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GREEN TEA CONSUMPTION ENHANCES SURVIVAL OF EPITHELIAL OVARIAN CANCER

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Our study investigates whether tea consumption can enhance the survival of patients with epithelial ovarian cancer, a prospective cohort study was conducted in Hangzhou, China. The cohort comprised 254 patients recruited during 1999–2000 with histopathologically confirmed epithelial ovarian cancer and was followed up for a minimum of 3 years. Two hundred forty four (96.1%) of the cohort or their close relatives were traced. The variables examined included their survival time and the frequency and quantity of tea consumed post-diagnosis. The actual number of deaths was obtained and Cox proportional hazards models were used to obtain hazard ratios and associated 95% confidence intervals (CI), adjusting for age at diagnosis, locality, BMI, parity, FIGO stage, histologic grade of differentiation, cytology of ascites, residual tumour and chemotherapeutic status. The survival experience was different between tea drinkers and non-drinkers ($p < 0.001$). There were 81 (77.9%) of 104 tea-drinkers who survived to the time of interview, compared to only 67 women (47.9%) still alive among the 140 non-drinkers. Compared to non-drinkers, the adjusted hazard ratios were 0.55 (95% CI = 0.34–0.90) for tea-drinkers, 0.43 (95% CI = 0.20–0.92) for consuming at least 1 cup of green tea/day, 0.44 (95% CI = 0.22–0.90) for brewing 1 batch or more of green tea/day, 0.40 (95% CI = 0.18–0.90) for consuming more than 500 g of dried tea leaves/year, and 0.38 (95% CI = 0.15–0.97) for consuming at least 2 g of dried tea leaves/batch. The corresponding dose-response relationships were significant ($p < 0.05$). We conclude that increasing the consumption of green tea post-diagnosis may enhance epithelial ovarian cancer survival.

Key words: *cohort study; green tea; ovarian cancer survival; hazard ratio*

Ovarian cancer is a major cause of mortality in women because of its typically insidious onset and consequential late diagnosis.[1] Due to lack of effective screening programs and the high proportion of diagnoses at advanced stages, ovarian cancer survival is low with the highest fatality-to-case ratio of all gynecological malignancies.[2] Furthermore, ovarian cancer tends to recur, even in patients who achieve a complete response to primary treatment of surgery and chemotherapy.[3] Practical strategies for tertiary prevention remain limited.[4]

Our previous case-control study of Chinese women showed that the risk of ovarian cancer declined with increasing frequency and duration of green tea consumption.[5] There has been considerable interest in the protective effect of tea against various cancers, particularly green tea.[6–9] The anticarcinogenic properties of tea have been demonstrated in laboratory and animal studies on ovarian cancer cell.[10,11] Progress has been made in understanding the molecular mechanisms of cancer chemo-prevention by tea and tea polyphenols. A recent study provided evidence that tea can block the activity of a cancer-associated enzyme *in vitro* and *in vivo*.[12]

Although the tumor inhibitory effects of tea have been shown under experimental conditions, there has been no published epidemiological evidence of improved outcome in ovarian cancer survival due to tea consumption.[13] To evaluate whether tea consumption can enhance ovarian cancer survival, a prospective cohort study was conducted on patients originally participated in our previous case-control study. The cohort was followed up by measuring the frequency, quantity and type of tea they consumed after diagnosis of cancer.

MATERIAL AND METHODS

Study design and participants

The cohort comprised 254 patients with epithelial ovarian cancer residing in Zhejiang province, China, who originally participated in our case-control study conducted during 1999–2000.[5] Their diagnoses were histopathologically confirmed after surgery. The International Histological Classification of Ovarian Tumours recommended by the International Federation of Gynecology and Obstetrics (FIGO) was used.[14] Distribution of the pathological diagnoses is listed in Table I.

The cohort was followed up for mortality post-diagnosis by telephone interview between March and June 2003. We attempted to track down all patients in the cohort using their contact telephone numbers and addresses as recorded in our original case-control study. Those participants who had changed their telephone numbers were traced in the community with the assistance from local community and village committees. Local community and village committees in Zhejiang province maintain a register of individual residents that includes personal details such as date of birth and death and contact phone numbers. Participants without a home telephone were followed-up through the community or village committee office phone. Five patients were lost to follow-up because they moved out of the province, whereas another 5 patients had changed their place of residence but their new addresses and telephone numbers were unavailable. A total of 244 subjects were located and available for analyses, representing a follow-up rate of 96.1%. The project was approved by the Human Research Ethics Committee of Curtin University and informed consent was obtained from each participant.

Questionnaire and interview

Subjects were briefed regarding the aims of the study, confidentiality and anonymity issues. An appointment for interview was made after obtaining their verbal consent *via* an initial telephone contact. Of the 244 participants, 146 women were interviewed in person by phone. For the remaining 98 cases, their next-of-kin were interviewed instead because the patients were either deceased (96 deaths) or too ill to be interviewed (2 women). These 98 proxies comprised husbands (66%), children (21%), siblings (4%), parents (3%) and other relatives (5%). All interviews were conducted by the first author and usually took about 15 min. A

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TABLE I – DISTRIBUTION OF DIAGNOSIS OF OVARIAN IN 244 CANCER PATIENTS

Pathological diagnosis of epithelial ovarian cancer	Frequency (%)
Serous cystadnocarcinoma	102 (41.8)
Mucinous cystadnocarcinoma	34 (13.9)
Endometrioid cystadnocarcinoma	21 (8.6)
Mixed epithelial cystadnocarcinoma	7 (2.9)
Undifferentiated carcinoma	35 (14.3)
Borderline malignancy	37 (15.2)
Clear cell carcinoma	5 (2.0)
Transitional cell carcinoma	1 (0.4)
Malignant Brenner's tumor	2 (0.8)

TABLE II – QUESTIONS FOR ASSESSING TEA CONSUMPTION POST-DIAGNOSIS

Question
a. Have you ever drunk tea since diagnosis?
No
Yes
b. What type of tea do you usually drink?
Green tea
Black tea
Both
Oolong tea
c. What is your frequency of tea consumption since diagnosis?
Never or hardly ever
Once a month
2–3 times a month
Once a week
2–3 times a week
4–6 times a week
Once a day
2–3 times a day
4 or more times a day
d. How often do you brew a new batch of tea since diagnosis?
Never or hardly ever
Once a month
2–3 times a month
Once a week
2–3 times a week
4–6 times a week
Once a day
2–3 times a day
4 or more times a day
e. What is the average amount in Liang of dried tea leaves you consume per year?
f. If you have changed your tea drinking habit after diagnosis, please state your reason and provide details.

test–retest study was undertaken on 30 pairs of patient and proxy to assess the discrepancy in responses between the 2 groups.

A structured questionnaire was used to collect individual information on survival status, date of death (if deceased), as well as tea consumption, smoking and alcohol drinking post-diagnosis. To ascertain all ovarian cancer-related deaths, information was sought from community registration files or hospital medical records. Tea exposure was measured by a quantitative questionnaire adapted from our previous case-control studies.[5,6] The patients were first classified as either 'never' or 'ever' tea drinkers post-diagnosis. Information was then sought from all 'ever' drinkers on their consumption patterns, namely type of tea, frequency of consumption and number of new batches of tea brewed and quantity of dried tea leaves consumed per year. The specific questions for assessing tea consumption post-diagnosis are given in Table II. The quantity of dried tea leaves consumed was measured in Liang (equivalent to 50 g). The amount of dried tea leaves used depends on individual preference, but usually varies between 2 and 4 g. The quantity of dried tea leaves (g) per batch consumed by the participants was then estimated. For those who changed their tea drinking patterns after the onset of the disease, the reasons for quitting or starting tea drinking post-diagnosis were recorded.

Data on the following variables were retrieved from medical records in the participating hospitals: FIGO stage, histologic type, grade of differentiation, cytology of ascites, residual disease after surgery and regime and frequency of chemotherapy. Baseline data from the previous case-control study were also utilised. These included demographic characteristics, usual height and weight (5 years pre-diagnosis), factors related to hormone, reproductive history and family cancer history.[15]

Statistical analysis

The data were coded and analysed using the SPSS package.[16] Survival time (in years) was calculated from the date of diagnosis to the date of death (event) or date of interview (censored). The Kaplan-Meier technique was applied to compare the survival experiences by tea drinking status post-diagnosis. Intraclass correlation coefficient (ICC) and Kappa statistics were used to examine the agreement in reported tea consumption between the patients and their next-of-kin pre- and post-diagnosis.

Univariate analysis was first undertaken to screen potentially significant variables for subsequent multivariate analysis. A separate proportional hazards model was fitted to each categorical or quantitative tea consumption variable of interest, together with the corresponding linear trend test. The effects of tea consumption post-diagnosis on ovarian cancer survival were assessed in terms of adjusted hazard ratios and associated 95% confidence intervals (CI) accounting for age at diagnosis, locality, usual BMI, parity, FIGO stage, grade of differentiation, ascites, residual lesions after debulking surgery and chemotherapeutic status. These variables had been reported to influence ovarian cancer survival[17,18] or were significant confounders according to the univariate results.

RESULTS

After more than 3 years of follow-up, 96 of 244 cases in the original cohort were deceased. All the deaths were due to ovarian cancer and most of them died from recurrence of the disease, except for 2 patients whose deaths were recorded as being related to the side effects of chemotherapy.

Selected characteristics of ovarian cancer patients by survival status are shown in Table III. Compared to the survivors, the deceased patients were older and of greater parity, had a higher BMI pre-diagnosis and fewer of them drank tea post-diagnosis. A larger proportion of the deceased patients were diagnosed at advanced stage, with ascites and poorly differentiated histopathologic grade and had residual lesions $\geq$2 cm after surgery. There were no significant differences between the living and deceased patients in terms of residential locality, oral contraceptive use and family history of ovarian cancer.

For the 30 cases both patient and her next-of-kin were interviewed, no significant differences in reported tea consumption was found between the 2 groups. ICC ranged from 0.88 for quantity of dried tea leaves consumed to 0.96 for frequency of new batches brewed. The agreement for tea drinking was high ($\kappa = 0.93$), further supporting the reliability of information provided by the proxies.

The distribution and survival times of ovarian cancer patients by tea drinking status are shown in Table IV. About 30% of the cohort had changed their tea-drinking habits post-diagnosis. The agreement between tea drinking pre- and post-diagnosis for the entire cohort of 244 women was moderate ($\kappa = 0.44$), and ICC was 0.68 for the number of cups of tea consumed each day. There was no difference between the surviving and deceased patients in terms of changes in tea drinking patterns and amounts post-diagnosis. Although more deceased patients had stopped drinking tea post-diagnosis, as reported by their proxies, than surviving patients, the difference was not statistically significant. All of those who stopped drinking tea post-diagnosis believed that tea would offset the treatment effects of Chinese herbs. For those who started to drink tea post-diagnosis, the most common reason reported was to improve taste after chemotherapy, except one patient who thought tea drinking could benefit her recovery from the disease.

TABLE III – SELECTED CHARACTERISTICS OF OVARIAN CANCER PATIENTS BY SURVIVAL STATUS[1]

Selected characteristics	Alive (n = 148)		Dead (n = 96)	
	n	%	n	%
Age at diagnosis (years): mean (SD)[3]	44.1 (13.7)		51.1 (9.0)	
< 40	57	38.5	7	7.3
40–49	37	25.0	40	41.7
50–59	30	20.3	29	30.2
≥ 60	24	16.2	20	20.8
Locality				
Urban	57	38.5	30	31.2
Rural	91	61.5	66	68.8
BMI (5 years pre-diagnosis, kg/m^2)[2]				
< 25	129	87.2	68	70.8
≥ 25	19	12.8	28	29.2
Tea drinking post-diagnosis[3]				
No	67	45.3	73	76.0
Yes	81	54.7	23	24.0
Parity (full term pregnancy)[3]				
0	27	18.2	8	8.3
1	59	39.9	22	22.9
≥ 2	62	41.9	66	68.8
Oral contraceptive use				
Never	118	79.7	73	76.0
Ever	30	20.3	23	24.0
Ovarian cancer in first degree relatives				
No	145	98.0	93	97.0
Yes	3	2.0	3	3.0
FIGO stage[3]				
I	94	63.5	3	3.1
II	14	9.5	1	1.1
III	38	25.7	80	83.3
IV	2	1.3	12	12.5
Histopathologic grade[3]				
Well differentiated	78	52.7	6	6.3
Moderately differentiated	16	10.8	20	20.8
Poorly differentiated	30	20.3	61	63.5
Not available	24	16.2	9	9.4
Ascites[3]				
No	86	58.1	2	2.1
Yes	62	41.9	94	97.9
Residual lesions[3]				
< 2 cm	134	90.5	23	24.0
≥ 2 cm	14	9.5	73	76.0

[1]n = 244.–[2]$p < 0.05$.–[3]$p < 0.01$.

TABLE IV – DISTRIBUTION AND SURVIVAL TIME OF 244 OVARIAN CANCER PATIENTS BY TEA DRINKING STATUS

	Alive		Dead		Survival time
	n	%	n	%	mean years (95% CI)
Tea drinking					
Pre- and post-diagnosis	62	76.5	18	78.3	5.39 (4.94–5.85)
Post-diagnosis only	19	23.5	5	21.7	5.47 (4.75–6.18)
Non-tea drinking					
Pre- and post-diagnosis	48	71.6	43	58.9	4.19 (3.66–4.72)
Post-diagnosis only	19	28.4	30	41.1	3.52 (2.86–4.17)

There were 81 (77.9%) of 104 tea-drinkers who survived at the time of interview, compared to only 67 women (47.9%) still alive among the 140 non-drinkers. The crude survival curves by green tea consumption post-diagnosis are given in Figure 1. The survival experience was different between tea drinkers and non-drinkers post-diagnosis, with strong evidence ($p < 0.001$) from the log-rank test against the equality of survival distributions. As shown in Table IV, the mean survival times were similar between the 2 subgroups of tea drinkers, and also between the 2 subgroups of non-tea drinkers, the respective differences being non-significant statistically.

Among the 104 tea-drinkers, 96 (92%) drank only green tea, the remaining 8 women drank black tea or both types of tea. Therefore, effect of tea drinking, if any, could be attributed to the consumption of green tea. The mean quantity of dried tea leaves per batch was 2.1 g (SD 1.75 g) among the subjects. Crude and adjusted hazard ratios by tea drinking status, frequency of tea drinking, number of new batches brewed and the quantity of dried tea leaves consumed per year and per batch are shown in Table V. The hazard ratios declined with increasing frequency and quantity of green tea consumption. Compared to non-drinkers, the adjusted hazard ratios were 0.55 (95% CI = 0.34–0.90) for tea-drinkers, 0.43 (95% CI = 0.20–0.92) for consuming at least 1 cup of green tea/day, 0.44 (95% CI = 0.22–0.90) for brewing 1 batch or more of green tea/day, 0.40 (95% CI = 0.18–0.90) for consuming more than 500 g of dried tea leaves/year and 0.38 (95% CI = 0.15–0.97) for consuming at least 2 g of dried tea leaves/batch, all with significant linear trends.

To account for the difference in survival experience between invasive and borderline malignancy, we have stratified the data and analyzed cases with invasive epithelial ovarian cancer separately. The results from excluding women with borderline diseases were similar to those of the full data and thus were omitted for brevity.

We have also examined the interaction between green tea consumption post-diagnosis (and pre-diagnosis) and clinical parameters FIGO stage, BMI, histopathologic grading, ascites, residual lesions using multivariate Cox regression analysis. All the 2-way interaction effects were not statistically significant, except the interaction term between tea consumption post-diagnosis and residual lesions that was only marginally significant ($p = 0.03$).

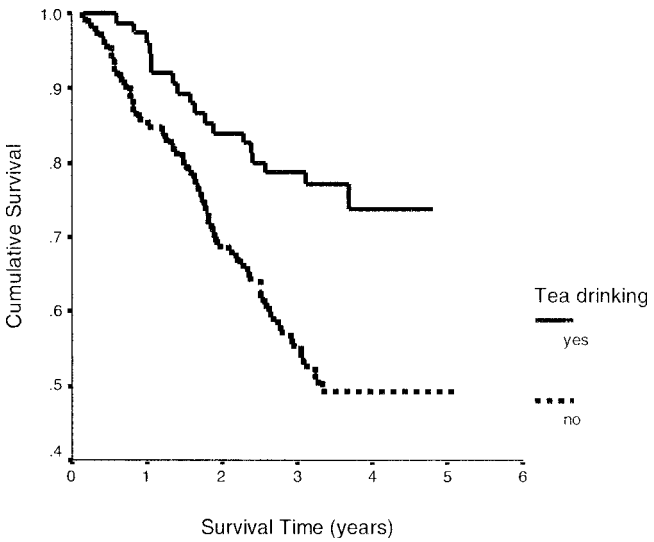

FIGURE 1 – Survival time curves by tea consumption post-diagnosis.

DISCUSSION

A new finding from this prospective cohort study was that increasing frequency and quantity of green tea consumption post-diagnosis may enhance the survival of Chinese women with epithelial ovarian cancer. The dose-response relationships were significant. In Japan, a 9-year follow-up study found green tea consumption was associated with a slowdown in cancer mortality and a later onset of cancer in all sites.[19] Regular green tea consumption also seemed to be preventive against recurrence of breast cancer,[20] but epidemiological evidence on the survival of the malignancy has been lacking.

Several issues should be taken into consideration when interpreting the findings of our study. A high follow-up rate of 96% was attained, and the cohort was neither related to the prognosis nor their tea drinking status when recruited in the original case-control study. The survival status of each patient was confirmed by independent sources. Another feature of our study was the effort made to ensure the accuracy of tea exposure post-diagnosis, because the onset of the disease and the initiation of treatment might change their personal tea-drinking habits. Tea consumption was measured by counting the number of (350–400 ml) cups drunk, the frequency of new batches of tea brewed, and the quantity of dried tea leaves consumed. The reasons for changing the tea drinking practice post-diagnosis were also obtained. Concordance of results between survivors and their next-of-kin confirmed the reproducibility of the questionnaire and the reliability of next-of-kin's proxy report. The percentages of alive and deceased groups who changed their tea drinking habit were not significantly different (Table IV), further supporting the reliability of information derived from the proxies. Information bias would be minimal concerning the relationship between tea consumption and ovarian cancer survival; indeed, some subjects believed that tea could offset the treatment effects of Chinese herbs.

A major limitation of the study was the lack of dietary information post-diagnosis. It is possible that those patients who changed their tea drinking habit post-diagnosis might change their diet as well. Therefore, the observed strong positive association

TABLE V – CRUDE AND ADJUSTED HAZARD RATIOS OF EPITHELIAL OVARIAN CANCER DEATH FOR TEA CONSUMPTION[1]

Variable	Distribution ($n = 244$)	Dead (%)	Crude hazard ratio	95% CI	Adjusted hazard ratio[3]	95% CI
Tea drinking						
No	140	52	1.0		1.0	
Yes	104	22	0.34	0.21–0.54	0.55	0.34–0.90
χ^2_1 test for linear trend				22.35[2]		5.72[1]
Frequency of tea drinking						
Never or seldom	151	50	1.0		1.0	
< 1 cup per day	49	29	0.56	0.31–1.01	0.74	0.39–1.39
≥ 1 cup per day	44	16	0.25	0.12–0.52	0.43	0.20–0.92
χ^2_1 test for linear trend				16.43[b]		4.96[1]
Number of new batches brewed						
Never or seldom	149	50	1.0		1.0	
< 1 batch per day	54	22	0.37	0.20–0.67	0.74	0.38–1.44
≥ 1 batch per day	41	22	0.36	0.18–0.72	0.44	0.22–0.90
χ^2_1 test for linear trend				13.45[2]		4.02[1]
Dried tea leaves consumed						
None	143	52	1.0		1.0	
< 500 grams per year	66	21	0.33	0.19–0.59	0.68	0.37–1.27
≥ 500 grams per year	35	20	0.30	0.14–0.65	0.40	0.18–0.90
χ^2_1 test for linear trend				19.45[2]		6.51[1]
Dried tea leaves consumed						
None	143	52	1.0		1.0	
< 2 grams per batch	70	23	0.36	0.21–0.62	0.64	0.36–1.12
≥ 2 grams per batch	31	16	0.24	0.10–0.59	0.38	0.15–0.97
χ^2_1 test for linear trend				27.37[2]		5.78[1]

[1]$p < 0.05$.–[2]$p < 0.01$.–[3]Estimates from Cox regression models included terms for age at diagnosis (years), locality (urban, rural), BMI (5 years pre-diagnosis), parity (full-term pregnancy), FIGO stage (I, II, III, IV), histopathologic grade (well, moderately, poorly differentiated, not available), ascites (no, yes), residual lesions (<2cm, ≥2cm), chemotherapy (no, yes).

between tea intake and survival may be due to confounding by certain dietary factors.

Tea is the most common beverage in southern China and there is little variation in the method of preparation. Green tea, the main type of tea consumed, is a local product and its consumption pattern has been stable among the study population. The common method is to brew dried tea leaves in a large cup using hot water without milk or sugar. Each new batch of tea is typically brewed once or twice for personal consumption. The use of a teapot and small cups is not popular among Zhejiang residents.[5] Because of this it is relatively easy to quantify tea consumption by counting the number of cups and the frequency of brewing a new batch of tea. Repeated infusion using the same batch enables the maximum extraction of the active constituents of tea. The bioavailability of tea polyphenols from this method of preparation has been documented in the literature.[8,9,21] Furthermore, the quantity of dried tea leaves consumed was measured, thus providing extensive measurements of tea exposure post-diagnosis.

The anticarcinogenic properties of the polyphenolic compounds present in green tea, including inhibition of proliferation and transformation, have been observed in cell and animal model studies.[22–24] The tea component theanine can enhance the antitumor activity of adriamycin and doxorubicin against ovarian sarcoma.[10,11] Progress has been made recently in understanding the molecular mechanisms of cancer chemo-prevention by tea and tea polyphenols. The green tea constituent, epigallocatechin-3-gallate, can induce apoptosis and cell cycle arrest in human carcinoma cells.[8] Evidence from *in vitro* and *in vivo* further suggested that tea can limit the growth of human cancer cells by a mechanism of blocking telomerase.[12] Because of the cancer chemopreventive effects in many animal tumor models, a tentative conclusion has been drawn that the modulating action of theanine is useful in clinical chemotherapy.[25]

Tea is one of the most widely consumed beverages in the world, second only to water.[26] It contains the most potent antioxidants found in any natural food or beverage.[21] In our study, increasing the consumption of green tea post-diagnosis was associated with an improved survival of ovarian cancer. We conclude that regular consumption of this tasty and inexpensive beverage may provide primary and tertiary prevention of epithelial ovarian cancer. Nevertheless, further studies are needed to confirm our findings.

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