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ORIGINAL PAPER

Case–control study of green tea consumption and the risk of endometrial endometrioid adenocarcinoma

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Abstract
Objective To investigate the association between green tea consumption and the risk of endometrial cancer restricted to endometrial endometrioid adenocarcinoma (EEA) using a case–control design in Japan.
Methods The cases were 152 patients with histopathologically diagnosed EEA, and the controls were 285 healthy women who were matched for age and area of residence with individual cases. The subjects completed a questionnaire regarding health-related lifestyle and reproductive history, and a food frequency questionnaire. Odds ratios (ORs) of EEA for frequency of green tea consumption were calculated by conditional logistic regression analysis.
Results We observed a significant inverse association between green tea consumption and the risk of EEA with a dose–response relationship. The multivariate-adjusted OR of EEA was 0.77 (95% CI: 0.37–1.58) for those in the second quartile of green tea consumption (5–6 cups/week–1 cup/day), 0.61 (0.30–1.23) in the third quartile (2–3 cups/day), and 0.33 (0.15–0.75) in the highest quartile (≥4 cups/day), as referenced with those in the lowest quartile (≤4 cups/week; p for trend = 0.007). This inverse association was consistently observed regardless of the presence or absence of factors such as obesity and menopause.
Conclusion Green tea consumption may be associated with a lower risk of EEA.

Keywords Green tea · Endometrial cancer · Endometrial endometrioid adenocarcinoma · Japanese

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Introduction

The incidence rate of endometrial cancer has been increasing in the Asia–Pacific region [1]. In Japan, the age-adjusted incidence rate of endometrial cancer was 6.2 (per 100,000 women) in 2001, representing an increase of four- to fivefold over the last three decades [2]. The incidence of endometrial cancer has increased 1.5-fold among Japanese migrants to the United States, and three- to fourfold among Japanese Americans born in the United States, as compared with Japanese women living in Japan [3]. These findings suggest that health-related lifestyle and environmental factors are related to the risk of endometrial cancer. Detection of modifiable risk factors for endometrial cancer is therefore imperative.

In recent years, green tea and its constituent catechins have received a great deal of attention because of their

possible anti-carcinogenic actions [4]. Green tea contains a large amount of catechins such as epigallocatechin-3-gallete, epigallocatechin, and epicatechin gallete. Although in vitro and animal experiments have demonstrated an effect of catechins against cancers [5–7], evidence from human studies is controversial [8–11].

There have been two case–control studies [12, 13] and one cohort study [14] regarding green tea consumption and endometrial cancer. The results were controversial, one study indicating a significant lower risk of endometrial cancer in a group consuming green tea than in a group not consuming tea [12], whereas others reported no significant association between green tea drinkers and non-drinkers [13, 14].

The purpose of this study was to clarify the association between green tea consumption and endometrial cancer using a case–control design in Japan. We restricted the cases to those that were histopathologically diagnosed as endometrial endometrioid adenocarcinoma (EEA). In addition, we controlled for many potential confounders, such as health-related lifestyle, reproductive, and dietary factors.

Materials and methods

Study design

The details of the design and setting of this study have already been described [15]. Briefly, we defined cases as women who met the following criteria: (1) those who were diagnosed as having endometrial cancer and underwent total hysterectomy at either Tohoku University Hospital between November 2002 and the end of March 2007 or Miyagi Cancer Center between June 2005 and the end of June 2006; (2) those under 80 years of age and residents of Miyagi Prefecture, Japan; (3) those whose cancer was histopathologically diagnosed as EEA; and (4) those with no history of cancer at any other organ or site.

During the above period, 240 patients met criteria (1) and (2). Of these patients, 201 gave their consent to participate in the study and completed the questionnaire before receiving surgical treatment. Postoperative histopathological examination indicated that 33 of the 201 patients had a histological type other than EEA (i.e., not meeting criterion 3), and that eight patients had a history of cancer (i.e., not meeting criterion 4). Thus, 160 patients met all the criteria. After excluding two patients who retracted their consent after surgical treatment, and six patients for whom we could not collect controls, finally 152 patients were entered as cases in this study.

The controls were selected from women attending a cancer-screening program at two screening facilities in Miyagi Prefecture. The cancer-screening programs included an upper GI examination, fecal occult blood test, mammography, cervical cytology, and transvaginal ultrasonography. If the latter revealed endometrial thickening or if a participant complained of irregular genital bleeding, endometrial cytodiagnosis was performed. Women who were asymptomatic, in good health, and had no history of hysterectomy or cancer were invited to participate as controls, matched for age (±5 years) and area of residence [northern Miyagi prefecture (rural area), central Miyagi prefecture (Sendai city; urban area), or southern Miyagi prefecture (rural area)]. Consent was obtained from 88% of those who satisfied the above criteria, and a total of 285 women were entered as controls; 2 for each of 133 cases and 1 for each of 19 cases.

The study protocol was approved by the institutional review board of Tohoku University Graduate School of Medicine. The protocol was explained to all the participants, and written consent was obtained. A gynecologist explained the study protocol to the cases and obtained their consent at the time of admission for surgery. For the controls, an experienced nurse explained the study protocol and obtained their consent on the day of cancer screening.

Study variables

We distributed self-administered questionnaires to both the cases and the controls and collected them from the cases during their hospital stay and from the controls by mail. Any missing answer in the questionnaire was completed by telephonic interviews with the subjects.

The questionnaire contained the following information: date of birth, body height, body weight, residence, education level, medical history (diabetes or cancer), smoking habit, and reproductive factors (age at menarche, number of pregnancies, oral contraceptive use, and menopausal status). The questionnaire also contained a food frequency questionnaire (FFQ) inquiring about foods and beverages consumed.

In this FFQ, we asked the subjects to recall the frequency of average consumption of 141 food items and beverages five years prior to the inquiry. There were nine categories of responses to the question on green tea consumption: "almost never (<1 cup/week)," "1–2 cups/week," "3–4 cups/week," "5–6 cups/week," "1 cup/day," "2–3 cups/day," "4–6 cups/day," "7–9 cups/day," "≥10 cups/day." In the study area, the volume of a typical cup of green tea is 100 ml. The reliability and validity of the questionnaire have already been assessed [16, 17]. The Spearman coefficient of the correlation between the green tea consumption entered in the questionnaire and that observed in the dietary records was 0.53, and the correlation between consumption of green tea measured twice, one year apart, was 0.64.

Statistical analysis

We performed univariate analyses (t test or χ^2 test) to compare the selected variables between the cases and controls. We then examined the association between the frequency of green tea consumption and the risk of EEA with multivariate adjustment by conditional logistic regression analysis, dividing the participants into quartiles according to the frequency of green tea consumption: "≤4 cups/week," "5–6 cups/week–1 cup/day," "2–3 cups/day," and "≥4 cups/day." The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated as the risk of EEA for green tea consumption, with the group representing the lowest quartile of green tea consumption as the referent. Trend tests were performed by including the ordinal variable into the model.

In these analyses, we constructed three multivariate models with different sets of covariates. We selected all available covariates which have been adjusted for in the previous studies. Here, we would present the list of potential covariates with references. Model 1 considered physical or social factors and reproductive factors: BMI (kg/m^2) [12, 13, 15, 18] (continuous variable), education [12, 15] (junior high school or lower, high school, or college/university or higher), number of pregnancies [12, 13, 15, 18] (none, 1–3, or ≥4), use of oral contraceptive [15, 18] (never user or ever user), age at menarche [12, 15, 18] (<13 or ≥13 year), menopausal status [12, 15, 18] (premenopausal or postmenopausal), smoking status [13, 15, 18] (never smoker, ex-smoker, or current smoker), and diabetes mellitus [15, 18] (absence or presence). Model 2 considered dietary factors: daily total energy intake [12, 15, 18] (kcal, continuous variable), consumption of miso (soybean paste) soup [11, 12, 18] and tofu [11, 12, 18] (soybean curd; for each food, <1 time/week, 1–6 times/week, or ≥1 time/day), consumption of fish [11, 13], meat [11, 13], and fruit [11–13] (for each food, <1 time/week, 1–4 times/week, or ≥5 times/week), consumption of vegetables [11–13] (≤4 or ≥5 times/week), and consumption of alcohol [11–13] (never, <3, or ≥3 times/week). Model 3 considered consumption of beverages: coffee [11, 13, 15], oolong tea [11], and black tea [11] (for each beverage, ≤4 cups/week, 5–6 cups/week–1 cup/day, or ≥2 cups/day). Then, we constructed the final model including the covariates that were selected according to their relative contribution to the individual models or clinical importance.

We tested for interactions, the differences in −2 log (likelihood) of the models with and without interaction terms were compared with the χ^2 distribution with the same number of degrees of freedom as the interaction terms. All statistical analyses were performed with SAS software, version 9.1 (SAS Institute, Cary, NC) [19]. All reported p values were two-tailed and were considered statistically significant if <0.05.

Results

The characteristics of the subjects are shown in Table 1. The mean age (±SD) of the participants was 54.3 year (±10.3 year) for the cases and 53.3 year (±9.4 year) for the controls ($p = 0.31$). As compared with the controls, the cases were more likely to be obese ($p < 0.001$), have a lower level of education ($p < 0.001$), and have diabetes mellitus ($p < 0.001$). They were less likely to consume meat ($p = 0.020$), vegetables ($p = 0.027$), coffee ($p = 0.002$), and green tea ($p = 0.035$). No significant differences in any other variables were found.

The conditional logistic regression analysis indicated significant inverse associations between green tea consumption and the risk of EEA (Table 2). The crude OR, as referenced with those in the lowest quartile of green tea consumption (≤4 cups/week), was 0.85 (95% CI: 0.49–1.45) for those in the second quartile (5–6 cups/week–1 cup/day), 0.60 (0.35–1.03) for those in the third quartile (2–3 cups/day), and 0.51 (0.28–0.92) for those in the highest quartile (≥4 cups/day; p for trend = 0.011). We included a variety of potential confounders in the multivariate models (models 1, 2, and 3). The result did not change substantially for multivariate models 1 through 3.

In the final multivariate model, we chose the following variables as covariates: BMI, level of education, number of pregnancies, menopausal status, smoking status, diabetes mellitus, daily total energy intake, consumption of miso soup, consumption of tofu, and consumption of coffee. The multivariate OR of EEA, as referenced with the lowest quartile of green tea consumption (≤4 cups/week), was 0.77 (95% CI: 0.37–1.58) for those in the second quartile (5–6 cups/week–1 cup/day), 0.61 (0.30–1.23) for those in the third quartile (2–3 cups/day), and 0.33 (0.15–0.75) for those in the highest quartile (≥4 cups/day; p for trend = 0.007).

The result did not change even when we divided the subjects into quintiles according to green tea consumption. In the final model, the multivariate OR of EEA, as referenced with those in the lowest quintile (≤2 cups/week), was 0.75 (95% CI: 0.30–1.87) for those in the second quintile (3–6 cups/week), 0.66 (0.29–1.53) for those in the third quintile (1 cup/day), 0.55 (0.26–1.18) for those in the fourth quintile (2–3 cups/day), and 0.30 (0.13–0.71) for those in the highest quintile (≥4 cups/day; p for trend = 0.007).

We tested for interaction term of each covariate in the final model (BMI, education, number of pregnancies, menopausal status, diabetes mellitus, smoking status, miso soup consumption, tofu consumption, total caloric intake, coffee consumption). Consequently, total caloric intake was found to be the only covariates with a significant interaction term (p for interaction = 0.006). Otherwise, the inverse

Table 1 Characteristics of EEA cases and controls

Characteristic	Cases ($n = 152$)	Controls ($n = 285$)	p value
Matching variables			
Age at study registry, mean (SD)	54.3 (10.3)	53.3 (9.4)	0.31
Area of residence in Miyagi prefecture (%)			
Northern area (rural area)	44	45	1.00
Central area (urban area)	47	47	
Southern area (rural area)	9	8	
Selected variables as possible to confounding factors			
Body mass index (kg/m^2, %)			
<25.0	52	80	<0.001
≥25.0	48	19	
Education (%)			
Junior high school or less	15	4	<0.001
High school	43	48	
College/university or higher	38	46	
No. of pregnancies (%)			
None	17	15	0.80
1–3	66	66	
≥4	16	18	
Use of oral contraceptives (%)			
Never user	94	93	0.33
Ever user	5	7	
Age at menarche, mean (SD)	13.0 (1.6)	13.1 (1.5)	0.53
Menopausal status (%)			
Premenopause	32	35	0.46
Postmenopause	67	64	
Smoking status (%)			
Never smoker	84	85	0.80
Ex-smoker	7	6	
Current smoker	8	8	
Diabetes mellitus (%)			
Absence	81	95	<0.001
Presence	14	2	
Energy intake, mean in kcal/day (SD)	1,592 (572)	1,523 (596)	0.24
Miso (soybean paste) soup (%)			
<1 time/week	7	4	0.29
1–6 times/week	42	41	
≥1 time/day	51	56	
Tofu (soybean products, %)			
<1 time/week	26	27	0.49
1–6 times/week	66	62	
≥1 time/day	7	11	
Fish (%)			
<1 time/week	4	3	0.78
1–4 times/week	73	71	
≥5 times/week	23	26	
Meat (%)			
<1 time/week	18	10	0.020
1–4 times/week	76	78	
≥5 times/week	6	12	

Table 1 continued

Characteristic	Cases ($n = 152$)	Controls ($n = 285$)	p value
Vegetable (%)			
≤4 times/week	20	12	0.027
≥5 times/week	80	88	
Fruit (%)			
<1 time/week	10	8	0.41
1–4 times/week	41	37	
≥5 times/week	49	55	
Alcohol (%)			
Never	61	54	0.22
<3 times/week	27	28	
≥3 times/week	12	18	
Coffee (%)			
≤4 cups/week	44	27	0.002
5–6 cups/week–1 cup/day	23	30	
≥2 cups/day	33	43	
Oolong tea (%)			
≤4 cups/week	75	74	0.93
5–6 cups/week–1 cup/day	13	14	
≥2 cups/day	12	11	
Black tea (%)			
≤4 cups/week	85	82	0.73
5–6 cups/week–1 cup/day	9	12	
≥2 cups/day	6	6	
Green tea (%)			
≤4 cups/week	34	25	0.035
5–6 cups/week–1 cup/day	24	21	
≥2 cups/day	41	54	

EEA endometrial endometrioid adenocarcinoma, *SD* standard deviation

association between frequency of green tea consumption and the risk of EEA was consistently observed in most of the strata, for example, obesity or not obesity (the OR of EEA was 0.55 and 0.14 for those of green tea consumption ≥4 cups/day in BMI <25.0 and ≥25, respectively), premenopause or postmenopause (the OR of EEA was 0.52 and 0.25 for those of green tea consumption ≥4 cups/day in premenopause and postmenopause, respectively).

Discussion

We examined the association between green tea consumption and the risk of EEA in Japanese women using a case–control study design. A significant inverse dose–response relationship between the frequency of green tea consumption and the risk of EEA was observed. The association was stable regardless of whether the participants were divided into quartiles or quintiles according to green tea consumption. In addition, this association was consistently observed regardless of the presence or absence of factors such as obesity, lower education, nulliparity, menopause, and so forth. These results suggest that green tea consumption may be associated with a lower risk of EEA.

There have been two case–control studies and one prospective cohort study regarding green tea consumption and endometrial cancer: one case–control study from China and the others from Japan. In the Shanghai Endometrial Cancer Study, Xu et al. investigated the association between tea consumption and endometrial cancer [12]. In this article, 1,204 endometrial cancer cases and 1,212 age-matched as controls were analyzed, and "primarily green tea drinkers" (those who drank green tea more often than other types of tea) had an OR of 0.8 (95% CI: 0.6–0.9) compared to "non-tea drinkers." On the other hand, from the hospital-based epidemiological research program at Aichi Cancer Center (HERPACC) in Japan, Hirose et al. conducted a case–control study of 229 women with endometrial cancer and 12,425 outpatients without cancer as controls, and they reported that no association was observed between green tea consumption and endometrial cancer, with an OR of

Table 2 Odds ratio (OR) of EEA according to quartile of green tea consumption (152 cases and 285 controls)

Green tea consumption	<4 cups/week	5–6 cups/week–1 cup/day	2–3 cups/day	>4 cups/day	*p* for trend
No. of cases/controls	52/71	37/60	34/80	29/74	
Crude OR (95% CI)	1.00 (referent)	0.85 (0.49–1.45)	0.60 (0.35–1.03)	0.51 (0.28–0.92)	0.011
Model 1 OR (95% CI)	1.00 (referent)	0.80 (0.42–1.54)	0.71 (0.37–1.35)	0.40 (0.19–0.84)	0.019
Model 2 OR (95% CI)	1.00 (referent)	0.90 (0.50–1.61)	0.61 (0.34–1.11)	0.41 (0.21–0.78)	0.037
Model 3 OR (95% CI)	1.00 (referent)	0.84 (0.48–1.50)	0.55 (0.31–0.98)	0.44 (0.23–0.82)	0.005
Final model OR (95% CI)	1.00 (referent)	0.77 (0.37–1.58)	0.61 (0.30–1.23)	0.33 (0.15–0.75)	0.007

Model 1: Adjusted for BMI in kg/m^2 (continuous variables), education (junior high school or less, high school, or college/university or higher), number of pregnancies (none, 1–3, or ≥4), use of oral contraceptives (never user or ever user), age at menarche in years (<13 or ≥13), menopausal status (premenopause or postmenopause), smoking status (never smoker, ex-smoker, or current smoker), and diabetes mellitus (absence or presence)

Model 2: Adjusted for daily total energy intake in kcal (continuous variables), miso soup consumption (<1 time/week, 1–6 times/week, or ≥1 time/day), tofu consumption (<1 time/week, 1–6 times/week, or ≥1 time/day), fish consumption (<1 time/week, 1–4 times/week, or ≥5 times/week), meat consumption (<1 time/week, 1–4 times/week, or ≥5 times/week), vegetable consumption (≤4 or ≥5 times/week), fruit consumption (<1 time/week, 1–4 times/week, or ≥5 times/week), and alcohol consumption (none, <3, or ≥3 times/week)

Model 3: Adjusted for coffee consumption (≤4 cups/week, 5–6 cups/week–1 cup/day, or ≥2 cups/day), oolong tea consumption (≤4 cups/week, 5–6 cups/week–1 cup/day, or ≥2 cups/day), and black tea consumption (≤4 cups/week, 5–6 cups/week–1 cup/day, or ≥2 cups/day)

Final model: Adjusted for BMI in kg/m^2 (continuous variables), education (junior high school or less, high school, or college/university or higher), number of pregnancies (none, 1–3, or ≥4), menopausal status (premenopause or postmenopause), smoking status (never smoker, ex-smoker, or current smoker), diabetes mellitus (absence or presence), total calorie intake in kcal (continuous variables), miso soup consumption (<1 time/week, 1–6 times/week, or ≥1 time/day), tofu consumption (<1 time/week, 1–6 times/week, or ≥1 time/day), and coffee consumption (≤4 cups/week, 5–6 cups/week–1 cup/day, or ≥2 cups/day)

1.33 (95% CI: 0.75–2.35) for the group that drank ≥7 cups/day of Japanese tea (same as green tea) versus those who drank <1 cup/day (occasional or non-drinkers), although the OR for the group drinking 1–6 cups/day of green tea was not reported [13].

These two case–control studies reported insufficient information regarding the relation between green tea consumption and the risk of endometrial cancer. The Shanghai study did not examine the frequency of green tea consumption in detail, and thus, the dose–response relationship could not be investigated. As the main purpose of the HERPACC study was to examine the association between coffee consumption and the risk of endometrial cancer, they presented limited information regarding the frequency of green tea consumption and the risk of endometrial cancer.

In the previous cohort study, Shimazu et al. investigated population-based prospective study in 53,724 Japanese women and 117 cases of endometrial carcinoma. There was an inverse association between green tea consumption and the incidence of endometrial carcinoma. The HRs (95% CIs) for endometrial carcinoma in women who drank green tea 1–2, 3–4, and ≥5 cups/day compared with ≤4 days/week were 1.04 (0.62–1.74), 0.79 (0.47–1.35), 0.75 (0.44–1.30; p for trend = 0.22). However, this association was not statistically significant. As Shimazu et al. admitted, it could be partly explained by insufficient statistical power.

We consider the following as strengths of our study. First, because the cases were restricted to EEA patients, the study population was homogeneous. EEA accounts for >80% of endometrial cancers, and it is a representative histological type, being a so-called hormone-related malignancy [20–22]. Second, our study attempted to control extensively for potentially confounding variables: age, obesity, smoking status, reproductive factors, diabetes mellitus, food consumption (soy foods or other dietary foods), and beverage consumption (coffee, black tea, and oolong tea). A significant inverse association was found even after adjustment for these variables. Third, we divided the replies regarding frequency of green tea consumption into nine categories ranging from "almost never (<1 cup/week)" to "≥10 cups/day" into quartiles or quintiles, and the results indicated a decrease in the risk of EEA that appeared to show a dose–response relationship.

We regard the following as limitations of our study. First, we did not ask the subjects whether they had received hormone replacement therapy, which is an established risk factor for EEA. However, since the proportion of women receiving hormone replacement therapy in Japan is only about 2% [23], it would have had little impact on this study. Second, because of the case–control study design, memory errors regarding green tea consumption and recall bias might have affected the present result. Third, it is very important to consider the selection bias of the control group on a case–control study. The controls were selected from two cancer-screening facilities, which make a contract with the large companies or governmental agencies in the area. Thus, the socio-economic status of the controls might be higher than general population. The health-related lifestyle

was also different between our controls and the general population (women) in the area [24]. Regarding green tea, 24% of our controls consumed >4 cups of green tea/day, while 43% of the general women consumed >5 cups of green tea/day. Regarding smoking habit, 14% of our controls and 12% of the general women were smokers or ex-smokers. Regarding alcohol drinking, 46% of the controls were current drinkers that was higher than general women (32%). In summary, the controls were not free from selection biases, but the direction and the degree of its effect on the association were unclear.

In the previous prospective cohort studies we conducted, we failed to find significant associations between green tea consumption and the incidence risk of gastric cancer [24, 25], colorectal cancer [26], prostate cancer [27], and breast cancer [28]. Cohort studies are considered to have a higher level of evidence than case–control studies. However, a case–control study has the advantage of collecting a sufficient number of cases of rare diseases in a short period. It takes a long time to investigate the risk of endometrial cancer using a cohort study design in Japan, because the age-adjusted incidence rate in Japan is 6.2 (per 100,000 women, 2001) [2], much lower than in North America or Europe. In addition, green tea is a very popular beverage in Japan, also unlike Western countries where tea drinkers consume mainly black tea.

The association between green tea consumption and the incidence risk of cancers at varying sites has been extensively investigated, and most studies agreed with null association for stomach [8, 10, 24, 25] (mostly, men), lung [11], colorectum [8, 11], breast [28], esophagus [8, 29], and pancreas [30]. On the other hand, there have been some reports indicating the inverse association between green tea consumption and such cancers as stomach among women [10], ovarium [31], and endometrium [12]. These results would lead us to the hypothesis that the anticarcinogenic action, if any, of green tea might be dependent upon sex, possibly through sex-related hormone. This hypothesis should be further tested at experimental and epidemiological settings.

In this study, we observed that green tea consumption was associated with a significantly lower risk of EEA, with a dose–response relationship. This finding should be verified further in another population using another study design such as a prospective cohort study.

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