Cancer Causes Control (2011) 22:985–993
DOI 10.1007/s10552-011-9771-2

ORIGINAL PAPER

Green tea and coffee consumption and its association with thyroid cancer risk: a population-based cohort study in Japan

Takehiro Michikawa · Manami Inoue · Taichi Shimazu · Shizuka Sasazuki · Motoki Iwasaki · Norie Sawada · Taiki Yamaji · Shoichiro Tsugane

Received: 18 October 2010 / Accepted: 23 April 2011 / Published online: 12 May 2011

Abstract
Background The anticarcinogenic potential of green tea and coffee might be expected to reduce the risk of thyroid cancer, but epidemiological evidence is sparse. We examined green tea and coffee consumption in association with thyroid cancer risk in a general Japanese population.
Methods We analyzed data from a prospective cohort of 100,507 persons (48,802 men; 51,705 women) aged 40–69. Green tea and coffee consumption were assessed via a self-administered questionnaire. During a mean 14.2-year follow-up, we documented 159 thyroid cancer cases (26 in men; 133 in women), and Cox regression were used to calculated hazard ratios (HRs).
Results Green tea consumption was not found to be associated with thyroid cancer risk in general. However, when women were stratified by menopausal status, the multivariable HR for ≥5 cups/day versus <1 cup/day was 1.66 (95% confidence interval (CI) = 0.85–3.23, trend $p = 0.04$) in premenopausal women, and was 0.47 (95% CI = 0.23–0.96, trend $p = 0.06$) in postmenopausal women. We found no association between coffee consumption and thyroid cancer risk in either sex.
Conclusions High green tea consumption may be positively associated with premenopausal thyroid cancer risk, but inversely associated with postmenopausal thyroid cancer risk.

Keywords Green tea · Coffee · Thyroid cancer · Menopausal status · Cohort study

Introduction

The worldwide age-standardized incidence of thyroid cancer is 1.5 per 100,000 person-years for men and 4.7 for women, accounting for approximately 1% of all new cancer cases [1, 2]. Although the incidence is relatively low, thyroid cancer is a major form of malignant neoplasm in women under 45 years of age [3]. The only established risk factor for thyroid cancer is exposure to ionizing radiation [4]. Consumption of such dietary items as fish, vegetables, and beverages (tea and coffee) is suspected to be associated with thyroid cancer risk, but no conclusive evidence is available [5–7]. Since diet is a fundamental aspect of human life, clarifying the role of dietary factors in thyroid cancer prevention is important. Certain beverages are consumed on a daily basis and constitute an important part of people's diet. In Japan, the widely popular beverages are green tea and coffee, which are consumed daily by approximately 75 and 40% of the general Japanese population, respectively [8]. From the public health viewpoint, therefore, the effects of green tea and coffee consumption on thyroid cancer risk are of particular interest.

Evidence has gradually accumulated that high consumption of green tea and coffee may reduce the risk of

This study is conducted for Japan Public Health Center-based Prospective Study Group. The members of the Japan Public Health Center-based Prospective Study Group are listed in "Appendix".

T. Michikawa · M. Inoue (✉) · T. Shimazu · S. Sasazuki · M. Iwasaki · N. Sawada · T. Yamaji · S. Tsugane
Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: mnminoue@ncc.go.jp

T. Michikawa
Department of Preventive Medicine and Public Health, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

some forms of cancer [9]: the catechins in green tea and chlorogenic acids in coffee are antioxidants, whose activities are thought to play a role in cancer prevention [10, 11]. Reports that oxidative stress is involved in the development of thyroid cancer [12, 13] suggest that green tea and coffee consumption reduce the risk of thyroid cancer. However, reported epidemiological investigations are limited to several case–control studies [7, 9, 14, 15]. Furthermore, the reported studies investigated the association between tea consumption in general rather than green tea consumption specifically and thyroid cancer. As far as we know, there have been no prospective cohort studies on green tea and coffee consumption in association with thyroid cancer risk.

The aim of this study was to examine the associations between green tea and coffee consumption and thyroid cancer risk in a large population-based cohort study of Japanese men and women. We hypothesized that in women the effects of green tea and coffee consumption on thyroid cancer risk would be modified by menopausal status, because these beverages are known to influence circulating levels of sex hormones [16, 17], and female hormones appear to be associated with thyroid carcinogenesis [4, 5]. Therefore, we also investigated whether any association differed between pre- and postmenopausal women.

Participants and methods

Study population

The Japan Public Health Center-based Prospective (JPHC) Study started with Cohort I in 1990; Cohort II was studied in 1993 and 1994. The self-administered baseline questionnaire, which included questions on anthropometry, medical history, health screening, lifestyle, dietary habits, and menstrual and reproductive history (for women), was distributed to a total of 140,420 residents (68,722 men; 71,698 women) aged 40–69 of 11 prefectural public health center areas (administrative area of local government in Japan is known as prefecture). Details of the study design have been previously described [18]. The study protocol was approved by the institutional review board of the National Cancer Center, Japan.

For the present analysis, we excluded one public health center (Katsushika, Tokyo), because it had no data on cancer incidence; various participants were also excluded as ineligible because of non-Japanese nationality, emigration before the start of the follow-up period, incorrect birth date, and duplicate registration. Of the remaining 133,060 residents (65,651 men; 67,409 women), 80% returned responses. Those who reported a history of any type of cancer, and those who failed to supply data on green tea or coffee consumption and/or gave incomplete information on menopausal status were further excluded, leaving a total of 100,507 participants (48,802 men; 51,705 women) for inclusion in the analysis.

Exposure assessment

The self-administered questionnaire included questions about the frequency and amount of green tea and coffee consumption. Responses were divided into 6 categories: almost never; 1–2 times/week; 3–4 times/week; 1–2 cups/day; 3–4 cups/day; and $\geq$5 cups/day. We did not collect information on the type of coffee (decaffeinated or caffeinated), because decaffeinated coffee is not commonly consumed in Japan. The validity of the responses on green tea and coffee consumption in this population has already been reported. Spearman's rank correlation coefficients between the questionnaire responses and 28-day dietary records for men and women were 0.57 and 0.63 for green tea, respectively, and 0.42 and 0.38 for coffee, respectively [19].

Follow-up

Participants were followed up from the baseline survey until 31 December 2007. In this study, person-years of observation were defined as the time from the date of response to the baseline questionnaire to the date of thyroid cancer diagnosis, the date of emigration from the study area, the date of death, or the end of the study period, whichever came first. Participants who were lost to follow-up were censored on the last confirmed date of their presence in the study area. Changes in residence status, including survival, were confirmed annually via the residential registry in each area. Deaths, certified according to the requirements of the Ministry of Health, Labour and Welfare, were ascertained from local public health centers. Resident and death registration are required by the Basic Residential Register Law and Family Registry Law, respectively, and the registries are believed to be complete. Of the study participants, 10,344 (10.3%) died, 9,115 (9.1%) moved out of the study area, and 401 (0.4%) were lost to follow-up within the study period.

Cases of thyroid cancer were identified through a specific cancer registry system for the JPHC Study, which was established to collect cancer incidence data on the subjects living within the study area via voluntary reports from major local hospitals and data from population-based cancer registries, with permission from each local government responsible for the cancer registries. Death certificates were used as a supplementary information source. The site and histology of each case were coded according to the International Classification of Diseases for Oncology, Third Edition (code: C73.9) [20]. The earliest date of

diagnosis was used in cases with multiple thyroid cancers at different times. During 1,430,788 person-years of follow-up (mean follow-up period: 14.2 years), we documented 159 new thyroid cancer cases (26 in men; 133 in women). Diagnosis was confirmed by histologic or cytologic examination in 94.3% of cases. The distribution of histologic types was papillary carcinoma in 133 (83.6%), follicular carcinoma in 7 (4.4%), anaplastic carcinoma in 1 (0.6%), and other or unknown histologic types in 18 (11.4%).

Statistical analysis

STATA version 11.0 (Stata Corporation, College Station, Texas) was used for analyses.

Green tea consumption was divided into 4 categories for statistical analysis: <1 cup/day; 1–2 cups/day; 3–4 cups/day; ≥5 cups/day. For coffee consumption, we classified the subjects into only 3 categories, because small number of cases occurred in the higher categories: almost never; 1–4 times/week; ≥1 cup/day.

Hazard ratios (HRs) and 95% confidence intervals (CIs) of thyroid cancer risk according to green tea and coffee consumption categories were estimated with the Cox proportional hazards model, taking the lowest consumption category as the reference. We tested the assumptions of proportional hazards by using scaled Schoenfeld residuals and an Aalen-Nelson plot of the cumulative rate on a log scale, and found no violation of proportionality. Among the suspected risk factors for thyroid cancer shown in Table 1 (based on evidence from past studies [5, 6]), the following variables were adjusted for as potential confounding factors: age at baseline (continuous); study area (10 public health centers); smoking history (never, past, or current for men, and never/past, or current for women); passive smoking in the workplace (yes, no); alcohol consumption (none, occasional, regular); body mass index (continuous); green vegetable consumption (<3 days/week, 3–4 days/week, almost daily); consumption of seaweed, the major source of iodine in Japan [21] (<3 days/week, 3–4 days/week, almost daily); health screening in the previous year (which might have increased the detection rate of thyroid cancer) (yes, no); green tea or coffee consumption. For women, we additionally adjusted for menopausal status at baseline (premenopausal, natural or induced menopausal) and use of exogenous female hormones (never, ever). We also analyzed pre- and postmenopausal (natural or induced menopausal) women separately. A test for interaction between green tea and coffee consumption and menopausal status was performed by using likelihood ratio test. HRs for a one-category increase in green tea and coffee consumption were also calculated with the Cox proportional hazards model by treating consumption categories as a continuous variable.

In addition, we conducted a number of subgroup analyses to confirm our primary results: (1) including only subjects who had never smoked, because smoking influences the secretion of a thyroid-stimulating hormone associated with thyroid cancer risk [4]; (2) including only women who had never used exogenous female hormones, because estrogens are considered to play an etiologic role in thyroid carcinogenesis [4]; (3) excluding localized cases (cancer confined within the thyroid gland) in order to rule out subclinical cases [22]; (4) including only microscopically confirmed cases; (5) including only cases of papillary carcinoma, the most common type of thyroid cancer; (6) excluding subjects diagnosed within the first 2 years to avoid any potential effect of preclinical conditions.

Results

Baseline characteristics of the participants according to green tea and coffee consumption are shown in Table 1. Of the subjects of both sexes in the higher green tea consumption category, the proportion of the higher age groups increased. The subjects who consumed large amounts of green tea tended also to consume more green vegetable, fish and seaweed, and to consume less coffee. Of those in the higher coffee consumption category, few were in the over-60 age bracket. The subjects who consumed large amounts of coffee tended to be taller, to be current smokers, and to consume less green vegetable, fish, seaweed, and green tea; the women in this group tended to drink alcohol regularly. Among women, the percentage of those falling into the following categories increased in proportion to green tea consumption, and in inverse proportion to coffee consumption: underwent health screening in the previous year; postmenopausal; late age at menarche; early age at first live birth.

As shown in Table 2, green tea consumption was not generally associated with thyroid cancer risk in either men or women, although in women, we observed weak evidence for effect modification according to menopausal status (p for interaction = 0.10): in premenopausal women, green tea consumption was positively associated with thyroid cancer risk [multivariable HR for ≥5 cups/day compared with <1 cup/day = 1.66 (95% CI = 0.85–3.23), and for a one-category increase = 1.24 (1.00–1.54)]. We could not collect information on subjects' menopausal status at diagnosis of thyroid cancer, so some supposed premenopausal cases might actually have been postmenopausal. Consequently, we repeated our analyses using data only on subjects in the 40–44 age stratum at baseline. The results were similar to the primary results [cases = 38, multivariable HR for a one-category increase = 1.23 (95% CI = 0.91–1.65)]. Also, the results were not materially

Table 1 Baseline characteristics of participants according to green tea and coffee consumption

	Green tea consumption				Coffee consumption		
	<1 cup/day	1–2 cups/day	3–4 cups/day	≥5 cups/day	Almost never	1–4 times/week	≥1 cup/day
Women							
Number of participants	12,693	10,892	14,380	13,740	16,335	15,011	20,359
Age (%)							
40–49 years	51.4	46.6	37.8	31.3	25.2	39.5	55.5
50–59 years	39.5	38.8	40.8	44.6	48.1	42.3	34.5
60–69 years	9.1	14.6	21.4	24.1	26.7	18.2	10.0
Height (cm), mean (SD)	151.8 (5.6)	152.3 (5.6)	152.1 (5.5)	151.9 (5.5)	151.1 (5.7)	151.9 (5.5)	152.8 (5.4)
Body mass index, mean (SD)	23.5 (3.2)	23.2 (3.1)	23.3 (3.1)	23.5 (3.2)	23.6 (3.3)	23.5 (3.1)	23.2 (3.1)
Current smokers (%)	7.8	6.5	5.4	7.0	4.4	4.4	10.1
Passive smoking in the workplace (%)	25.5	28.7	26.8	27.7	21.6	24.6	33.3
Regular drinkers (%)	13.4	14.5	12.8	12.0	9.2	11.2	17.6
Green vegetable consumption, ≥3 days/week (%)	65.5	65.0	68.7	70.7	68.9	68.7	65.9
Fish consumption, ≥3 days/week (%)	45.0	47.7	53.0	54.6	53.6	52.5	46.1
Seaweed consumption, ≥3 days/week (%)	52.7	50.1	53.7	57.0	55.7	55.7	50.3
Green tea consumption, ≥3 cups/day (%)					59.7	59.6	46.3
Coffee consumption, ≥1 cup/day (%)	43.9	49.2	38.7	28.1			
Health screening in the previous year, yes (%)	76.7	78.3	79.7	80.4	82.6	80.7	74.6
Age at menarche, ≥16 years (%)	26.1	24.4	26.3	32.7	35.6	28.6	20.4
Menopausal status, premenopausal (%)	50.6	47.7	38.8	31.7	25.5	39.4	56.4
Parity, nulliparous (%)	5.9	5.9	5.6	6.0	5.8	5.3	6.3
Age at first live birth, ≥30 years (%)	9.9	9.1	8.4	8.0	8.1	8.3	9.8
Use of exogenous female hormones, ever user (%)	14.7	10.8	9.8	10.8	11.1	11.5	11.7
Men							
Number of participants	12,688	11,526	12,895	11,693	14,642	14,379	19,781
Age (%)							
40–49 years	51.5	46.0	39.2	30.5	31.4	39.6	51.4
50–59 years	39.0	38.8	40.4	46.5	46.3	42.8	36.0
60–69 years	9.5	15.2	20.4	23.0	22.3	17.6	12.6
Height (cm), mean (SD)	164.0 (6.3)	164.6 (6.3)	164.3 (6.3)	163.5 (6.3)	163.2 (6.4)	163.8 (6.2)	165.0 (6.2)
Body mass index, mean (SD)	23.8 (3.0)	23.5 (2.8)	23.3 (2.8)	23.4 (2.8)	23.5 (2.9)	23.6 (2.8)	23.4 (2.8)
Current smokers (%)	51.4	53.0	51.8	54.2	43.3	49.6	61.5
Passive smoking in the workplace (%)	57.0	63.0	59.7	58.7	52.1	58.5	65.8
Regular drinkers (%)	67.2	72.2	69.8	64.8	69.5	69.4	67.1
Green vegetable consumption, ≥3 days/week (%)	54.0	51.9	57.5	62.4	59.9	57.9	52.9
Fish consumption, ≥3 days/week (%)	43.1	46.0	50.6	52.2	52.3	48.8	44.1
Seaweed consumption, ≥3 days/week (%)	39.5	38.7	43.2	48.5	46.3	44.0	38.5
Green tea consumption, ≥3 cups/day (%)					54.8	53.8	44.6
Coffee consumption, ≥1 cup/day (%)	43.0	47.8	40.5	30.8			
Health screening in the previous year, yes (%)	77.6	80.8	80.7	79.2	79.8	80.1	79.0

SD standard deviation

altered after counting only cases in women aged 50 or younger at diagnosis (the median age of natural menopause in this population) [cases = 32, multivariable HR for a one-category increase = 1.34 (95% CI = 0.97–1.85)]. In contrast, high green tea consumption tended to lower the risk of thyroid cancer in postmenopausal women when adjustment was made for the potential confounding factors [multivariable HR for ≥5 cups/day compared with <1 cup/day = 0.47 (95% CI = 0.23–0.96), and for a one-category increase = 0.80 (0.65–1.01)]. Including only natural menopausal women did not change the results substantially [cases = 49, multivariable HR for a one-category

Table 2 Hazard ratios (HRs) and 95% confidence intervals (CIs) of thyroid cancer in relation to green tea consumption

Category of consumption	Green tea consumption				
	<1 cup/day	1–2 cups/day	3–4 cups/day	≥5 cups/day	One-category increase
Women					
Number of subjects	12,693	10,892	14,380	13,740	
Number of cases	39	19	41	34	
Person-years of follow-up	189,627	157,226	206,013	199,774	
Age and area adjusted HR (95% CI)	Reference	0.68 (0.39–1.18)	1.18 (0.76–1.85)	0.98 (0.61–1.57)	1.03 (0.89–1.21)
Multivariable HR (95% CI)[a]	Reference	0.64 (0.37–1.14)	1.10 (0.70–1.75)	0.91 (0.56–1.48)	1.01 (0.87–1.18)
Premenopausal women					
Number of subjects	6,428	5,195	5,577	4,361	
Number of cases	19	10	21	18	
Person-years of follow-up	95,398	74,791	80,285	64,256	
Age and area adjusted HR (95% CI)	Reference	0.80 (0.37–1.72)	1.60 (0.85–2.99)	1.60 (0.83–3.06)	1.22 (0.99–1.51)
Multivariable HR (95% CI)[b]	Reference	0.84 (0.38–1.82)	1.64 (0.86–3.12)	1.66 (0.85–3.23)	1.24 (1.00–1.54)
Postmenopausal women					
Number of subjects	6,265	5,697	8,803	9,379	
Number of cases	20	9	20	16	
Person-years of follow-up	94,228	82,434	125,728	135,517	
Age and area adjusted HR (95% CI)	Reference	0.57 (0.26–1.26)	0.84 (0.44–1.58)	0.59 (0.30–1.16)	0.87 (0.71–1.08)
Multivariable HR (95% CI)[b]	Reference	0.48 (0.21–1.10)	0.69 (0.36–1.34)	0.47 (0.23–0.96)	0.80 (0.65–1.01)
Men					
Number of subjects	12,688	11,526	12,895	11,693	
Number of cases	7	7	7	5	
Person-years of follow-up	179,096	156,607	177,174	165,268	
Age and area adjusted HR (95% CI)	Reference	1.17 (0.41–3.38)	0.96 (0.33–2.79)	0.66 (0.21–2.13)	0.88 (0.62–1.24)
Multivariable HR (95% CI)[a]	Reference	1.13 (0.39–3.27)	0.95 (0.33–2.78)	0.71 (0.22–2.28)	0.89 (0.63–1.26)

[a] Adjusted for age (continuous), area (10 public health centers), smoking history (never, past, or current for men; and never/past, or current for women), passive smoking in the workplace (yes, no), alcohol consumption (none, occasional, regular), body mass index (continuous), consumption of green vegetable and seaweed (<3 days/week, 3–4 days/week, almost daily), health screening in the previous year (yes, no), and coffee consumption (almost never, 1–4 times/week, ≥1 cup/day). For women, additionally adjusted for menopausal status (premenopausal, natural or induced menopausal) and use of exogenous female hormones (never, ever)

[b] Adjustments as in footnote a except menopausal status (premenopausal, natural or induced menopausal) and additionally adjusted for menopausal status (natural, induced) for postmenopausal women

increase = 0.81 (95% CI = 0.62–1.05)]. When we recategorized subjects into 2 groups for green tea consumption: <1 cup/day; daily (≥1 cup/day), the multivariable HR was 0.55 (95% CI = 0.32–0.96) for postmenopausal women who drank green tea daily.

We conducted several analyses of subgroups stratified according to baseline menopausal status and calculated the HRs of thyroid cancer risk for a one-category increase in green tea consumption (Table 3). The results were essentially unchanged for both pre- and postmenopausal women. Additionally, we tried to assess whether these results could be generalized to other types of tea including black tea and oolong tea (almost never, 1–4 times/week, ≥1 cup/day). However, these beverages were not found to be associated with thyroid cancer risk, regardless of menopausal status (data not shown).

We found no association between coffee consumption and thyroid cancer risk in either sex (Table 4), with no difference between pre- and postmenopausal women (p for interaction = 0.28).

Discussion

To the best of our knowledge, this is the first population-based prospective cohort study to investigate the associations between green tea and coffee consumption and thyroid cancer risk. This study found that the association between green tea consumption and thyroid cancer risk might vary according to menopausal status. Although statistical tests for interaction between green tea consumption and menopausal status did not produce any significant

Table 3 Subgroup analyses of the association between green tea consumption and risk of thyroid cancer in women according to menopausal status at baseline

	Premenopausal women		Postmenopausal women	
	Green tea consumption		Green tea consumption	
	Number of cases	One-category increase HR (95% CI)[a]	Number of cases	One-category increase HR (95% CI)[a]
All cases	68	1.24 (1.00–1.54)	65	0.80 (0.65–1.01)
Never smokers	65	1.21 (0.97–1.50)	62	0.81 (0.64–1.03)
Never users of exogenous female hormones	57	1.22 (0.96–1.54)	61	0.80 (0.63–1.01)
Excluding localized cases	36	1.14 (0.85–1.53)	32	0.87 (0.63–1.19)
Microscopically confirmed cases	63	1.21 (0.97–1.51)	63	0.83 (0.66–1.04)
Cases of papillary carcinoma	60	1.26 (1.01–1.59)	51	0.86 (0.67–1.10)
Excluding cases within the first 2 years	55	1.19 (0.94–1.51)	53	0.84 (0.66–1.08)

HR hazard ratio, *CI* confidence interval

[a] Adjusted for age (continuous), area (10 public health centers), smoking history (never, past, or current for men; and never/past, or current for women), passive smoking in the workplace (yes, no), alcohol consumption (none, occasional, regular), body mass index (continuous), consumption of green vegetable and seaweed (<3 days/week, 3–4 days/week, almost daily), health screening in the previous year (yes, no), coffee consumption (almost never, 1–4 times/week, ≥1 cup/day), use of exogenous female hormones (never, ever), and menopausal status (natural, induced) for postmenopausal women)

evidence ($p = 0.10$), the statistical power to detect interactions is known to be generally weak [23]. The present study found no association between green tea consumption and thyroid cancer risk in men, or between coffee consumption and thyroid cancer risk in either sex.

Many health benefits are attributed to green tea, and its anticarcinogenic effects have been studied extensively in relation to its abundant antioxidant contents (catechins, carotenoids, tocopherols, ascorbic acid, and minerals) [9, 10]. Interestingly, the thyroid gland requires hydrogen peroxide, a reactive oxygen species, for thyroid hormone biosynthesis, and recent studies indicate that the development of thyroid cancer might be partly explained by abnormalities in the hydrogen peroxide generating systems [13]. Given its antioxidant potential, it seems reasonable to assume that green tea would have a preventive effect on thyroid carcinogenesis. However, the present study indicated such an effect only in postmenopausal women. Higher expressions of epidermal growth factor receptors have been reported in postmenopausal women with papillary carcinoma [24], so it is possible that our findings are the result of another green tea activity by catechins: its inhibitory effect on the epidermal growth factor signaling pathway that mediates cell proliferation and survival signaling [25].

Among premenopausal women, we observed that green tea consumption was positively associated with thyroid cancer risk after adjusting for subjects' participation in health screening, which might have increased the detection rate of thyroid cancer. The results were similar even after we excluded cases of cancer localized within the thyroid gland, which was likely to be detected in health screening. Although the biological mechanism of the association between green tea consumption and increased thyroid cancer risk in premenopausal women is unclear, we think an estrogen-related mechanism is likely. Estrogen receptor α (ERα) is not found in normal thyroid glands, but it is known to be present in thyroid cancer cells [26]. Furthermore, ERα expression is higher in premenopausal thyroid cancer than in postmenopausal thyroid cancer [27]. In a study of human thyroid cancer cells, anti-apoptotic protein Bcl-2 was up-regulated by ERα agonists [28]. Meanwhile, green tea catechins, especially epigallocatechin-3-gallate (EGCG), have been found to exhibit estrogenic activity. In vitro, 17β-estradiol plus EGCG levels equivalent to those found in human plasma after green tea drinking induced a higher level of estrogenic activity through ERα than 17β-estradiol alone [29, 30]. Given the elevated levels of ERα in premenopausal thyroid cancer cells, green tea catechins may promote the growth of these cells through ERα. Our study suggests a new interpretation. However, the results we obtained from a relatively small number of cases in each stratified category according to menopausal status may be due to chance, so further epidemiological studies on this topic are needed.

In additional analyses, we found no associations between black tea and oolong tea consumption and thyroid cancer risk, supporting our hypothesis that the biological mechanism of green tea's association with thyroid cancer can be at least partly explained by catechins; other types of tea contain lower levels of catechins than green tea [10]. However, it also has to be recognized that black tea and oolong tea are consumed less frequently than green tea and

Table 4 Hazard ratios (HRs) and 95% confidence intervals (CIs) of thyroid cancer in relation to coffee consumption

Category of consumption	Coffee consumption			
	Almost never	1–4 times/week	≥1 cup/day	One-category increase
Women				
Number of subjects	16,335	15,011	20,359	
Number of cases	42	42	49	
Person-years of follow-up	239,647	221,009	291,984	
Age and area adjusted HR (95% CI)	Reference	1.06 (0.69–1.63)	0.97 (0.63–1.59)	0.98 (0.79–1.22)
Multivariable HR (95% CI)[a]	Reference	0.98 (0.63–1.54)	0.96 (0.62–1.48)	0.97 (0.78–1.22)
Premenopausal women				
Number of subjects	4,162	5,909	11,490	
Number of cases	13	23	32	
Person-years of follow-up	62,218	87,853	164,661	
Age and area adjusted HR (95% CI)	Reference	1.27 (0.64–2.51)	1.05 (0.55–2.02)	0.99 (0.73–1.35)
Multivariable HR (95% CI)[b]	Reference	1.25 (0.63–2.48)	1.11 (0.57–2.15)	1.02 (0.75–1.39)
Postmenopausal women				
Number of subjects	12,173	9,102	8,869	
Number of cases	29	19	17	
Person-years of follow-up	177,429	133,156	127,323	
Age and area adjusted HR (95% CI)	Reference	0.91 (0.51–1.63)	0.93 (0.50–1.72)	0.96 (0.71–1.31)
Multivariable HR (95% CI)[b]	Reference	0.79 (0.42–1.48)	0.92 (0.49–1.73)	0.94 (0.68–1.29)
Men				
Number of subjects	14,642	14,379	19,781	
Number of cases	9	5	12	
Person-years of follow-up	204,999	203,768	269,378	
Age and area adjusted HR (95% CI)	Reference	0.60 (0.20–1.79)	1.28 (0.52–3.12)	1.15 (0.71–1.87)
Multivariable HR (95% CI)[a]	Reference	0.56 (0.19–1.67)	1.18 (0.48–2.91)	1.11 (0.68–1.81)

[a] Adjusted for age (continuous), area (10 public health centers), smoking history (never, past, or current for men; and never/past, or current for women), passive smoking in the workplace (yes, no), alcohol consumption (none, occasional, regular), body mass index (continuous), consumption of green vegetable and seaweed (<3 days/week, 3–4 days/week, almost daily), health screening in the previous year (yes, no), and green tea consumption (<1 cup/day, 1–2 cups/day, 3–4 cups/day, ≥5 cups/day). For women, additionally adjusted for menopausal status (premenopausal, natural or induced menopausal) and use of exogenous female hormones (never, ever)

[b] Adjustments as in footnote a except menopausal status (premenopausal, natural or induced menopausal) and additionally adjusted for menopausal status (natural, induced) for postmenopausal women

coffee in Japan. In our study population, 3% and 12% drank black tea and oolong tea every day, respectively. Because of the smaller variations in the consumption of these beverages and the small number of cases in the high consumption category, our findings should be interpreted cautiously.

We found no association between coffee consumption and thyroid cancer risk. A pooled analysis of case–control studies of thyroid cancer gave adjusted odds ratios for >30 cups of coffee/month versus none of 1.0 (95% CI = 0.5–1.8) in men and 0.9 (0.6–1.2) in women [7]. This is compatible with our results. However, some case–control studies have indicated that coffee consumption tends to decrease the risk of thyroid cancer [14, 15]. One was a report from Japan that gave an adjusted odds ratio of thyroid cancer for everyday coffee drinkers compared with infrequent drinkers of 0.6 (95% CI = 0.3–1.04) among women aged 20–79 [15]. The authors proposed that the caffeine increases intracellular cyclic adenosine monophosphate levels, which has an inhibitory effect on tumor growth [14, 15]. The earlier studies in this area, however, have methodological limitations due to case–control design, suggesting the need for more prospective studies to examine the effects of coffee consumption on thyroid cancer risk.

The present study had a prospective design and a low proportion of loss to follow-up (0.4%), thereby minimizing the potential for selection and recall biases. In addition, the study participants were selected from the general Japanese population. Given the high level of green tea consumption across Asia [31] and the large variation in green tea consumption among individual Japanese, our population was appropriate for an examination of the association between green tea consumption and thyroid cancer risk. However, it had some limitations. The major limitation is that we could

not obtain information on subjects' menopausal status at diagnosis of thyroid cancer. Because of the long follow-up period (mean follow-up period: 14.2 years), supposed premenopausal cases might actually have been postmenopausal. Therefore, we confirmed our primary results by performing 2 additional analyses: using data only on women in the 40–44 age stratum; and counting cases only in women aged 50 or younger at diagnosis. In addition, using self-reported of green tea and coffee consumption at a single point means that some misclassifications of exposure levels to these beverages are unavoidable. But such misclassifications are likely to have been non-differential with respect to the outcome, leading to an attenuation of risk estimates. Thirdly, information on socioeconomic status was not obtained from all of the participants. Socioeconomic status may have a bearing on the frequency with which subjects receive health screening, so it could also be linked to the detection of thyroid cancer and thus be a source of detection bias. Finally, our findings might be residually confounded by unmeasured or unidentified risk factors for thyroid cancer (e.g. external radiation). In this population, there was only one case of thyroid cancer among the participants who had a history of benign thyroid diseases, which is a suspected risk factor for thyroid cancer [5]. Thus, this factor cannot be considered to have affected the results.

In conclusion, high green tea consumption may be positively associated with premenopausal thyroid cancer risk, but inversely associated with postmenopausal thyroid cancer risk. This finding may suggest an etiologic difference between pre- and postmenopausal thyroid cancer.

Acknowledgments The authors thank all staff members in each study area. We are indebted to the Aomori, Iwate, Ibaraki, Niigata, Osaka, Kochi, Nagasaki, and Okinawa Cancer Registries for providing their incidence data. This work was supported by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare, Japan (until 2009), and by Management Expenses Grants from the Government to the National Cancer Center (since 2010). It has also supported by a Grant-in-Aid for the Third-Term Comprehensive Control Research for Cancer from the Ministry of Health, Labour and Welfare, Japan, and by a Grant-in-Aid from Keio Medical Association.

Conflict of interest The authors have no conflicts of interest to disclose.

Appendix

Members of the Japan Public Health Center-based Prospective Study (JPHC Study, principal investigator: S. Tsugane) Group are: S. Tsugane, M. Inoue, T. Sobue, and T. Hanaoka, National Cancer Center, Tokyo; J. Ogata, S. Baba, T. Mannami, A. Okayama, and Y. Kokubo, National Cardiovascular Center, Osaka; K. Miyakawa, F. Saito, A. Koizumi, Y. Sano, I. Hashimoto, T. Ikuta and Y. Tanaba, Iwate Prefectural Ninohe Public Health Center, Iwate; Y. Miyajima, N. Suzuki, S. Nagasawa, Y. Furusugi, and N. Nagai, Akita Prefectural Yokote Public Health Center, Akita; H. Sanada, Y. Hatayama, F. Kobayashi, H. Uchino, Y. Shirai, T. Kondo, R. Sasaki, Y. Watanabe, Y. Miyagawa, Y. Kobayashi and M. Machida, Nagano Prefectural Saku Public Health Center, Nagano; Y. Kishimoto, E. Takara, T. Fukuyama, M. Kinjo, M. Irei, and H. Sakiyama, Okinawa Prefectural Chubu Public Health Center, Okinawa; K. Imoto, H. Yazawa, T. Seo, A. Seiko, F. Ito, F. Shoji and R. Saito, Katsushika Public Health Center, Tokyo; A. Murata, K. Minato, K. Motegi, T. Fujieda and S. Yamato, Ibaraki Prefectural Mito Public Health Center, Ibaraki; K. Matsui, T. Abe, M. Katagiri, and M. Suzuki, Niigata Prefectural Kashiwazaki and Nagaoka Public Health Center, Niigata; M. Doi, A. Terao, Y. Ishikawa, and T. Tagami, Kochi Prefectural Chuo-higashi Public Health Center, Kochi; H. Sueta, H. Doi, M. Urata, N. Okamoto, and F. Ide, and H. Goto, Nagasaki Prefectural Kamigoto Public Health Center, Nagasaki; H. Sakiyama, N. Onga, H. Takaesu, and M. Uehara, Okinawa Prefectural Miyako Public Health Center, Okinawa; F. Horii, I. Asano, H. Yamaguchi, K. Aoki, S. Maruyama, M. Ichii, and M. Takano, Osaka Prefectural Suita Public Health Center, Osaka; Y. Tsubono, Tohoku University, Miyagi; K. Suzuki, Research Institute for Brain and Blood Vessels Akita, Akita; Y. Honda, K. Yamagishi, S. Sakurai and N. Tsuchiya, Tsukuba University, Ibaraki; M. Kabuto, National Institute for Environmental Studies, Ibaraki; M. Yamaguchi, Y. Matsumura, S. Sasaki, and S. Watanabe, National Institute of Health and Nutrition, Tokyo; M. Akabane, Tokyo University of Agriculture, Tokyo; T. Kadowaki, Tokyo University, Tokyo; M. Noda and T. Mizoue, International Medical Center of Japan, Tokyo; Y. Kawaguchi, Tokyo Medical and Dental University, Tokyo; Y. Takashima and Y. Yoshida, Kyorin University, Tokyo; K. Nakamura, Niigata University, Niigata; S. Matsushima and S. Natsukawa, Saku General Hospital, Nagano; H. Shimizu, Sakihae Institute, Gifu; H. Sugimura, Hamamatsu University, Shizuoka; S. Tominaga, Aichi Cancer Center Research Institute, Aichi; H. Iso, Osaka University, Osaka; M. Iida, W. Ajiki, and A. Ioka, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka; S. Sato, Chiba Prefectural Institute of Public Health, Chiba; E. Maruyama, Kobe University, Hyogo; M. Konishi, K. Okada, and I. Saito, Ehime University, Ehime; N. Yasuda, Kochi University, Kochi; S. Kono, Kyushu University, Fukuoka.

References

1. International Agency for Research on Cancer (2010) Globocan 2008. Cancer incidence and mortality worldwide in 2008. Available at: http://globocan.iarc.fr/. Accessed 6 Sept 2010
2. Sherman SI (2003) Thyroid carcinoma. Lancet 361:501–511
3. Wu X, Groves FD, McLaughlin CC, Jemal A, Martin J, Chen VW (2005) Cancer incidence patterns among adolescents and young adults in the United States. Cancer Causes Control 16:309–320
4. Hall P, Adami HO (2008) Thyroid cancer. In: Adami HO, Hunter D, Trichopoulos D (eds) Textbook of cancer epidemiology, 2nd edn. Oxford University Press, New York, pp 636–652
5. Dal Maso L, Bosetti C, La Vecchia C, Franceschi S (2009) Risk factors for thyroid cancer: an epidemiological review focused on nutritional factors. Cancer Causes Control 20:75–86
6. Preston-Martin S, Franceschi S, Ron E, Negri E (2003) Thyroid cancer pooled analysis from 14 case-control studies: what have we learned? Cancer Causes Control 14:787–789
7. Mack WJ, Preston-Martin S, Dal Maso L et al (2003) A pooled analysis of case-control studies of thyroid cancer: cigarette smoking and consumption of alcohol, coffee, and tea. Cancer Causes Control 14:773–785
8. Kurahashi N, Inoue M, Iwasaki M, Sasazuki S, Tsugane S (2008) Coffee, green tea, and caffeine consumption and subsequent risk of bladder cancer in relation to smoking status: a prospective study in Japan. Cancer Sci 100:284–291
9. Binns CW, Lee AH, Fraser ML (2008) Tea or coffee? A case study on evidence for dietary advice. Public Health Nutr 11: 1132–1141
10. Cabrera C, Artacho R, Gimenez R (2006) Beneficial effects of green tea—a review. J Am Coll Nutr 25:79–99
11. Nkondjock A (2009) Coffee consumption and the risk of cancer: an overview. Cancer Lett 277:121–125
12. Sadani GR, Nadkarni GD (1996) Role of tissue antioxidant defence in thyroid cancers. Cancer Lett 109:231–235
13. Ohye H, Sugawara M (2010) Dual oxidase, hydrogen peroxide and thyroid diseases. Exp Biol Med (Maywood) 235:424–433
14. Linos A, Linos DA, Vgotza N, Souvatzoglou A, Koutras DA (1989) Does coffee consumption protect against thyroid disease? Acta Chir Scand 155:317–320
15. Takezaki T, Hirose K, Inoue M et al (1996) Risk factors of thyroid cancer among women in Tokai, Japan. J Epidemiol 6:140–147
16. Nagata C, Kabuto M, Shimizu H (1998) Association of coffee, green tea, and caffeine intakes with serum concentrations of estradiol and sex hormone-binding globulin in premenopausal Japanese women. Nutr Cancer 30:21–24
17. Kotsopoulos J, Eliassen AH, Missmer SA, Hankinson SE, Tworoger SS (2009) Relationship between caffeine intake and plasma sex hormone concentrations in premenopausal and postmenopausal women. Cancer 115:2765–2774
18. Tsugane S, Sobue T (2001) Baseline survey of JPHC study—design and participation rate. Japan public health center-based prospective study on cancer and cardiovascular diseases. J Epidemiol 11:S24–S29
19. Tsubono Y, Kobayashi M, Sasaki S, Tsugane S (2003) Validity and reproducibility of a self-administered food frequency questionnaire used in the baseline survey of the JPHC study cohort I. J Epidemiol 13:S125–S133
20. World Health Organization (2000) International classification of diseases for oncology, 3rd edn. World Health Organization, Geneve
21. Working group of dietary reference intakes for Japanese (2009) Dietary reference intakes for Japanese, 2010. Diichi Publishing Co, Tokyo, Japan (in Japanese)
22. Davies L, Welch HG (2006) Increasing incidence of thyroid cancer in the United States, 1973–2002. JAMA 295:2164–2167
23. Piantadosi S, Gail MH (1993) A comparison of the power of two tests for qualitative interactions. Stat Med 12:1239–1248
24. Candanedo-Gonzalez FA, Gamboa-Dominguez A (2007) Postmenopause is associated with recurrence of differentiated papillary thyroid carcinoma. Med Hypotheses 69:209–213
25. Liang YC, Lin-shiau SY, Chen CF, Lin JK (1997) Suppression of extracellular signals and cell proliferation through EGF receptor binding by (-)-epigallocatechin gallate in human A431 epidermoid carcinoma cells. J Cell Biochem 67:55–65
26. Chen GG, Vlantis AC, Zeng Q, van Hasselt CA (2008) Regulation of cell growth by estrogen signaling and potential targets in thyroid cancer. Curr Cancer Drug Targets 8:367–377
27. Kawabata W, Suzuki T, Moriya T et al (2003) Estrogen receptors (alpha and beta) and 17beta-hydroxysteroid dehydrogenase type 1 and 2 in thyroid disorders: possible in situ estrogen synthesis and actions. Mod Pathol 16:437–444
28. Zeng Q, Chen GG, Vlantis AC, van Hasselt CA (2007) Oestrogen mediates the growth of human thyroid carcinoma cells via an oestrogen receptor-ERK pathway. Cell Prolif 40:921–935
29. Yang CS, Chen L, Lee MJ, Balentine D, Kuo MC, Schantz SP (1998) Blood and urine levels of tea catechins after ingestion of different amounts of green tea by human volunteers. Cancer Epidemiol Biomarkers Prev 7:351–354
30. Kuruto-Niwa R, Inoue S, Ogawa S, Muramatsu M, Nozawa R (2000) Effects of tea catechins on the ERE-regulated estrogenic activity. J Agric Food Chem 48:6355–6361
31. Mukhtar H, Ahmad N (2000) Tea polyphenols: prevention of cancer and optimizing health. Am J Clin Nutr 71:1698S–1702S