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Tea consumption reduces ovarian cancer risk

Andy H. Lee *, Dada Su, Maria Pasalich, Colin W. Binns

School of Public Health, Curtin University, Perth, WA, Australia

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ABSTRACT

Objective: To ascertain the relationship between tea drinking and the risk of ovarian cancer among southern Chinese women, a case–control study was conducted in southern China during 2006–2008. *Methods*: Five hundred incident patients with histologically confirmed epithelial carcinoma of the ovary and 500 controls (mean age 59 years) were recruited from four public hospitals in Guangzhou. Information on frequency, quantity and duration of tea drinking, amount of dried tea leaves brewed, together with habitual diet and lifestyle characteristics, was obtained face-to-face from participants using a validated and reliable questionnaire. Logistic regression analyses were performed to assess the association between tea consumption variables and the ovarian cancer risk. *Results*: The control subjects reported higher tea consumption levels and prevalence (78.8%) than the ovarian cancer patients (51.4%). Regular drinking of green tea, black tea and/or oolong tea was associated with a lower risk of ovarian cancer, the adjusted odds ratio being 0.29 (95% confidence interval 0.22–0.39) after accounting for confounding factors. When compared with non-drinkers, apparent inverse dose–response relationships were observed for years of drinking, number of cups and quantity of tea consumed, as well as amount of dried tea leaves brewed ($p < 0.01$). *Conclusion*: Regular tea consumption is associated with a reduced risk of ovarian cancer for southern Chinese women.

1. Introduction

Ovarian cancer is the eighth most common cancer in women and the second most common gynaecological cancer, accounting for about 140,000 deaths annually worldwide [1]. The incidence of ovarian cancer per 100,000 females is only 3.8 in China, much lower than Western countries such as the USA (8.8) and Australia (7.7) [1]. The large differences in rates between countries suggest that dietary, lifestyle and environmental factors may influence the etiology of ovarian cancer, apart from genetic and familial risk factors [2]. Because ovarian cancer has few symptoms during its initial stages, it is typically diagnosed at an advanced stage [3]. Treatment of the malignancy is difficult and somewhat controversial [4,5]. Therefore, strategies that can enhance primary prevention are invaluable.

Tea is a natural beverage widely consumed around the world. There has been considerable interest in the protective role played by tea and its components, both *in vitro* and *in vivo* [6–8]. Recent experimental studies have demonstrated the chemo-preventive properties of tea polyphenols. Such compounds are known to offer protection against all stages of carcinogenesis by suppressing tumor promotion and inflammation, due to their antioxidant properties against free radicals, blocking signal transduction and nuclear oncogene expression, trapping of ultimate carcinogens, and inducing apoptosis and cell cycle arrest [9,10].

Despite the advances in laboratory experiments and animal studies, epidemiological evidence is still emerging and equivocal, mainly due to different tea consumption patterns and habits between populations, and particularly a lack of accurate measurements on tea exposure in most studies [8]. A literature search located 12 human observational studies investigating tea consumption and the ovarian cancer risk [11–22], but their results have been inconsistent. Furthermore, long-term tea consumption was seldom assessed. The onset of cancer typically requires many years to develop, information on long-term tea exposure is thus important. Taking these issues into consideration, the present case–control study aims to investigate whether tea consumption has an etiological association with the ovarian cancer risk among southern Chinese women, in view of their tea drinking practice specific to this region of China.

2. Patients and methods

2.1. Participants and eligibility criteria

A hospital-based one to one case–control study was conducted in the Guangdong Province of southern China, between August

* Corresponding author at: School of Public Health, Curtin Health Innovation Research Institute, Curtin University, GPO Box U 1987, Perth, WA 6845, Australia. Tel.: +61 8 92664180; fax: +61 8 92662958.
E-mail address: Andy.Lee@curtin.edu.au (A.H. Lee).

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2006 and July 2008. Subjects were recruited from four public hospitals within Guangzhou, the capital city of Guangdong: The Overseas Hospital affiliated with Jinan University, Zhujiang Hospital, General Hospital of Guangzhou Military Command, and Second Affiliated Hospital of Zhongshan University. Cases were defined to be incident patients who had been histopathologically diagnosed with cancer of the ovary within the past 12 months. Eligible cases 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. All hospital medical records and laboratory pathology reports were reviewed to ensure complete ascertainment of cases. Pathological diagnoses were determined by the International Histological Classification of Ovarian Tumors [23]. Patients were excluded when ovarian cancer was histopathologically confirmed to be neither the primary nor final diagnosis, or if they admitted to suffer memory problems affecting their recall of past events. Five hundred patients with epithelial carcinoma of the ovary consented to participate and were capable of being interviewed after consecutively recruited 504 cases from the four hospitals.

During the same period, 512 controls were recruited from inpatient wards of the departments of ophthalmology, orthopedic, respiratory disease, gastroenterology and physiotherapy. These women were frequency matched to cases within 5 years of age. The same age limit and residency requirement also applied. Additional exclusion criteria 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. Criterion (2) was needed to minimise the risk of misclassification, as some women might have been cases, but were not told or unaware of their disease. For criterion (4), a woman should be excluded as a true control if she had been on a modified diet due to her medical condition.

A systematic selection process for controls was adopted throughout the recruitment period. Inpatient ward numbers were initially selected by random sampling. After screening potential controls for case-matching based on the hospital daily census sheets, all eligible subjects had their diagnosis confirmed by histopathological reports to avoid misclassification. Twelve women who declined to be interviewed or not satisfying the eligibility conditions were subsequently excluded, resulting in a final sample of 500 controls available for analysis. There were no differences in age and major demographics between the excluded subjects and the consented participants.

2.2. Interview procedure

An appointment for interview was arranged with the assistance from nursing staff to minimize interference with treatment at the ward. Controls were interviewed before their discharge from hospital. All subjects were assured confidentiality and their right to withdraw without prejudice before obtaining their formal consent. The interviews, averaging 45 min in duration, were conducted face-to-face by research assistants in either Mandarin or the Cantonese dialect. All research assistants were fluent in both dialects, and were trained by the second author for the interviews following a standardised protocol. The presence of next-of-kin was encouraged to help the recall of dietary habits. However, all participants were blinded to the study hypothesis. The standardized study protocol was approved by the Human Research Ethics Committee of Curtin University (approval number HR 78/2006), the hospital administrations and the doctors in-charge of the relevant wards. Access to medical records and pathology reports was granted by the participating hospitals.

2.3. Questionnaire and exposure measurements

A structured questionnaire was administered to collect demographic data and lifestyle characteristics including age, weight (kg), height (m), education level, smoking status and alcohol consumption. Information on reproductive history, hormonal status and heredity was also obtained. Self-reported data were verified with medical records whenever available.

Information on habitual food and beverage consumption was obtained using a 125-item semi-quantitative food frequency questionnaire developed for the southern Chinese population [24,25]. This validated instrument covered most of the food and beverage items commonly consumed 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 [26]. We then estimated participant's total energy intake (kcal) by summing the energy intake across individual items consumed.

Specific questions on tea drinking were appended to the food frequency questionnaire. The reliability and reproducibility of these questions have been established for southern China [27]. Subjects were first classified as tea drinkers or non-drinkers (less than once per month). The tea drinkers were asked to report their frequency of habitual intake (number of cups per month, week or day), duration of regular tea drinking (in years), types of tea drank (green, black and oolong), and average amount of dried tea leaves used for brewing tea in "jin" (500 g) and "liang" (50 g) per year. Quantity of liquid tea consumed was measured in terms of the standard cup size of 180 ml. The common method of tea preparation in southern China is to brew dried tea leaves in a tea pot or tea cup using hot water without adding milk or sugar.

2.4. Statistical analysis

Comparisons of characteristics between case and control groups were made using chi-square and *t*-tests. To investigate the effects of tea exposure on the ovarian cancer risk, separate unconditional logistic regression analyses were performed for tea drinking (yes or no), duration of drinking, frequency of intake, quantity consumed, and amount of dried tea leaves brewed. The continuous consumption variables were classified into four increasing levels of exposure, with non-drinkers taken as the reference category. Both crude and adjusted odds ratios (OR) and associated 95% confidence intervals (CI) were reported, and tests for linear trend were conducted to assess the dose–response relationship. Analysis by tea type was not undertaken because most of the tea drinkers regularly drank a combination of green, black and oolong teas.

Besides tea consumption, independent 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, tertiary), smoking status (never, ever), alcohol drinking (no, yes), total energy intake (kcal) and family history of ovarian or breast cancer (no, yes). These variables were considered plausible risk factors according to the literature. Statistical analyses were performed using the SPSS package version 20.

3. Results

Characteristics of the sample by case–control status are presented in Table 1. The participants were 59 years of age on average and predominantly post-menopausal. Most of them were non-smokers, still married, and seldom drank alcoholic beverages

Table 1
Comparison of demographic and risk factors between case and control groups.

Variable	Cases		Controls		p^a
	n	(%)	*n*	(%)	
Mean age at interview (SD): years	59.07	(5.68)	59.71	(6.46)	0.10
Mean body mass index (SD): 5 years ago, kg/m^2	21.70	(2.54)	21.12	(2.28)	<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)	
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)	
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
No	417	(83.4)	380	(76.0)	
Yes	83	(16.6)	120	(24.0)	
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 cancer in first degree relatives					0.29
No	486	(97.2)	491	(98.2)	
Yes	14	(2.8)	9	(1.8)	
Breast cancer in first degree relatives					1.00
No	494	(98.8)	494	(98.8)	
Yes	6	(1.2)	6	(1.2)	

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

Table 2
Comparison of tea consumption variables between case and control groups.

Tea consumption	Cases	Controls	Total	p^a
Tea drinking: *n*	257 (51.4%)	394 (78.8%)	651 (65.1%)	<0.01
Green tea drinking: *n*[b]	156	233	389	
Oolong tea drinking: *n*[b]	134	216	350	
Black tea drinking: *n*[b]	53	93	146	
Tea drinkers only				
Mean duration of drinking (SD): years	18.3 (9.4)	22.7 (11.3)	21.0 (10.8)	<0.01
Mean tea leaves used (SD): grams/year	710.6 (790.8)	974.5 (1052.8)	870.3 (966.0)	<0.01
Mean quantity consumed (SD): ml/week	2189 (1846)	2922 (2110)	2633 (2040)	<0.01
Frequency of intake: cups/day				<0.01
<1	79 (30.7%)	92 (23.4%)	171 (26.3%)	
1–3	122 (47.5%)	148 (37.6%)	270 (41.5%)	
≥4	56 (21.8%)	154 (39.1%)	210 (32.3%)	

[a] Chi-square or *t*-test for difference between cases and controls.
[b] Not mutually exclusive.

on a regular basis. Very few women had a family history of ovarian or breast cancer. However, ovarian cancer patients tended to have less oral contraceptive use and lower parities but higher mean body mass index than women without the disease. The two groups were similar with respect to other demographic and lifestyle factors.

Table 2 compares the habitual tea consumption pattern between cases and controls. Among the tea drinkers, about 60% regularly drank green tea in combination with oolong tea and/or black tea. This mixed tea drinking habit appeared to be consistent for women in both groups, but the overall prevalence of tea

Table 3
Crude and adjusted odds ratios (95% confidence intervals) of ovarian cancer risk for tea consumption in southern Chinese women.

Tea consumption	Cases *n* (%)	Controls *n* (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	Test for trend
Tea drinking					67.73[b]
No	243 (48.6)	106 (21.2)	1.00	1.00	
Yes	257 (51.4)	394 (78.8)	0.29 (0.22, 0.38)	0.29 (0.22, 0.39)	
Duration of drinking (years)					80.06[b]
0	243 (48.6)	106 (21.2)	1.00	1.00	
≤20	172 (34.4)	202 (40.4)	0.37 (0.27, 0.50)	0.38 (0.27, 0.52)	
21–30	76 (15.2)	118 (23.6)	0.28 (0.20, 0.41)	0.29 (0.20, 0.43)	
≥31	9 (1.8)	74 (14.8)	0.05 (0.03, 0.11)	0.06 (0.03, 0.13)	
Frequency of intake (cups/day)					79.12[b]
0	243 (48.6)	106 (21.2)	1.00	1.00	
<1	79 (15.8)	92 (18.4)	0.38 (0.26, 0.55)	0.37 (0.25, 0.54)	
1–3	122 (24.4)	148 (29.6)	0.36 (0.26, 0.50)	0.36 (0.25, 0.51)	
≥4	56 (11.2)	154 (30.8)	0.16 (0.11, 0.23)	0.18 (0.12, 0.27)	
Quantity consumed (ml/week)					50.05[b]
0	243 (48.6)	106 (21.2)	1.00	1.00	
≤1400	130 (26.0)	146 (29.2)	0.39 (0.28, 0.54)	0.38 (0.27, 0.54)	
1401–3500	84 (16.8)	114 (22.8)	0.32 (0.22, 0.46)	0.33 (0.22, 0.48)	
≥3501	43 (8.6)	134 (26.8)	0.14 (0.09, 0.21)	0.16 (0.10, 0.24)	
Tea leaves used (g/year)					38.02[b]
0	243 (48.6)	106 (21.2)	1.00	1.00	
≤500	176 (35.2)	210 (42.0)	0.37 (0.27, 0.50)	0.38 (0.27, 0.52)	
501–1000	44 (8.8)	83 (16.6)	0.23 (0.15, 0.36)	0.25 (0.16, 0.39)	
≥1001	37 (7.4)	101 (20.2)	0.16 (0.10, 0.25)	0.16 (0.10, 0.26)	

[a] Estimates from separate logistic regression models adjusting for age (years), parity, oral contraceptive use (never, ever), BMI (5 years ago), menopausal status (pre, post), education level (none/primary, secondary, tertiary), smoking status (never, ever), alcohol drinking (no, yes), family history of ovarian or breast cancer (no, yes) and total energy intake (kcal).
[b] $p < 0.01$.

drinking (irrespective of tea type) was apparently higher among the controls (78.8%) than the cases (51.4%). Moreover, the tea consumption levels of controls were about 35% greater than those of ovarian cancer patients, whose average cumulative exposure to tea drinking was 22.7 years and 18.3 years, respectively.

Table 3 summarises the results of logistic regression analyses in relation to tea consumption. Overall, regular tea drinking was associated with a lower risk of ovarian cancer, the adjusted OR being 0.29 (95% CI 0.22–0.39) after accounting for plausible confounding factors. When compared with non-drinkers, apparent inverse dose–response relationships were observed for all aspects of tea exposure, namely, duration of drinking (years), frequency (number of cups) and quantity (ml) of tea consumed, and the amount of dried tea leaves brewed. In particular, the greatest reduction in ovarian cancer risk could be achieved by long term tea drinking over 30 years. Among the confounding factors, both parity and oral contraceptive use were associated with the ovarian cancer risk ($p < 0.01$).

4. Discussion

This was the first study that documented in detail the association between tea consumption and the ovarian cancer risk in southern Chinese women. All cases included in the study were histologically confirmed incident ovarian cancer patients, and all controls had been carefully screened and subsequently confirmed with pathology to avoid misclassification of the case–control status. Another strength of the study was that accurate measurements on long term tea exposure were made using a validated and reliable questionnaire specifically developed for the southern Chinese population. In addition to recording the frequency of intake, information was also obtained on duration of drinking and average amount of dried tea leaves brewed. These exposure measures are important to determine and ascertain the effect of habitual tea consumption.

It is possible that some ovarian cancer patients may restrict their tea intake since the onset of the disease. To avoid reverse causation, the reference period for habitual tea consumption was set at five years before diagnosis for cases and five years before interview for controls. Indeed, the average duration of tea drinking was about 21 years among the 651 tea drinkers in our sample, and none of them reported any change in drinking habits within the past five years. However, the separate effects of green tea, black tea and oolong tea could not be determined due to the mixed tea drinking behaviours of the southern Chinese women.

Our results indicated that the risk of ovarian cancer could decrease by drinking tea regularly. Moreover, apparent inverse dose–response relationships were found for all aspects of tea exposure including years of drinking, number of cups and quantity consumed, and the amount of tea leaves brewed. The protective effect of tea and its components is supported by a growing body of literature from experimental studies. Previous animal and *in vitro* studies and clinical trials have demonstrated that polyphenols and other antioxidant compounds contained in tea can inhibit carcinogenesis in a variety of organs [28–30]. As summarised by recent reviews, tea polyphenols, particularly epigallocatechin-3-gallate (EGCG), suppress enzyme activities and signal transduction pathways, limiting cell proliferation and inducing apoptosis. Tea polyphenols have been shown to inhibit cell invasion, proteasome activity, angiogenesis and metastasis [31–33].

This study suggests that tea consumption is associated with a lower risk of ovarian cancer, and the risk can be further reduced by a longer term or higher dose of tea exposure. The findings are consistent with those from our previous case–control study undertaken in Hangzhou, China [19], where the adjusted OR was 0.39 (95% CI 0.27–0.57) for daily tea drinkers and 0.23 (95% CI 0.14–0.31) for those drinking over 30 years, when compared to non-tea drinkers. Among the different types of tea considered, green tea appeared to have the strongest protective effect [19].

However, a small case–control study in Taiwan reported little association between tea drinking (assessed as yes or no) and the risk of developing ovarian cancer; the adjusted OR being 0.79 (95% CI 0.47–1.32) [20].

The present findings are contrary to results from European/Western countries [13,16,21,22], where a consistent inverse association could not be established. A case–control study from the USA found no relation between either black tea or green tea consumption and the ovarian cancer risk [21]. Compared to non-drinkers, the adjusted OR was 1.1 (95% CI 0.6–2.0) for drinking at least 2.5 cups of black tea weekly and 0.9 (95% CI 0.5–1.6) for drinking over 1 cup of green tea weekly. However, frequent (*i.e.* daily) tea intake was not assessed [21]. A large Australian case–control study reported an OR of 1.1 (95% CI 0.76–1.61) for drinking more than 4 cups of tea daily *versus* none, but concluded "no strong evidence" for the need to modify tea drinking habits [13]. An early prospective cohort study conducted in the USA observed only weak association, with relative risks of 0.53 for weekly tea intake and 0.98 for at least 2 cups of tea per day (p for trend = 0.64) [22], whereas another large cohort study involving almost 50,000 Canadian women concluded no association between tea intake and ovarian cancer [16]. Women who drank 2–3 cups of tea daily had a non-significant decreased risk (hazard ratio 0.81, 95% CI 0.53–1.23), but the risk increased for those who consumed over 4 cups daily (hazard ratio 1.07, 95% CI 0.64–1.79), when compared to non-tea drinkers [16]. The contradictory evidence may be attributed to the differences in tea consumption pattern and drinking habit among the various populations. In particular, the type of tea consumed and the method of preparation vary across countries and geographical regions. Unlike women in Western countries who typically drink black tea, our study population commonly drinks green tea (60% of tea drinkers) in combination with oolong and/or black teas. Furthermore, milk and sugar are not added after brewing the dried tea leaves with hot water. Scientific evidence has shown that the addition of milk to liquid tea will inhibit the antioxidant activity of tea [34]. In particular, the milk protein casein binds to the tea catechins [35], most notably EGCG, consequently decreasing the concentration of free polyphenols [36]. These differences may partially explain the discrepancies with previous reports.

A major limitation of the present case–control study concerns the inherent retrospective cross-sectional design so that any cause-effect relationship could not be established. Our results could also be affected by several sources of bias. Information bias was unlikely because all participants were blind to the study hypothesis, while the potential protective effect of tea drinking has not been confirmed in China. The habitual tea consumption pattern should not be affected by the case–control status. Dietary assessment was based on self-report using a validated and reliable questionnaire specifically developed for the southern Chinese population. While the participants could recall tea consumption without any difficulty, their responses to dietary questions would inevitably incur some recall error. Therefore, face-to-face interviews were conducted in the presence of their next-of-kin to improve the accuracy of their answers. In addition, recruitment bias was minimized by sampling from different hospitals. Selection bias was unavoidable since all participants were voluntary and the hospital-based controls were not randomly selected from the community. The four participating hospitals serve the entire catchment region so that our participants were still representative of the target southern Chinese population. Residual confounding is another possibility, even though plausible risk factors have been accounted for in the multivariable logistic regression models. There is also no evidence from the literature supporting habitual tea consumption as a marker of healthy lifestyle among southern Chinese women. Nevertheless, further replications of the study and cohort studies are recommended before generalizing the findings to other populations.

In conclusion, an inverse association was found between tea consumption and the risk of ovarian cancer in a southern Chinese population, with apparent dose–response relationships for higher tea exposure especially long term drinking. Tea is a safe and inexpensive beverage. Its consumption should be encouraged because of the potential benefit in preventing this common and deadly disease for women.

Conflict of interest

There are no potential conflicts of interest for all authors.

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