Ovarian cancer risk is reduced by prolonged lactation: a case-control study in southern China

Dada Su, Maria Pasalich, Andy H Lee, and Colin W Binns

ABSTRACT

Background: Ovarian cancer is an important neoplasm that is difficult to diagnose and treat; therefore, prevention is the preferable strategy. Growing evidence indicates a protective effect of breastfeeding on ovarian cancer risk.

Objective: The objective was to investigate the association between lactation and the risk of ovarian cancer among southern Chinese women.

Design: A case-control study was undertaken in Guangzhou, Guangdong Province, between August 2006 and July 2008. A validated and reliable questionnaire was used to obtain information on the months of lactation and number of children breastfed in a sample of 493 incident ovarian cancer patients and 472 hospital-based controls (mean age: 59 y). Logistic regression analyses were performed to assess the association between breastfeeding and the risk of ovarian cancer.

Results: Significant inverse dose-response relations were found for both duration of lactation and the number of children breastfed. The adjusted ORs were 0.09 (95% CI: 0.04, 0.19) for women with ≥31 mo of total lactation and those with ≤10 mo of lactation and 0.38 (95% CI: 0.27, 0.55) for women with ≥3 children breastfed compared with those with one child breastfed.


INTRODUCTION

Ovarian cancer is the seventh most common cause of cancer mortality among women (1) and accounts for 4.0% of all female cancers (2). Epithelial ovarian cancers constitute ~90% of all ovarian malignancies (3) and are usually diagnosed in the advanced stages of the disease (4). Ovarian cancer often has a poor prognosis, with an overall 5-y survival rate of ~45% (5). Possible causes include the repeated turnover of surface ovarian epithelium that occurs in ovulation (6) and increased proliferation of ovarian epithelium due to elevated gonadotropin concentrations (7). Two well-established protective risk factors for ovarian cancer are oral contraceptive use and higher parity (8–11), which are thought to reduce ovarian cancer risk by decreasing gonadotropin concentrations and suppressing ovulation (12). Breastfeeding also delays ovulation and inhibits the release of reproductive hormones implicated in ovarian cancer development (13).

Although there is a plausible biological mechanism for a protective effect of prolonged lactation on ovarian cancer, findings from the literature are somewhat inconsistent. Evidence indicates a reduced risk among women who have ever breastfed (14–19). An inverse association between duration of breastfeeding and ovarian cancer risk has been reported in some case-control studies (14, 19–25), whereas others have found no association (7, 26–29) or borderline significance (30). Data pooled from 2 prospective studies showed a significantly lower ovarian cancer risk in parous women who breastfed for ≥18 mo than in those who never breastfed (31). Few studies have investigated ovarian cancer risk in relation to the number of children breastfed; however, the findings suggest an inverse association (15, 25, 26, 32).

The incidence of ovarian cancer varies considerably between countries. In Europe, the incidence is 10.1/100,000 females, whereas in China the incidence is relatively lower at 3.8/100,000 females (1). In recent years, China has experienced a slight increase in the incidence of ovarian cancer, which may be of concern because of the aging population (33). Given this recent increase and the potential for breastfeeding as a protective factor in ovarian cancer development, further insight into the breastfeeding practices among Chinese women is warranted. The aim of this case-control study was to investigate the association between risk of epithelial ovarian cancer and duration of lactation, number of children breastfed, and the average duration of lactation per child among southern Chinese women.

SUBJECTS AND METHODS

Study design and participants

This 1:1 case-control study was undertaken in Guangzhou, the capital city of Guangdong Province in southern China, between August 2006 and July 2008. The subjects were recruited from 4 public hospitals: The Overseas Hospital (affiliated with Jinan University), Zhujiang Hospital, General Hospital of Guangzhou Military Command, and Second Affiliated Hospital of Zhongshan University. Eligible cases were those with a diagnosis of an incident, histopathologically confirmed epithelial ovarian tumor within the past 12 mo. Controls were recruited from inpatient

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tomy, or other malignant diseases, from the 4 hospitals, 500 patients with ovarian cancer consented to recall of past events. Of the total 504 cases consecutively recruited for diagnosis or if they confessed to memory problems affecting their recall of past events. Of the total 504 cases consecutively recruited from the 4 hospitals, 500 patients with ovarian cancer consented to participate and were capable of being interviewed.

During the same period, 512 eligible controls were identified and approached to be interviewed. These women were frequency matched to cases by age (within 5 y). The exclusion criteria for controls were as follows: 1) previous diagnosis of ovarian cancer or other malignant diseases, 2) a history of bilateral oophorectomy, 3) memory problems, and 4) long-term physical activity restriction, nonresidency, and advanced age (>75 y). Potential controls were initially screened by using the hospital daily census records. On days when more control subjects appeared to be available than could be interviewed, a selection of ward and patient identification was made by using random numbers. All eligible inpatients had their diagnosis subsequently confirmed by histopathologic reports to avoid misclassification of the case-control status. This systematic selection process was adopted throughout the recruitment period. Twelve women who declined the interview or who did not satisfy the eligibility conditions were later excluded, which resulted in a sample of 500 controls available for interview. In this study, the analysis was conducted on only those women with at least one live birth (493 cases and 488 controls) because of the strong association between parity and breastfeeding.

### Interview

An appointment for face-to-face interview was then arranged with each participant in conjunction with nursing staff to avoid interference with treatment at the ward and before being discharged from the hospital. The subjects were interviewed in the presence of their next of kin whenever possible, to minimize recall error. All participants provided formal consent before the interview. They were also assured of confidentiality and their right to withdraw without prejudice. The interviews usually took ~45 min to complete and 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 no. HR 78/2006).

### Exposure measurements

A structured questionnaire based on the Hawaii Cancer Research Survey (35) was administered to obtain demographic and personal characteristics, including age, weight (kg), height (m), educational level, smoking status, and alcohol consumption. Information on habitual physical activity, dietary intake, hormonal status, and heredity was also collected. Self-reported anthropometric data were systematically cross-checked with corresponding entries in medical records, and any discrepancy found was subsequently rectified.

Information on reproductive history, including lactation history, was obtained. Participants were asked in detail about each of their pregnancies, including the outcome of the pregnancy. Women with at least one live birth were asked to report the number of children breastfed and average duration of lactation per child (in mo).

### Statistical analysis

Only women who had at least one live birth were included in the analysis. The sample of controls with at least one live birth but no breastfed children was excluded from the analysis, because there was no comparison group from the cases. This resulted in a final sample of 493 cases and 472 controls. The total duration of breastfeeding (mo) was calculated by multiplying the variables “number of children breastfed” and “average duration of lactation per child (mo).”

Descriptive statistics were first used to compare the sample characteristics between the case and control groups. Unconditional logistic regression analyses were then performed to ascertain the association between breastfeeding and ovarian cancer risk. The “number of children breastfed” variable was classified into 3 levels, with women who had breastfed one child used as the reference group. The breastfeeding duration variables were divided into approximate quartiles based on the distribution of controls, with the lowest quartile used as the reference category.

In addition to reporting crude and adjusted ORs and associated 95% CIs, tests for linear trend were conducted to assess the dose-response relation between breastfeeding and risk of ovarian cancer. Other independent variables included in the logistic regression models were age at interview (continuous: y), parity, oral contraceptive use (never or ever), ovarian and/or breast cancer in a first-degree relative (no or yes), educational level (none/primary, secondary, or vocational/tertiary), menopausal status (pre- or post-), alcohol drinking (no or yes), and smoking status (never or ever). These variables were either established or plausible risk factors from the literature. All statistical analyses were undertaken by using the SPSS package version 20 (SPSS Inc).

### RESULTS

The characteristics of case and control women who had at least one live birth are shown in Table 1. The 2 groups appeared to be similar with respect to demographic and lifestyle factors. However, women with epithelial ovarian cancer had less oral contraceptive use and lower parities than did their counterparts without the disease. In addition, cases had a significantly higher mean BMI. The breastfeeding patterns of cases and controls are compared in Table 2. Both duration of breastfeeding per child and total duration of breastfeeding were significantly greater among the controls. The number of children breastfed also differed significantly between groups, with fewer cases breastfeeding ≥3 children.
The logistic regression results in relation to breastfeeding are presented in Table 3. A strong inverse association between lactation and ovarian cancer and a 4-fold protective effect for duration of breastfeeding were observed. The adjusted OR was 0.37 (95% CI: 0.22, 0.62) for women whose average duration of lactation per child was ≥13 mo compared with those whose average duration of lactation per child was ≤7 mo. The estimated OR for women with ≥31 mo compared with ≤10 mo of total lactation was 0.09 (95% CI: 0.04, 0.19). A lower risk was evident for women who breastfed ≥3 children than for those who breastfed only 1 child (adjusted OR: 0.38; 95% CI: 0.27, 0.55). The corresponding dose-response relations were also significant (P < 0.01).

DISCUSSION

In this case-control study of Chinese parous women, the number of children breastfed and the duration of breastfeeding were inversely associated with ovarian cancer risk. These findings are consistent with those of our previous study in Hangzhou (25) and support the positive results from other countries (14, 19–23). The 2007 World Cancer Research Fund report states that...
Breastfeeding is associated with delayed ovulation and a prolonged period of amenorrhea (43–46). Lactation suppresses ovulation via elevated concentrations of prolactin, which inhibit the secretion of gonadotropins (follicle-stimulating hormone and luteinizing hormone) (47, 48). The process of ovulation involves recurrent repair of ovarian epithelium and exposure to estrogen-rich follicular fluid (6). This proliferation of epithelial cells forms the basis of the theory of incessant ovulation, which suggests that a greater number of ovulations increases the probability of spontaneous mutations and hence increases the risk of ovarian cancer (6, 36). Lactation may influence ovarian cancer development in this way, by reducing the number of ovulatory cycles. The gonadotropin hypothesis suggests that high concentrations of gonadotropins cause ovarian epithelial cells to become trapped within the surrounding connective tissue, which may lead to the formation of inclusion cysts (7, 49, 50). These hormones have been shown to be elevated in postmenopausal women (51), and it is during the postmenopausal stage that diagnoses of ovarian cancer are more common (4). Furthermore, many studies have reported increased expression of gonadotropin receptors among women with ovarian cancer (52–55). Two other theories that propose a reduced ovarian cancer risk during breastfeeding are the ‘invasive ovulation’ and ‘ovarian stromal’ theories. These theories propose that a higher concentration of gonadotropins during breastfeeding increases the proliferation of ovarian tissue, which results in a greater number of ovulations and hence a reduced risk of ovarian cancer.

### TABLE 2
Comparison of breastfeeding variables between the case and control groups

<table>
<thead>
<tr>
<th>Breastfeeding outcome</th>
<th>Cases</th>
<th>Controls</th>
<th>Both</th>
<th>$P^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of children breastfed [$n$ (%)]</td>
<td>190 (38.5)</td>
<td>144 (30.5)</td>
<td>334 (34.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>205 (41.6)</td>
<td>167 (35.4)</td>
<td>372 (38.5)</td>
<td></td>
</tr>
<tr>
<td>$\geq 3$</td>
<td>98 (19.9)</td>
<td>161 (34.1)</td>
<td>259 (26.8)</td>
<td></td>
</tr>
<tr>
<td>Duration of breastfeeding per child (mo)</td>
<td>8.46 ± 2.42$^\dagger$</td>
<td>10.06 ± 3.41</td>
<td>9.24 ± 3.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total duration of breastfeeding (mo)</td>
<td>16.33 ± 10.96</td>
<td>23.65 ± 17.12</td>
<td>19.91 ± 14.76</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

$^1$ Sixteen controls with parity $\geq 1$ but no breastfed children were excluded from the analysis.

$^2$ A chi-square or $t$ test was used to determine differences between cases and controls.

$^\dagger$ Mean ± SD (all such values).

There is only limited evidence of a protective effect of lactation on ovarian cancer (36). More recently, this position has been altered to some degree, as evidenced by a current review that listed breastfeeding as a factor that may lower the risk of ovarian cancer (37) and a meta-analysis of 9 case-control studies reporting a 30% decreased risk in women who had ever breastfed (38). A combined analysis of 2 prospective cohorts found a significant 2% decrease in ovarian cancer risk with each month of breastfeeding (31). Similar results were reported in an early collaborative analysis of 5 population-based case-control studies (RR: 0.99/mo; $P < 0.01$) (39). A review of reproductive factors and risk of ovarian cancer found that the evidence of an association between breastfeeding duration and ovarian cancer risk was inconsistent but stated that most studies indicate an inverse association (40). A reduced risk of ovarian cancer appeared to be dependent on menopausal status in 2 case-control studies from Australia and the United States, and inverse relationships were found only among premenopausal women (41, 42).

### TABLE 3
Crude and adjusted ORs (95% CIs) for ovarian cancer risk of lactation in southern Chinese women with at least one live birth

<table>
<thead>
<tr>
<th>Breastfeeding outcome</th>
<th>Cases</th>
<th>Controls$^\dagger$</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR$^\ddagger$ (95% CI)</th>
<th>$P$-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of children breastfed$^\ddagger$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>1</td>
<td>190 (38.5)</td>
<td>144 (30.5)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>205 (41.6)</td>
<td>167 (35.4)</td>
<td>0.93 (0.69, 1.25)</td>
<td>0.84 (0.62, 1.15)</td>
<td></td>
</tr>
<tr>
<td>$\geq 3$</td>
<td>98 (19.9)</td>
<td>161 (34.1)</td>
<td>0.46 (0.33, 0.64)</td>
<td>0.38 (0.27, 0.55)</td>
<td></td>
</tr>
<tr>
<td>Average duration of breastfeeding per child</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$\leq 7$ mo</td>
<td>178 (36.1)</td>
<td>102 (21.6)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>8–10 mo</td>
<td>240 (48.7)</td>
<td>185 (39.2)</td>
<td>0.74 (0.55, 1.01)</td>
<td>0.78 (0.57, 1.08)</td>
<td></td>
</tr>
<tr>
<td>11–12 mo</td>
<td>45 (9.1)</td>
<td>126 (26.7)</td>
<td>0.21 (0.14, 0.31)</td>
<td>0.22 (0.14, 0.34)</td>
<td></td>
</tr>
<tr>
<td>$\geq 13$ mo</td>
<td>30 (6.1)</td>
<td>59 (12.5)</td>
<td>0.29 (0.18, 0.48)</td>
<td>0.37 (0.22, 0.62)</td>
<td></td>
</tr>
<tr>
<td>Total duration of breastfeeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$\leq 10$ mo</td>
<td>182 (36.9)</td>
<td>109 (23.1)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>11–20 mo</td>
<td>203 (41.2)</td>
<td>154 (32.6)</td>
<td>0.79 (0.58, 1.08)</td>
<td>0.64 (0.45, 0.92)</td>
<td></td>
</tr>
<tr>
<td>21–30 mo</td>
<td>78 (15.8)</td>
<td>103 (21.8)</td>
<td>0.45 (0.31, 0.66)</td>
<td>0.31 (0.19, 0.50)</td>
<td></td>
</tr>
<tr>
<td>$\geq 31$ mo</td>
<td>30 (6.1)</td>
<td>106 (22.5)</td>
<td>0.17 (0.11, 0.27)</td>
<td>0.09 (0.04, 0.19)</td>
<td></td>
</tr>
</tbody>
</table>

$^\dagger$ Sixteen controls with parity $\geq 1$ but no breastfed children were excluded from the analysis.

$^\ddagger$ Estimates from separate logistic regression models included terms for age at interview (continuous; y), parity, oral contraceptive use (never or ever), ovarian and/or breast cancer in a first-degree relative (no or yes), education (none/primary, secondary, or vocational/tertiary), menopausal status (pre- or post-), alcohol drinking (no or yes), and smoking status (never or ever).

$^\ddagger$ Adjustment was made for all variables listed above except parity.
cancer risk from breastfeeding involve retrograde transportation of endogenous carcinogens through the fallopian tubes (56) and progesterone deficiency (57).

Our findings should be interpreted with consideration of the strengths and limitations of this study. A reliable and validated instrument was used to obtain information regarding the number of children breastfed, months of lactation, and average duration of lactation per child. Adjustment was made for potential confounding variables such as oral contraceptive use, ovarian and/or breast cancer in a first-degree relative, and menopausal status; however, residual confounding may still exist. Another strength of this study was the implementation of a standardized identification procedure, which ensured that the ascertainment of cases was maximized and complete. To avoid misclassification of the case-control status, only incident patients who had been histopathologically diagnosed with epithelial ovarian cancer within the past 12 mo were recruited, and all controls were confirmed. A high response rate (98%) was achieved in the recruitment of inpatients through assistance by the medical doctors and full support from the nursing staff.

Face-to-face interviews were conducted in the presence of the participants’ next of kin to assist with recall and to improve the accuracy of their responses. Of the women with at least one live birth, 16 controls had not breastfed, whereas all of cases reported having breastfed. This may reflect some recall bias in self-reports of breastfeeding; however, the rates of ever breastfeeding are typically high in this region of China. All interviews followed the same procedure for both cases and controls, whereas 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 4 participating hospitals serve the entire catchment region so that our subjects were still representative of the target population. The average duration of breastfeeding per child was analyzed by using quartiles (≤7, 8–10, 11–12, and ≥13 mo). A recent study examined the relation between average duration of breastfeeding and ovarian cancer risk using categories that capture prolonged lactation (ie, ≥18 mo) compared with no breastfeeding (14). Comparisons of larger and more distinct differences in average duration of breastfeeding were not possible in this study given the inadequate sample size. Average duration of breastfeeding was <10 mo, and only 3.4% of the sample had an average duration of breastfeeding >15 mo.

In summary, prolonged lactation was found to protect against ovarian cancer in this population of Chinese parous women. Our results agree with current national guidelines, which promote the maternal benefits of breastfeeding. This study adds further knowledge to the relatively limited amount of research from countries with a low incidence of this disease and provides more detail on the breastfeeding variables associated with a reduced risk of ovarian cancer.

We gratefully acknowledge the willing cooperation given by the patients and medical and nursing staff from the participating hospitals.

The authors’ responsibilities were as follows—CWB, AHL, and DS: designed the research; DS: conducted the research; MP: performed the statistical analyses; AHL and MP: interpreted the results and wrote the manuscript; and AHL and CWB: critically revised the manuscript. All authors read and approved the final manuscript. None of the authors declared a conflict of interest.

REFERENCES
