permanently. Recent data suggest that about 5 % of the Singapore population is working or living abroad [45], although the proportion of Singaporeans who renounce Singaporean citizenship is low [46]. Overall, this is unlikely a major threat to validity in this study. Given the low incidence of ovarian cancer, there might be insufficient ovarian cancer cases to assess parity interactions and associations of risk factors by histological subtypes with appropriate power. Hence, any parity interaction and subtype-specific association identified in this study should be considered to be preliminary.

In conclusion, parity and gravidity were inversely associated, while long ovulatory period length was positively associated with ovarian cancer risk in this longitudinal study of Asian women. Results from this study suggest that the effect of repeated ovulation on ovarian cancer may be greater than gonadotropin stimulation. There was a borderline inverse association of oral contraceptive use but no significant association of breastfeeding with ovarian cancer risk. Histological subtype analysis was restricted to the serous subtype due to limited ovarian cancer cases in this study. Nonetheless, this study found that length of ovulatory period and duration of oral contraceptive use were positively and borderline negatively associated with serous ovarian cancer risk, respectively, which are results consistent with the literature. No evidence suggested that there was any interaction between parity and other ovarian cancer risk factors. Further investigation of risk factor differences by histological subtypes is needed.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to report.

Informed consent Informed consent was obtained from all individual participants included in the study.

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