Preserved foods associated with increased risk of ovarian cancer

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ABSTRACT

Objective: To investigate the association between consumption of preserved foods and risk of epithelial ovarian cancer in southern Chinese women.

Methods: A hospital-based case-control study was undertaken in Guangzhou, Guangdong Province, from 2006 to 2008. Participants were 500 incident epithelial ovarian cancer patients and 500 controls, with a mean age 59 years. Information on habitual food consumption was obtained by face-to-face interview using a validated and reliable food frequency questionnaire. Logistic regression analyses were performed to assess the association between preserved foods intake and the ovarian cancer risk.

Results: The ovarian cancer patients consumed more preserved foods (median 15.5, interquartile range (IQR) 18.2 g/day) than controls (median 13.8, IQR 20.5 g/day), $p < 0.001$. The adjusted odds ratios of ovarian cancer was 1.78 (95% confidence interval 1.35 to 2.34) for women consuming more than 13.5 g of preserved vegetables and preserved meats per day relative to those below. Similar two-fold increases in risk at high level of intake were also evident for serous and mucinous subtypes of epithelial ovarian tumours.

Conclusion: Intake of preserved foods was positively associated with the incidence of epithelial ovarian cancer in southern Chinese women.

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Keywords: China; Ovarian cancer; Preserved foods

INTRODUCTION

Ovarian cancer has the eighth highest incidence of all cancers in women, with approximately 225,000 new cases reported worldwide in 2008 [1]. The disease ranks second in terms of gynaecological malignancies [2] and is the 7th most common cause of cancer-related deaths among women [1]. Currently, there is no effective screening method available for detection [3]. Symptoms are vague, non-specific, and generally appear in the advanced stages of the disease, contributing to the high case-fatality ratio [4].

There is considerable geographic variation in the incidence of ovarian cancer, with higher rates in developed countries. The age-standardised rate in China is low at 3.8 per 100,000 women, when compared to the USA (8.8) and Europe (10.1) [1]. The large difference in incidence rates between countries has generated interest in the role of dietary and lifestyle factors in ovarian cancer aetiology, besides genetic and familial risk factors, the knowledge of which may contribute to the primary prevention of the disease.

Preserved food products are widely consumed in many countries. Previous research has suggested their consumption may be linked to the development of a number of cancers, including cancer of the prostate, oesophagus, colorectal, and stomach [5-8]. In particular, a case-control study in China found that high intake of preserved (salted) vegetables can increase the risk of ovarian cancer by more than three-fold [9]. Similarly, a recent analysis of two Australian case-control studies revealed a significant 18% increased risk for women with the highest intake of processed meat [10]. Most other epidemiological studies have reported increased risk with greater consumption of preserved foods, albeit non-significant results [8, 11-14], with some observing lack of association [15] or little reduction in risk [16].

Several types of preserved foods are popular in southern China, including preserved meats, pickled vegetables and salted fish. In view of the limited epidemiological evidence, the present study aimed to assess the association between habitual preserved foods consumption and the risk of ovarian cancer among southern Chinese women.

METHODS

Study design and subjects

A case-control study was conducted in Guangzhou, the capital city of Guangdong Province of southern China, between August 2006 and July 2008. Subjects were recruited from four public hospitals, namely, The Overseas Hospital (affiliated with Jinan University), Zhujiang Hospital, General Hospital of Guangzhou Military Command, and Second Affiliated Hospital of Zhongshan University. Cases were incident patients who had been histopathologically diagnosed with epithelial ovarian cancer within the past 12 months. Controls were recruited from inpatient wards of the Departments of ophthalmology, orthopedic, respiratory disease, gastroenterology and physiotherapy. To be eligible, all subjects were required to be under 75 years of age and have resided in the metropolitan Guangzhou area for at least the past ten years.

Potential cases were identified by searching the daily census of the hospitals. To ensure complete ascertainment of cases, all hospital medical records and laboratory pathology reports were reviewed during the recruitment period. Pathological diagnoses were based on the International Histological Classification of Ovarian Tumors [17]. Patients were excluded when ovarian cancer was histopathologically confirmed to be neither the primary nor final diagnosis, or if they confessed to have memory problems affecting their recall of past events.

Of the total 504 cases consecutively recruited from the four hospitals, 500 patients with cancer of the ovary 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 ($\pm$ 5 years). Exclusion criteria for controls were (1) previous diagnosis of ovarian cancer or other malignant diseases; (2) a history of bilateral oophorectomy; (3) having memory problems; (4) on long-term modification of diet for medical reasons; in addition to non-residency and advanced age exceeding 75 years. Subjects to be approached for inclusion as controls were initially screened using the hospital daily census sheets. A selection of ward and patient ID was made using random numbers each day whenever more control subjects appeared to be available than could be interviewed. All eligible inpatients had their diagnosis subsequently confirmed by histopathological 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 not satisfying the eligibility conditions were later excluded, resulting in a final sample of 500 controls available for analysis. No statistically significant differences were found between the two groups in terms of age and main demographic variables.

Interview

An appointment for face-to-face interview at the ward was arranged with each participant after consulting the nursing staff to avoid interference with treatment. Whenever possible, subjects were interviewed in the presence of their next-of-kin to help the recall of dietary habits. All participants gave formal consent before the interview. They were also assured of confidentiality and their right to withdraw without prejudice. Each interview, conducted in

either Mandarin or the Cantonese dialect, took on average 45 minutes to complete. 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).

Questionnaire and exposure measurements

A structured questionnaire was administered to obtain demographic and lifestyle characteristics including age, weight (kg), height (m), education level, smoking status and alcohol consumption, as well as reproductive history, hormonal status and heredity. Self-reported data were cross-checked with medical records whenever available.

Participants were also requested to estimate their average time engaged in physical activities using validated questions [18]. Intensity was classified by the amount of energy or effort a person expends in performing the activity. Physical activity at each intensity level was quantified in terms of metabolic equivalent tasks (MET)-hours per week, with intensity codes 7.5, 6.0 and 4.5 MET assigned to strenuous sports, vigorous work and moderate activity, respectively. Total physical activity was then calculated by summing the product of MET score and activity duration over the three intensity levels.

Information on habitual food and beverage consumption was obtained using a 125-item semi-quantitative food frequency questionnaire developed and tested for the southern Chinese population [19, 20]. This validated instrument covered commonly consumed foods (including preserved products) in southern China. Frequency and amount of intake were recorded in detail. The reference recall period for dietary variables was set at five years before diagnosis for cases and five years before interview for controls. The energy content of each food or

beverage item was obtained from the Chinese food composition tables [21]. We then estimated participant's total energy intake (kcal) by summing the energy intake across individual items consumed.

Statistical analysis

Descriptive statistics were first used to summarize the sample characteristics. Total preserved foods intake (g/day) was defined as the sum of daily consumption of preserved meats (sausage, ham, salted duck egg, salted fish) and preserved vegetables (dried turnip, salted mustard, pickled vegetables, pickled Chinese cabbage). For the comparison of intake between case and control groups, median (interquartile range) and Mann-Whitney tests were applied in view of the skewed distributions of these consumption variables.

Unconditional logistic regression analyses were then performed to investigate the effects of habitual preserved foods consumption on the ovarian cancer risk. Each consumption variable was dichotomized into low and high levels of exposure based on the corresponding 50th percentile among controls, due to the relatively low daily intake by the control group. To investigate the risk of ovarian cancer by specific histologic subtype, we compared selected case subtype to the entire control group using adjusted odds ratios (OR) and associated 95% confidence intervals (CI). Confounding variables included in the logistic regression models were age at interview (years), parity, oral contraceptive use (never, ever), body mass index (5 years ago), menopausal status (pre, post), education level (none or primary, secondary, vocational or tertiary), tobacco smoking (never, ever), alcohol drinking (no, yes), marital status (never married, married, widowed or divorced or separated), physical activity (MET-hours/week), total energy intake (kcal/day), and family history of ovarian or breast cancer

(no, yes). These variables were either established or plausible risk factors from the literature. All statistical analyses were undertaken using the SPSS package version 20.

RESULTS

Table 1 gives the distribution of histologic subtypes of epithelial ovarian tumours. Half of all case tumours were classified as serous, and mucinous tumours comprised 16% of the cases. Table 2 presents characteristics of the sample by case-control status. The participants were 59 years of age on average and predominantly post-menopausal. Most of them had attained secondary school education or above, were non-smokers and seldom drank alcoholic beverages on a regular basis. Very few women had a family history of ovarian or breast cancer. However, women with ovarian cancer tended to have less oral contraceptive use and lower parities but higher mean body mass index than their counterparts without the disease. They also appeared to be less physically active in daily life.

Table 3 compares habitual preserved foods consumption between case and control groups. The ovarian cancer patients reported higher intake levels of preserved foods, especially preserved vegetables, than the control subjects. The differences were statistically significant according to Mann-Whitney tests. Table 4 summarizes the results of logistic regression analyses. Substantial increases in ovarian cancer risk were evident for high consumptions of preserved foods. Overall, the adjusted OR of ovarian cancer was 1.78 (95% CI 1.35 to 2.34) among women consuming over 13.5 g of preserved vegetables and preserved meats per day, $p < 0.001$. Similar two-fold increases in risk were also evident for serous and mucinous subtypes of epithelial ovarian tumours, with the exception of preserved meats for the mucinous subtype. Analyses were not performed for other histologic subtypes due to the low number of cases available.

DISCUSSION

A positive association was found between the intake of preserved foods and the risk of epithelial ovarian cancer among southern Chinese women. The risk was particularly high for preserved vegetables, with more than two-fold increase in risk for consuming over 2 grams per day. Our findings are in partial agreement with a previous case-control study conducted in Hangzhou, China, which observed a positive association between pickled vegetable intake and ovarian cancer risk, yet a non-significant decrease in risk for preserved meat [9]. They also support the results of three cohort studies [8, 13, 14] and two earlier case-control studies [10, 12]. Furthermore, a meta-analysis of seven epidemiological studies (four case-control studies and three cohort studies) reported that women with the highest intake of preserved foods had a 20% greater risk of ovarian cancer [10].

Preserved foods generally contain large amounts of nitrates and nitrites which may act as the precursors for the generation of *N*-nitroso compounds [22, 23]. These compounds are mutagenic and considered to be potential carcinogens [24, 25]. Processed meats also contribute to the formation of heterocyclic amines [26] which are carcinogenic in animal models. In addition, they contain saturated fat which has been linked to carcinogenesis [27]. The processing and preservation of vegetables may reduce the levels of antioxidants, vitamins and minerals which are thought to be responsible for the anti-cancer effects of vegetables [11].

In this study, a standardized identification procedure was implemented which ensured that ascertainment of cases was maximized and complete. To avoid misclassification of the case-control status, we recruited only incident patients who had been histopathologically

diagnosed with epithelial ovarian cancer within the past 12 months, and all controls had been carefully screened and subsequently confirmed with pathology. 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. Habitual food consumption was measured using a validated and reliable questionnaire specifically developed for the southern Chinese population, with information on frequency and quantity of intake recorded in detail. To determine and ascertain the effect of preserved foods, information on other exposures and confounding factors such as tobacco smoking, alcohol drinking and physical activity was also collected. It is possible that some ovarian cancer patients may modify their dietary habits since the onset of the disease. To avoid reverse causation, the reference period for habitual preserved foods consumption was set at five years before diagnosis for cases and five years before interview for controls. Moreover, no participant reported any change in eating habits for medical reasons within the past five years.

A major limitation of this study concerns the inherent retrospective cross-sectional design so that any cause-effect relationship could not be established. Although the recall of habitual preserved foods consumption should not be affected by the case-control status, dietary assessment was based on self-report so that responses from participants would inevitably incur some recall error. Therefore, face-to-face interviews were conducted in the presence of their next-of-kin to help memory recall and to improve the accuracy of their answers. 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 subjects were still representative of the target population. Recruitment bias was also minimized by sampling from different hospitals. Information bias and recall bias were unlikely because all participants were blind to the study

hypothesis, while the detrimental effects of preserved food products on ovarian cancer have not been established in southern China at the time of interview. Finally, residual confounding might still exist even though established risk factors have been controlled for in the multivariable logistic regression analyses. There is no evidence from the literature supporting consumption of preserved foods as a marker of unhealthy lifestyle among southern Chinese women.

In conclusion, a positive association was found between habitual preserved foods intake and ovarian cancer incidence in southern China. Further prospective cohort studies are required to confirm the effects of long term consumption. In the meantime, women are recommended to minimize the intake of preserved food products to avoid the apparent increase in ovarian cancer risk.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

Word Count: 2,340

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TABLE LEGEND

Table 1. Distribution of histologic subtypes of epithelial ovarian tumours among cases

Table 2. Characteristics of participants by case-control status

Table 3. Comparison of preserved foods consumption between case and control groups

Table 4. Adjusted odds ratios (95% confidence intervals) of epithelial ovarian cancer risk for preserved foods intake in southern Chinese women

Table 1.

Pathological diagnosis	n (%)
Serous cystadenocarcinoma	250 (50.0%)
Mucinous cystadenocarcinoma	80 (16.0%)
Endometrioid cystadenocarcinoma	19 (3.8%)
Mixed epithelial cystadenocarcinoma	13 (2.6%)
Undifferentiated carcinoma	59 (11.8%)
Borderline malignancy	65 (13.05)
Clear cell carcinoma	7 (1.4%)
Transitional cell carcinoma	4 (0.8%)
Malignant Brenner's tumour	3 (0.6%)

Table 2.

Variable	Cases n (%)	Controls n (%)	p [a]
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%)	
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%)	
Smoking status			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%)	
Parity			< 0.01
0	8 (1.6%)	14 (2.8%)	
1	172 (34.4%)	143 (28.6%)	
2	219 (43.8%)	176 (35.2%)	
≥ 3	101 (20.2%)	167 (33.4%)	
Oral contraceptive use			< 0.01
Never	417 (83.4%)	380 (76.0%)	
Ever	83 (16.6%)	120 (24.0%)	

Menopausal status			0.24
Pre	28 (5.6%)	20 (4.0%)	
Post	472 (94.4%)	480 (96.0%)	
Family history of ovarian or breast cancer			0.39
No	480 (96.0%)	485 (97.0%)	
Yes	20 (4.0%)	15 (3.0%)	
Age at interview (years): mean (SD)	59.07 (5.68)	59.71 (6.46)	0.10
Body mass index (5 years ago, kg/m^2): mean (SD)	21.70 (2.54)	21.12 (2.28)	< 0.01
Physical activity (MET-hours/week): mean (SD)	16.21 (14.1)	18.84 (13.0)	< 0.01

[a] Chi-square or t-test for difference between cases and controls

Table 3.

	Cases			Controls
Daily intake (g)	All median (IQR)	Serous median (IQR)	Mucinous median (IQR)	median (IQR)
Total preserved foods	15.5** (18.2)	16.6** (17.7)	14.6* (15.4)	13.8 (20.5)
Preserved vegetables	3.6** (8.9)	3.6** (8.9)	4.0** (8.9)	1.8 (10.7)
Preserved meats	8.9 (8.2)	11.1* (9.2)	8.4 (5.9)	8.4 (7.7)

* $p < 0.05$, ** $p < 0.001$ for Mann-Whitney test between cases and controls

Table 4.

	Cases						Controls (n = 500)
	All (n = 500)		Serous (n = 250)		Mucinous (n = 80)		
Daily intake (g)	n (%)	Adjusted OR[a] (95% CI)	n (%)	Adjusted OR[a] (95% CI)	n (%)	Adjusted OR[a] (95% CI)	n (%)
Total preserved foods		$p < 0.001$		$p < 0.001$		$p = 0.004$	
≤ 13.5	210 (42.0%)	1	97 (38.8%)	1	31 (38.8%)	1	247 (49.4%)
> 13.5	290 (58.0%)	1.78 (1.35, 2.34)	153 (61.2%)	2.11 (1.50, 2.98)	49 (61.3%)	2.15 (1.27, 3.62)	253 (50.6%)
Preserved vegetables		$p < 0.001$		$p < 0.001$		$p < 0.001$	
≤ 2.0	164 (32.8%)	1	77 (30.8%)	1	25 (31.3%)	1	265 (53.0%)
> 2.0	336 (67.2%)	2.85 (2.16, 3.77)	173 (69.2%)	3.27 (2.29, 4.67)	55 (68.8%)	3.46 (1.99, 6.00)	235 (47.0%)
Preserved meats		$p = 0.002$		$p < 0.001$		$p = 0.927$	
≤ 9.0	250 (50.0%)	1	112 (44.8%)	1	49 (61.3%)	1	282 (56.4%)
> 9.0	250 (50.0%)	1.52 (1.16, 1.99)	138 (55.2%)	1.97 (1.41, 2.76)	31 (38.8%)	0.98 (0.58, 1.64)	218 (43.6%)