

# Reproductive factors for ovarian cancer in southern Chinese women

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**Objective:** To investigate the association between reproductive factors and the risk of ovarian cancer among southern Chinese women.

**Methods:** A hospital-based case-control study was undertaken in Guangzhou, Guangdong Province, between 2006 and 2008. A structured questionnaire was used to obtain information on parity, oral contraceptive use and other reproductive factors in a sample of 500 incident ovarian cancer patients and 500 controls (mean age, 59 years). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression models.

**Results:** High parity was inversely associated with ovarian cancer, with an adjusted OR 0.43 (95% CI, 0.30 to 0.62) for women who had given birth to 3 or more children compared to women who had given no more than one birth. Ever use of oral contraceptives was also protective against ovarian cancer; adjusted OR 0.56 (95% CI, 0.40 to 0.78). No association was found for hormone replacement therapy, menopausal status, hysterectomy and family history of ovarian and/or breast cancer.

**Conclusion:** High parity and oral contraceptive use are associated with a lower risk of ovarian cancer in southern Chinese women.

**Keywords:** China, Oral contraceptives, Ovarian cancer, Parity

## INTRODUCTION

Ovarian cancer ranks as the seventh most common cause of cancer mortality among women [1], accounting for 4.2% of cancer deaths [2]. It is the eighth most common cancer in women, with approximately 225,000 new cases reported worldwide in 2008 [1]. The incidence of ovarian cancer varies geographically. The age-standardised rate (per 100,000 females) is only 3.8 in China, relatively lower than developed countries such the USA (8.8) and Australia (7.7) [1]. The majority of ovarian malignancies are epithelial in origin [3] and are often diagnosed in the advanced stages of the disease due to

the subtle and non-specific symptoms [4]. There is currently no effective screening method available for the detection of this disease [5], which has an overall five-year survival rate of approximately 45% [6].

Numerous studies have linked reproductive factors with ovarian cancer. Long-term oral contraceptive use and higher parity are consistently associated with a reduced ovarian cancer risk [7-19]. Hysterectomy has been suggested to be protective, estimated to confer a 30%-50% risk reduction [20-23]. The evidence regarding use of hormone replacement therapy is somewhat conflicting, with some studies reporting a greater risk of ovarian cancer [19,24], and others revealing no association [9,12,25]. In contrast, increased ovarian cancer risk has been reported for postmenopausal women [13,26,27] and having a family history of breast or ovarian cancer [12,28].

The majority of studies examining the relationship between reproductive factors and ovarian cancer have been conducted in countries with a high incidence of the disease. The aim

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of this case-control study was to investigate associations between ovarian cancer risk and reproductive factors among southern Chinese women, a low incidence population.

## MATERIALS AND METHODS

This case-control study was undertaken in Guangzhou, the capital city of Guangdong Province in Southern China, between August 2006 and July 2008. Participants were recruited from four public hospitals, i.e., the Overseas Hospital (affiliated with Jinan University), General Hospital of Guangzhou Military Command, Zhujiang Hospital and Second Affiliated Hospital of Zhongshan University. Cases were incident patients who had been histopathologically diagnosed with an epithelial ovarian tumour within the past 12 months. Half of all case tumours were classified as serous, and borderline malignancy cases were included. Controls were patients who were recruited from wards of the departments of physiotherapy, respiratory disease, gastroenterology, ophthalmology and orthopedics. Subjects were required to be less than 75 years of age, and residents of the metropolitan Guangzhou area for at least the past ten years.

Potential cases were identified from the daily census of the hospitals. To ensure complete ascertainment of cases, all hospital medical records and laboratory pathology reports were reviewed. Pathological diagnoses were derived from the International Histological Classification of Ovarian Tumors recommended by the International Federation of Gynecology and Obstetrics [29]. Patients were excluded when ovarian cancer was histopathologically confirmed to be neither the primary nor final diagnosis, or if they reported memory problems affecting their recall of past events. Of the total 504 ovarian cancer cases consecutively recruited from the four hospitals, 500 patients consented to participate and were capable of being interviewed.

During the same period, 512 eligible controls were identified and frequency matched to cases by age ( $\pm 5$  years). The following exclusion criteria applied for the controls: 1) previous diagnosis of ovarian cancer or other malignant diseases; 2) a history of bilateral oophorectomy; 3) memory problems; 4) on long-term mobility restriction; in addition to advanced age (i.e., exceeding 75 years) and non-residency. Whenever more control subjects appeared to be available than could be interviewed, a selection of ward and patient identification was made using random numbers. After initial screening of potential controls using the hospital daily census records, all eligible inpatients had their diagnosis confirmed by histopathological reports to avoid misclassification of the case-control

status. This systematic selection process was implemented throughout the recruitment period. Twelve women who did not satisfy the eligibility conditions or declined the interview were later excluded, resulting in a final sample of 500 controls available for analysis.

### 1. Interview

An appointment for a 45 minute face-to-face interview with each participant was arranged with the assistance of nursing staff, to avoid interference with treatment at the ward and before being discharged from hospital. All participants provided formal consent prior to the interview. They were also assured of confidentiality and their right to withdraw without prejudice. Participants were interviewed in the presence of their next-of-kin whenever possible, to minimize recall error. The interviews were conducted in either Mandarin or the Cantonese dialect. All participants were blinded to the study hypothesis. The project protocol was approved by the participating hospitals, the doctors-in-charge of the relevant wards, and the Human Research Ethics Committee of Curtin University (approval number HR 78/2006).

### 2. Measurements

A structured questionnaire used in a previous study in Hangzhou, China [27], was administered to obtain demographic and lifestyle characteristics, including age, weight (kg), height (m), location of residence, employment status, education level, smoking status, alcohol consumption and marital status. Detailed information on reproductive history, hormonal status and heredity was obtained. Self-reported data were verified against corresponding entries in medical records and any discrepancy found was subsequently rectified.

### 3. Statistical analysis

The sample characteristics of cases and controls were summarised using descriptive statistics. Univariate analysis was then undertaken to compare cases and controls in terms of reproductive factors. Odds ratios (ORs) and associated 95% confidence intervals (CIs) from unconditional logistic regression models were used to ascertain the association between reproductive factors and the risk of ovarian cancer. Only women who had at least one live birth were included in the multivariate analysis for parity, due to the low number of nulliparous women. For ease of analysis, oral contraceptive duration (months) was divided into approximate tertiles based on the distribution of controls, with the lowest tertile used as the reference category.

Tests for linear trend were also conducted for the corresponding continuous variables in the logistic regression

models to assess the dose-response relationship between reproductive factors and the ovarian cancer risk. The following established or plausible confounding factors were adjusted for in the logistic regression models: age at interview (years), smoking status (never, ever), alcohol drinking (no, yes), education level (none/primary, secondary, vocational/tertiary) and body mass index (5 years ago, kg/m<sup>2</sup>). In addition, mutual adjustment was made for parity ( $\leq 1$ ,  $\geq 2$ ), oral contraceptive use (never, ever), hormone replacement therapy (no, yes), menopausal status (pre, post), hysterectomy (no, yes) and family history of ovarian and/or breast cancer (no, yes). All statistical analyses were performed using the SPSS ver. 20 (IBM Co., Armonk, NY, USA).

## RESULTS

The sample characteristics of women with and without ovarian cancer are shown in Table 1. Compared to controls, women

**Table 1.** Characteristics of southern Chinese women with and without ovarian cancer

Variable	Cases	Controls	p-value*
Age at interview (yr)	59.0±5.6	59.7±6.4	0.10
BMI of 5 yr ago (kg/m <sup>2</sup> )	21.7±2.5	21.1±2.2	<0.01
Location of residence			0.32
Urban	362 (72.4)	375 (75.0)	
Rural	138 (27.6)	124 (24.8)	
Employment status			0.69
Unemployed/housewife	163 (32.6)	169 (33.8)	
Working	337 (67.4)	331 (66.2)	
Education level			0.90
None/primary	204 (40.8)	197 (39.4)	
Secondary	171 (34.2)	175 (35.0)	
Vocational/tertiary	125 (25.0)	128 (25.6)	
Tobacco smoking			0.49
Never	481 (96.2)	485 (97.0)	
Ever	19 (3.8)	15 (3.0)	
Alcohol drinking			0.16
No	352 (70.4)	372 (74.4)	
Yes	148 (29.6)	128 (25.6)	
Marital status			0.83
Never married	7 (1.4)	8 (1.6)	
Married	449 (89.8)	443 (88.6)	
Widowed/divorced/separated	44 (8.8)	49 (9.8)	

Values are presented as mean±SD or number (%). BMI, body mass index. \*Chi-square or t-test for difference between cases and controls.

with ovarian cancer had a significantly higher mean body mass index. The two groups appeared to be similar with respect to all other demographic and lifestyle factors. Table 2 provides a comparison of the reproductive factors by case-control status. A significant difference was observed for parity, with one third of controls given birth to 3 or more children, compared to 20% for cases. Ever use of oral contraceptives also differed significantly between groups, with fewer cases ever using oral contraceptives.

The logistic regression results for the reproductive factors are summarised in Table 3. A strong inverse association was evident between parity and ovarian cancer, with a 60% risk reduction among women who had given birth to 3 or more children, compared to women with parity  $\leq 1$  (adjusted OR 0.43; 95% CI, 0.30 to 0.62). The corresponding dose-response relationship was also significant ( $p < 0.001$ ). The adjusted OR of ever use of oral contraceptives was 0.56 (95% CI, 0.40 to 0.78), however the effect was not significant for oral contraceptive duration of usage. Hormone replacement therapy, meno-

**Table 2.** Comparison of reproductive factors between case and control groups

Reproductive factor	Cases	Controls	p-value*
Parity			<0.001
0	7 (1.4)	12 (2.4)	
1	172 (34.4)	145 (29.0)	
2	220 (44.0)	176 (35.2)	
$\geq 3$	101 (20.2)	167 (33.4)	
Oral contraceptive use			0.004
No	417 (83.4)	380 (76.0)	
Yes	83 (16.6)	120 (24.0)	
Oral contraceptive duration (mo) <sup>†</sup>	76.1±63.5	70.4±61.8	0.53
Hormone replacement therapy			1.00
No	493 (98.6)	493 (98.6)	
Yes	7 (1.4)	7 (1.4)	
Menopausal status			0.24
Pre	28 (5.6)	20 (4.0)	
Post	472 (94.4)	480 (96.0)	
Hysterectomy			0.88
No	478 (95.6)	477 (95.4)	
Yes	22 (4.4)	23 (4.6)	
Ovarian and/or breast cancer in first degree relatives			0.29
No	480 (96.0)	485 (97.0)	
Yes	20 (4.0)	15 (3.0)	

Values are presented as number (%) or mean±SD. \*Chi-square or t-test for difference between cases and controls. † Ever users of oral contraceptives.

**Table 3.** Ovarian cancer risk according to reproductive factors in southern Chinese women

Reproductive variable	Cases, no. (%)	Controls, no. (%)	Crude OR (95% CI)	Adjusted OR (95% CI)*	p for trend
Parity					<0.001
≤1	179 (35.8)	157 (31.4)	1.00	1.00	
2	220 (44.0)	176 (35.2)	1.10 (0.82–1.47)	0.96 (0.71–1.31)	
≥3	101 (20.2)	167 (33.4)	0.53 (0.38–0.74)	0.43 (0.30–0.62)	
Oral contraceptive use					0.001
No	417 (83.4)	380 (76.0)	1.00	1.00	
Yes	83 (16.6)	120 (24.0)	0.63 (0.46–0.86)	0.56 (0.40–0.78)	
Oral contraceptive duration (mo) <sup>†</sup>					0.586
≤36	28 (33.7)	43 (35.8)	1.00	1.00	
37–60	25 (30.1)	43 (35.8)	0.89 (0.45–1.77)	0.92 (0.45–1.90)	
≥61	30 (36.1)	34 (28.3)	1.36 (0.68–2.69)	1.19 (0.58–2.47)	
Hormone replacement therapy					0.929
No	493 (98.6)	493 (98.6)	1.00	1.00	
Yes	7 (1.4)	7 (1.4)	1.00 (0.35–2.87)	1.05 (0.35–3.21)	
Menopausal status					0.943
Pre	28 (5.6)	20 (4.0)	1.00	1.00	
Post	472 (94.4)	480 (96.0)	0.70 (0.39–1.26)	0.98 (0.49–1.93)	
Hysterectomy					0.636
No	478 (95.6)	477 (95.4)	1.00	1.00	
Yes	22 (4.4)	23 (4.6)	0.96 (0.53–1.74)	0.86 (0.46–1.62)	
Family history of ovarian and/or breast cancer					0.336
No	480 (96.0)	485 (97.0)	1.00	1.00	
Yes	20 (4.0)	15 (3.0)	1.35 (0.68–2.66)	1.41 (0.70–2.83)	

CI, confidence interval; OR, odds ratio.

\*Estimates from logistic regression models include terms for age (yr), smoking status (never, ever), alcohol drinking (no, yes), education (none/primary, secondary, vocational/tertiary), body mass index (5 yr ago, kg/m<sup>2</sup>), and mutually adjusted for parity (≤1, ≥2), oral contraceptive use (never, ever), hormone replacement therapy (no, yes), menopausal status (pre, post), hysterectomy (no, yes) and family history of ovarian and/or breast cancer (no, yes). † Ever users of oral contraceptives.

pausal status, hysterectomy and family history of ovarian and/or breast cancer were not significantly associated with the ovarian cancer risk.

## DISCUSSION

In this study, we found that ever use of oral contraceptives is associated with a reduced risk of ovarian cancer among southern Chinese women. This finding aligns with our previous study in Hangzhou [27] and supports the results of studies with women from higher incidence populations [13,18,26]. A similar protective effect was reported in a meta-analysis of 45 cohort and case-control studies from 21 countries, which found an overall relative risk of 0.73 (95% CI, 0.70 to 0.76) for ever users of oral contraceptives compared to never users [30].

A protective effect for oral contraceptive duration was not observed in this study. Previous research conducted in China similarly reported no association for oral contraceptive duration [31,32]. However, a recent review found that the estimated relative risk of ovarian cancer could decrease by around 20% for every 5 years use of hormonal contraception, and around 50% for 15 years of use [33]. Duration of oral contraceptive use among our study population may be insufficient to produce a protective effect, as only 32% of ever users consumed oral contraceptives for over 5 years. Increasing parity was also inversely associated with the ovarian cancer risk, consistent with several epidemiological studies [7-9,14,16,17,19] and a pooled analysis of 10 case-control studies from the United States [34].

The incessant ovulation hypothesis and the gonadotropin hypothesis are two well-known theories explaining the possible biological mechanisms behind ovarian cancer develop-

ment. The former suggests that repeated turnover of surface ovarian epithelium occurring in ovulation increases the odds of spontaneous genetic mutations and hence increases the risk of ovarian cancer [35,36]. In the latter hypothesis, elevated gonadotropin levels cause ovarian epithelial cells to become trapped within the surrounding connective tissue, which may lead to the formation of inclusion cysts [37-39]. Oral contraceptive use and higher parity are thought to reduce ovarian cancer risk by decreasing gonadotropin levels and suppressing ovulation [40].

Consideration must be given to the strengths and limitations of this study when interpreting the findings. The implementation of a standardized identification procedure ensured that ascertainment of cases was maximized and complete. To avoid misclassification of the case-control status, only incident patients who had been histopathologically diagnosed with ovarian cancer within the past 12 months were recruited, and all controls were confirmed. A high response rate (98%) was achieved in the recruitment of inpatients through support from the medical doctors and nursing staff. All interviews followed the same procedure for both case and control groups, while recruitment bias was minimized by sampling from different hospitals. Despite the low refusal rate, selection bias was unavoidable because all participants were voluntary and the hospital-based controls were not randomly selected from the community. Nevertheless, the four participating hospitals serve the entire catchment region so that our participants were still representative of the target population. Logistic regression analyses included adjustment for potential confounding variables such as body mass index. Nevertheless, residual confounding may still exist.

In conclusion, high parity and oral contraceptive use were found to reduce ovarian cancer risk in this population of southern Chinese women. Because diagnosis of ovarian cancer occurs usually in the late stages, the findings are important for cancer prevention in this low incidence population.

#### CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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