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ORIGINAL PAPER

Green tea consumption and risk of hematologic neoplasms: the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study)

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Abstract

Purpose Experimental studies suggested that green tea may have an anticancer effect on hematologic neoplasms. However, few prospective studies have been conducted.

Methods A total of 65,042 individuals aged 40–79 years participated in this study and completed a self-administered questionnaire about their lifestyle and medical history at baseline (1988–1990). Of these, 52,462 individuals living in 24 communities with information on incident hematologic neoplasms available in the cancer registry, who did not have a history of cancer and provided valid information on frequency of green tea consumption, were followed through 2009. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the incidence of hematologic neoplasms according to green tea consumption were analyzed.

Results The incidence of hematologic neoplasms during a median follow-up of 13.3 years was 323. Compared with the never-drinkers of green tea, the multivariate HRs and 95% CIs for total hematologic neoplasms in green tea drinkers of ≤ 2 cups/day, 3–4 cups/day, and ≥ 5 cups/day were 0.65 (0.42–1.00), 0.73 (0.47–1.13), and 0.63 (0.42–0.96), respectively. The association was more prominent for acute myeloid leukemias and follicular lymphomas.

Conclusions The present cohort study suggests a protective effect of green tea against hematologic neoplasms, especially acute myeloid leukemias.

Keywords Epigallocatechin-3-gallate · Hematologic neoplasm · Japan collaborative cohort study for evaluation of cancer risk · Preventive medicine · Green tea · Acute myeloid leukemia

Introduction

Experimental studies have suggested that consumption of green tea may prevent various cancers including hematologic neoplasms [1–3]. Green tea constituents such as epigallocatechin-3-gallate (EGCG) induce apoptosis in a variety of cancer cells including human myeloid leukemia cells [4–6]. EGCG induces apoptosis of acute myeloid leukemia cells by increasing the amount of intracellular reactive oxygen species [6]. However, the epidemiologic evidence is limited and controversial. A previous Japanese cohort study showed that a higher frequency of green tea consumption was associated with a lower risk of hematologic neoplasms [7]. Meanwhile, another Japanese cohort study found no significant association between green tea consumption and the risk of acute myeloid leukemia or myelodysplastic syndromes [8]. Case–control studies conducted in Taiwan [9] and China [10] reported that high intake of green tea was associated with lower risk of leukemias such as myeloid leukemia.

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The incidence of hematologic neoplasms is known to be relatively high among whites and to be relatively low among Asians [11]. Ecologically, tea production in 2013 was 1050 g/person in Asia, 120 g/person in the Americas, and 0.4 g/person in Europe [12]. In this context, we hypothesized that the difference in the incidence of hematologic neoplasms between white and Asian populations may be partly explained by green tea consumption. We used data from a population-based cohort study to examine the association between green tea consumption and risk of mortality from and incidence of hematologic neoplasms and their subtypes among Japanese men and women.

Materials and methods

Study population

The Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risk is a large community-based prospective study, conducted between 1988 and 1990. The details of the JACC study have been reported elsewhere [13]. In brief, a total of 110,585 individuals (46,395 men and 64,190 women), aged 40–79 years and living in 45 communities across Japan, participated in the study and completed self-administered questionnaires about their lifestyles and medical histories of cardiovascular disease and cancer. From these questionnaires, data on frequency of green tea consumption were available for 33,154 men and 46,028 women. We excluded 15 persons who answered that their daily green tea consumption was > 20 cups/day and 1461 persons who had a history of cancer at baseline. Among the remaining 77,706 participants (32,733 men and 44,973 women), we involved 52,462 individuals (21,791 men and 30,671 women) living in 24 communities with information on incident hematologic neoplasms available in the cancer registry. According to the guidelines of the Council for International Organizations of Medical Science, written informed consent to participate in this epidemiologic study was obtained from the participants or community representatives before they completed the questionnaire [14]. The ethics committees of Hokkaido University and the University of Tsukuba approved the study.

Assessment of green tea consumption and other variables

The participants were asked to state their average rate of green tea consumption during the previous year. They could select any of five frequency responses: "almost never," "1–2 cups/month," "1–2 cups/week," "3–4 cups/week," and "almost every day." Participants who selected the response "almost every day" were asked to state their average consumption of green tea in numbers of cups per day. We combined the four categories of consumption (1–2 cups/month, 1–2 cups/week, 3–4 cups/week, and 1–2 cups/day) into the single category ≤ 2 cups/day and classified the categories of consumption as never, < 2 cups/day, 3–4 cups/day, and ≥ 5 cups/day. Regarding reproducibility, the Spearman correlation coefficient between the two questionnaires, administered 1 year apart for 85 participants (8 men and 77 women), was 0.79 for green tea [15]. Regarding validity, the Spearman correlation coefficient between the averages of the two questionnaires and four 3-day dietary records and four 1-week dietary records was 0.47 (25.4 cups and 30.1 cups per week) for green tea [15]. When we restricted the data to the 77 women, the result was essentially the same.

In the baseline questionnaire, we also asked lifestyle questions related to age; sex; height; weight; smoking status; alcohol intake status; frequency of dietary intakes of fish, vegetable, meat, and bean products; and educational status (age of the highest school attainment). Body mass index (BMI) was calculated by dividing the self-reported weight in kilograms by the square of the self-reported height in meters. The average dietary intakes of fish, vegetable, meat, and bean products were evaluated on the basis of the responses regarding food frequency and converted to a daily amount of intake [15].

Follow-up and assessment of hematologic neoplasms

For each participant, person-years of follow-up was calculated from the date of filling out the baseline questionnaire to diagnosis of a neoplasm, death, moving out of the community, or the end of 2009, whichever occurred first; exceptions were made for 4 areas in 1999, four areas in 2003, and 2 areas in 2008. The median follow-up was 13.3 years (range 0.01–21.5 years). The diagnosis of neoplasms was based on a systematic review of the records of local major hospitals and of the population-based cancer registries conducting the follow-up. The investigators conducted a systematic review of the death certificates, all of which were forwarded to the public health center in the area of residency. The mortality data were sent centrally to the Ministry of Health and Welfare, and the underlying causes of death were coded according to the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD10). In Japan, registration of death is legally required and is believed to be followed across the country. Thus, all of the deaths that occurred in the cohort were ascertained by death certificates from a public health center, except for those of participants who died after they had moved from their original community, in which case the participant was censored. The incidence data were coded according to the ICD10. We defined hematologic neoplasms as C810–C969

and D460–D479, according to the ICD10. The cases were further categorized into lymphoid neoplasms (ICD10 codes C810–C889, C900–C903, C910–C919, C947, and D472); myeloid neoplasms (ICD10 codes C920–C944, D460–D471, and D473); leukemia of unspecified cell type (ICD10 codes C950–C959); and other and unspecified malignant neoplasms of lymphoid, and hematopoietic and related tissue (ICD10 codes C960–C969). Lymphoid neoplasms were further categorized into Hodgkin lymphomas (C810–C819) and non-Hodgkin lymphomas (C820–C919, C947, and D472). Non-Hodgkin lymphomas were further categorized into B cell non-Hodgkin lymphomas (C820–C829, C830–C839, C851, C852, C857, C880–C884, C900–C903, C911–C914, C918, and D472); T/NK cell non-Hodgkin lymphomas (C840–C849, C860–C866, C915–C917,and C947); acute lymphoid leukemias (C910); and non-Hodgkin lymphomas, not otherwise specified (C859 and C919). B cell non-Hodgkin lymphoma were further categorized into follicular lymphomas (C820–C829); diffuse large B cell lymphomas (C833); plasma cell neoplasms (C900–C903); and chronic lymphocytic leukemia/small lymphocytic lymphomas (C911, C830). Myeloid neoplasms were further categorized into acute myeloid leukemias (C920, C924–C926, C928, C930, C940, and C942); chronic myeloid leukemias (C921, C922, and C931); monocytic leukemias, unspecified (C939); myelodysplastic syndromes (D460–D469); and chronic myeloproliferative diseases (D471).

Statistical analysis

The age-adjusted means and proportions of potential confounding variables were calculated according to each category of green tea consumption, and the overall difference across the categories was tested by analysis of covariance. Age- and sex-adjusted and area-stratified hazard ratios (HRs) and 95% confidence intervals (CIs) for hematologic neoplasms were calculated in each category of green tea consumption and compared with the never-drinker group by use of the Cox proportional hazards model. In addition, categories of drinkers of ≥ 1 cup/month of green tea (ie, ≤ 2cups/day, 3–4 cups/day, and ≥ 5 cups/day) were pooled into the single category (any drinker), and the HRs and 95% CIs for hematologic neoplasms were calculated. For multivariate analyses, we included the following factors in the models: age (years); sex; smoking status (never, former, and current of 1–19 or ≥ 20 cigarettes/day); body mass index (< 18.5, 18.5–20.0, 20.0–23.0, 23.0–25.0, and ≥ 25.0 kg/m^2); alcohol intake status (never, former, and current < 23, 23 to < 46, 46 to < 69, and ≥ 69 g ethanol/day based on the Japanese traditional volume); fish intake as quintiles of the sum of consumption frequencies of raw fish, boiled fish paste, and dried fish (< 22.1, 22.4–35.2, 35.2–48.0, 48.2–71.7, and ≥ 72.0 g/day); vegetable intake as quintiles of the sum of consumption frequencies of spinach, carrots, tomatoes, cabbage, Chinese cabbage, and edible wild plants (< 51.8, 51.9–80.1, 80.1–102.0, 102.1–139.1, ≥ 139.1 g/day); meat intake as quintiles of the sum of consumption frequencies of beef, pork, processed meat, chicken, and liver (< 14.2, 14.3–23.5, 23.5–30.4, 30.4–41.9, ≥ 42.0 g/day); bean product intake as quintiles of the sum of consumption frequencies of boiled beans and soybean curd (< 14.8, 20.0–30.0, 32.0–32.8, 38.6–60.0, ≥ 62.0 g/day); energy intake (< 1171, 1172–1378, 1378–1574, 1574–1859, ≥ 1859 kcal/day); and educational status (education until 18 or ≥ 19 years of age). Missing data were allocated to another category for each covariate. The linear trend of HRs across the average daily consumption of green tea, converting the items of "almost-never" to 0, "1–2 cups/month" to 0.05, "1–2 cups/week" to 0.214, "3–4 cups/week" to 0.5, and "almost every day" to the number of cups of green tea consumed/day, was tested using the Cox proportional hazards model. To exclude the impact of reverse causation, we also performed the analyses excluding cases occurring 5 and 10 years from baseline. We also performed the analyses excluding death certificate-only cases. The proportional hazards assumption was tested using time by grean tea consumption interaction terms and was not violated for each outcome. All analyses were conducted using the SAS statistical package, version 9.4. The p values for the statistical tests were two-tailed, and values < 0.05 were considered significant.

Code availability

The computer code used to generate results that were central to this paper's conclusions is available from the corresponding author.

Results

Participant characteristics

The baseline characteristics of the study cohort according to green tea consumption are shown in Table 1. Both men and women with higher green tea consumption were older than those who did not drink it. As green tea consumption increased, the proportion of current smokers was higher in men but lower in women. The proportions of current alcohol drinker and mean body mass index did not differ markedly by green tea consumption in either men or women. Higher educational attainment was associated with higher consumption of green tea in both men and women. The mean consumptions of fish, vegetables, meat, beans, and energy intake were positively associated with green tea consumption in both men and women.

Table 1 Baseline characteristics according to green tea consumption in 21,791 men and 30,671 women

	Green tea consumption, cups/day				
	Never	≤ 2cups/day	3–4 cups/day	≥ 5 cups/day	*p* value
Men, n	1539	5552	5189	9511	
Age at baseline (years)	57.4	55.7	57.6	58.5	< 0.0001
Current smokers (%)	49.4	52.7	50.4	54.1	< 0.0001
Current drinkers (%)	70.2	76.0	76.8	74.5	< 0.0001
Body mass index (kg/m^2)	22.6	22.6	22.6	22.6	< 0.0001
College or higher education (%)	17.0	21.5	21.1	19.3	0.001
Fish intake (g/day)	41.8	45.9	45.4	48.9	< 0.0001
Vegetable intake (g/day)	82.6	87.7	89.0	94.4	< 0.0001
Meat intake (g/day)	27.0	29.0	28.9	30.0	< 0.0001
Bean product intake (g/day)	33.8	35.3	35.7	36.8	< 0.0001
Energy intake (kcal/day)	1596	1657	1668	1783	< 0.0001
Women, n	2620	7344	7923	12,784	
Age at baseline (years)	57.5	56.3	56.3	58.6	< 0.0001
Current smokers (%)	6.6	6.1	4.3	5.2	< 0.0001
Current drinkers (%)	21.6	26.7	25.2	23.3	< 0.0001
Body mass index (kg/m^2)	22.8	22.8	22.6	22.8	< 0.0001
College or higher education (%)	9.5	11.1	11.8	10.9	< 0.0001
Fish intake (g/day)	43.4	45.2	46.2	49.7	< 0.0001
Vegetable intake (g/day)	96.2	99.1	102.2	106.2	< 0.0001
Meat intake (g/day)	27.7	29.5	30.6	31.3	< 0.0001
Bean product intake (g/day)	37.8	39.8	40.1	41.8	< 0.0001
Energy intake (kcal/day)	1313	1359	1394	1447	< 0.0001

Green tea consumption and incidence of hematologic neoplasms

In the 52,462 participants, during a median follow-up of 13.3 years, there were 323 incident hematologic neoplasms: 219 lymphoid neoplasms (8 Hodgkin lymphomas, 211 non-Hodgkin lymphomas); 95 myeloid neoplasms (48 acute myeloid leukemias, 10 chronic myeloid leukemias, 1 monocytic leukemia, unspecified, 34 myelodysplastic syndromes, and 2 chronic myeloproliferative diseases); 6 leukemias of unspecified cell type; and 3 other and unspecified malignant neoplasms of lymphoid and hematopoietic and related tissue. Among the non-Hodgkin lynphomas, there were 108 B cell non-Hodgkin lymphomas; 10T/NK cell non-Hodgkin lymphomas; 5 acute lymphoid leukemias; and 88 non-Hodgkin lymphomas, not otherwise specified. B cell non-Hodgkin lymphomas included 10 follicular lymphomas, 16 diffuse large B cell lymphomas, 67 plasma cell neoplasms, 6 chronic lympocytic leukemia/small lymphocytic lymphomas, and 9 other B cell non-Hodgkin lymphomas. The frequency of green tea consumption was nonlinearly and inversely associated with risk of total hematologic neoplasms (Table 2). The multivariate HR (95% CI) of all hematologic neoplasms was 0.63 (0.42–0.96) for persons with ≥ 5 cups/day of green tea consumption. The multivariate HR (95% CI) for any green tea drinkers versus never-drinkers was 0.66 (0.45–0.98). Such an association was prominent for acute myeloid leukemias and follicular lymphomas. As for acute myeloid leukemias, follicular lymphomas, and chronic lympocytic leukemia/small lymphocytic lymphomas, the risks were lower in any drinkers. No such association was found for plasma cell neoplasms.

Similar results were observed after the exclusion of cases that occurred 5 and 10 years from baseline: the multivariate HRs for incident total hematologic neoplasms and acute myeloid leukemias for persons who drank ≥5 cups/day of green tea compared with never-drinkers were 0.51 (0.31–0.84) and 0.31 (0.11–0.89), respectively, when early 5-year incidence was excluded, and 0.51 (0.28–0.94) and 0.37 (0.09–1.47), respectively, when early 10-year incidence was excluded. Similar results were observed after the exclusion of death certificate-only cases; the multivariate HRs for incident total hematologic neoplasms and acute myeloid leukemias for persons who drank ≥ 5 cups/day green tea compared with never-drinkers were 0.64 (0.41–1.01) and 0.36 (0.14–0.95), respectively. We could not evaluate follicular lymphomas in the same manner because of the small numbers of cases.

Table 2 Age- and sex-adjusted and area-stratified multivariate hazard ratios and 95% confidence intervals of incidence of hematologic malignancies according to green tea consumption

	Green tea consumption, cups/day					
	Never	≤ 2cups/day	3–4 cups/day	≥ 5 cups/day	*p* value for trend	Any drinker[b]
Person-years	50,853	166,358	158,215	294,250		618,823
Number of persons	4,159	12,896	13,112	22,295		48,303
Total hematologic neoplasms						
No. of cases	31	69	78	145		292
Age- and sex-adjusted, area-stratified HR (95% CI)	1.0	0.65 (0.42–0.99)	0.73 (0.47–1.13)	0.63 (0.42–0.96)	0.63	0.66 (0.45–0.98)
Multivariate[a] HR (95% CI)	1.0	0.65 (0.42–1.00)	0.73 (0.47–1.13)	0.63 (0.42–0.96)	0.64	0.66 (0.45–0.98)
Lymphoid neoplasms						
No. of cases	19	49	56	95		200
Age- and sex-adjusted, area-stratified HR (95% CI)	1.0	0.78 (0.46–1.34)	0.86 (0.50–1.48)	0.69 (0.41–1.16)	0.69	0.76 (0.47–1.25)
Multivariate[a] HR (95% CI)	1.0	0.79 (0.46–1.35)	0.86 (0.50–1.49)	0.70 (0.41–1.19)	0.77	0.77 (0.47–1.27)
Hodgkin lymphomas						
No. of cases	0	3	2	3		8
Age- and sex-adjusted, area-stratified HR (95% CI)	–	–	–	–	–	–
Multivariate[a] HR (95% CI)	–	–	–	–	–	–
Non-Hodgkin lymphomas						
No. of cases	19	46	54	92		192
Age- and sex-adjusted, area-stratified HR (95%CI)	1.0	0.74 (0.43–1.28)	0.85 (0.49–1.46)	0.68 (0.40–1.16)	0.78	0.75 (0.46–1.22)
Multivariate[a] HR (95% CI)	1.0	0.75 (0.44–1.30)	0.85 (0.49–1.47)	0.70 (0.41–1.19)	0.86	0.76 (0.46–1.24)
B cell non-Hodgkin lymphomas						
No. of cases	10	27	25	46		98
Age- and sex-adjusted, area-stratified HR (95% CI)	1.0	0.76 (0.36–1.58)	0.69 (0.32–1.48)	0.59 (0.29–1.23)	0.52	0.68 (0.34–1.34)
Multivariate[a] HR (95% CI)	1.0	0.74 (0.35–1.54)	0.66 (0.31–1.42)	0.58 (0.28–1.20)	0.51	0.65 (0.33–1.30)
T/NK cell non-Hodgkin lymphomas						
No. of cases	1	1	3	5		9
Age- and sex-adjusted, area-stratified HR (95% CI)	1.0	0.32 (0.02–5.18)	0.97 (0.10–9.71)	0.73 (0.08–6.72)	0.61	0.66 (0.08–5.45)
Multivariate[a] HR (95% CI)	1.0	0.24 (0.01–4.86)	1.12 (0.09–13.32)	0.90 (0.08–9.87)	0.91	0.70 (0.08–6.62)
Non-Hodgkin lymphomas, NOS						
No. of cases	8	17	25	38		80
Age- and sex-adjusted, area-stratified HR (95% CI)	1.0	0.72 (0.31–1.69)	0.96 (0.42–2.20)	0.71 (0.32–1.60)	0.84	0.78 (0.37–1.67)
Multivariate[a] HR (95% CI)	1.0	0.76 (0.32–1.79)	1.01 (0.44–2.32)	0.76 (0.34–1.73)	0.72	0.83 (0.39–1.78)
Acute lymphoid leukemias						
No. of cases	0	1	1	3		5
Age- and sex-adjusted, area-stratified HR (95% CI)	-	–	–	–	–	–
Multivariate[a] HR (95% CI)	–	–	–	–	–	–
Follicular lymphomas						
No. of cases	2	2	2	4		8
Age- and sex-adjusted, area-stratified HR (95% CI)	1.0	0.19 (0.03–1.38)	0.22 (0.03–1.71)	0.19 (0.03–1.21)	0.69	0.20 (0.04–1.01)
Multivariate[a] HR (95% CI)	1.0	0.16 (0.02–1.27)	0.15 (0.02–1.32)	0.14 (0.02–0.99)	0.71	0.15 (0.03–0.88)
Diffuse large B cell lymphomas						
No. of cases	2	4	4	6		14

Table 2 (continued)

	Green tea consumption, cups/day					
	Never	≤ 2cups/day	3–4 cups/day	≥ 5 cups/day	*p* value for trend	Any drinker[b]
Age- and sex-adjusted, area-stratified HR (95% CI)	1.0	0.53 (0.10–2.98)	0.62 (0.11–3.59)	0.47 (0.09–2.49)	0.90	0.53 (0.12–2.41)
Multivariate[a] HR (95% CI)	1.0	0.53 (0.09–3.09)	0.71 (0.12–4.27)	0.49 (0.09–2.71)	0.91	0.55 (0.12–2.62)
Plasma cell neoplasms						
No. of cases	4	19	15	29		63
Age- and sex-adjusted, area-stratified HR (95% CI)	1.0	1.47 (0.49–4.39)	1.12 (0.36–3.50)	1.03 (0.34–3.10)	0.39	1.22 (0.43–3.48)
Multivariate[a] HR (95% CI)	1.0	1.36 (0.46–4.08)	1.03 (0.33–3.22)	0.95 (0.31–2.87)	0.33	1.13 (0.39–3.22)
Chronic lympocytic leukemia/small lymphocytic lymphomas						
No. of cases	2	0	0	4		4
Age- and sex-adjusted, area-stratified HR (95% CI)	1.0	–	–	–	–	0.12 (0.02–0.81)
Multivariate[a] HR (95% CI)	1.0	–	–	–	–	0.09 (0.01–0.96)
Myeloid neoplasms						
No. of cases	10	19	20	46		85
Age- and sex-adjusted, area-stratified HR (95% CI)	1.0	0.50 (0.23–1.08)	0.58 (0.26–1.30)	0.59 (0.28–1.25)	0.91	0.55 (0.27–1.10)
Multivariate[a] HR (95% CI)	1.0	0.49 (0.23–1.08)	0.58 (0.26–1.30)	0.58 (0.27–1.24)	0.83	0.54 (0.27–1.10)
Acute myeloid leukemias						
No. of cases	7	9	10	22		41
Age- and sex-adjusted, area-stratified HR (95% CI)	1.0	0.32 (0.12–0.89)	0.35 (0.13–0.98)	0.35 (0.14–0.90)	0.41	0.34 (0.15–0.81)
Multivariate[a] HR (95% CI)	1.0	0.33 (0.12–0.92)	0.37 (0.13–1.04)	0.35 (0.14–0.92)	0.36	0.35 (0.15–0.84)
Chronic myeloid leukemias						
No. of cases	0	2	3	5		10
Age- and sex-adjusted, area-stratified HR (95% CI)	–	–	–	–	–	–
Multivariate[a] HR (95% CI)	–	–	–	–	–	–
Myelodysplastic syndromes						
No. of cases	3	8	6	17		31
Age- and sex-adjusted, area-stratified HR (95% CI)	1.0	0.75 (0.20–2.87)	0.69 (0.16–2.99)	0.86 (0.23–3.28)	0.89	0.78 (0.22–2.68)
Multivariate[a] HR (95% CI)	1.0	0.69 (0.18–2.68)	0.63 (0.15–2.75)	0.81 (0.21–3.14)	0.86	0.72 (0.21–2.50)

[1]Multivariate model included age, sex, education level, cigarette smoking, alcohol intake, body mass index, fish intake, vegetable intake, meat intake, bean products intake, bean products intake, and energy intake

[2]Categories of green tea consumers of ≥ 1 cup/month of green tea (i.e., 1cup/month-2cups/day, 3–4 cups/day, and ≥ 5 cups/day)

Discussion

In this large prospective study of Japanese men and women, the frequency of green tea consumption was inversely associated with the incidence of hematologic neoplasms, more specifically, with the incidence of acute myeloid leukemias and follicular lymphomas. The exclusion of cases that occurred within 5 and 10 years from baseline did not largely alter the overall results, nor did the exclusion of death certificate-only cases.

Our results extend the evidence obtained from several previous studies of Asian populations. Two case–control studies from China and Taiwan showed significant inverse associations between green tea consumption and leukemia [9, 10]. A previous cohort study of 51,253 Japanese (Ohsaki Study) showed that persons who drank ≥ 5 cups of green tea a day had a lower risk of incident hematologic neoplasms (HR and 95% CI 0.58, 0.37–0.89) compared to those who drank < 1 cup/day, with a threshold of 5 cups/day after adjustment for age, sex, educational level, cigarette smoking, alcohol consumption, fish consumption, and soybean products consumption [7]. In that study, the inverse association was observed mainly for lymphoid neoplasms, not for myeloid neoplasms, although the neoplasms were not

classified into preciser subtypes. Another cohort study of 95,807 Japanese (JPHC Study) with 85 incident acute myeloid leukemias and 70 incident myelodysplastic syndromes did not find any associations between green tea consumption and any of the outcomes [8]. Unlike our study, neither the Ohsaki Study [7] nor the JPHC Study [8] distinguished never-drinkers of green tea from the < 1 cup/day category, and this, as well as the lower statistical power, may be a major reason why those studies did not detect an association between green tea consumption and risk of acute myeloid leukemias.

We consider that the anticancer effects of EGCG, a component of green tea, could explain our results, although there is poor evidence for the bioavailability of EGCG with < 1 cup/day of green tea consumption. A possible mechanism could be that EGCG induces apoptosis of cancer cells. Nakazato et al. showed that EGCG induced apoptosis in retinoic acid-resistant acute promyelocytic leukemia and acute myeloid leukemia and that reactive oxygen species were key mediators of apoptosis induced by EGCG in myeloid leukemic cells [6]. Notably, the apoptosis was observed in myeloperoxidase-positive leukemic cells, ie, myeloid leukemia cells, but not in myeloperoxidase-negative leukemic cells [16]. Another possible mechanism could be that EGCG inhibits cancer cell proliferation through a cell-surface receptor. Tachibana et al. showed that the growth of cells transfected with the 67-kDa laminin receptor was inhibited when the cells were treated with 0.1 μmol/L (equivalent to 2–3 cups of tea [17]) or 1.0 μmol/L (equivalent to 7–9 cups of tea [17]) EGCG [18]. This growth-suppressive effect was completely eliminated when the cells were treated with anti-67-kDa laminin receptor antibody before the addition of EGCG [17]. Montuori et al. reported that 42% of acute myeloid leukemia patients had enhanced expression of the 67-kDa laminin receptor [19]. These lines of biological evidence support our results and may explain the mechanisms of the observed association between green tea and hematologic malignancies, especially acute myeloid leukemias.

Our study has several limitations. First, we did not have enough information related to occupational exposures, such as ionizing radiation and benzene, which may affect the risk of hematologic neoplasms [20]. We believe that the impact of these exposures should not be very large at the population level. To minimize this impact, we adjusted for potential confounders in the statistical models, but the residual confounding by unmeasured variables should still be considered. Second, we did not have information on several risk factors for hematologic neoplasms, such as family history of hematologic neoplasms, past history of infection, immunologic disorders and chemotherapy, although these may be less likely to be correlated with green tea consumption. Third, there might be a measurement error derived from dietary questionnaires. However, the evaluation of dietary factors by questionnaires was validated by a previous study [15]. Fourth, we only have single measurements of dietary and lifestyle habits, which may change over time. Fifth, confounding by dietary components other than green tea should be considered, although we minimized this confounding by adjusting for as many dietary factors as possible. Sixth, our assessment of hematologic neoplasms was based on hospital records and death ICD codes. Although there is no direct evidence of the validity of ICD codes for hematologic neoplasms, the codes seem quite specific, but probably not sensitive enough to capture hematologic neoplasms. Thus, the approach used in the current study might have led to an underestimation of hematologic neoplasm events. Seventh, the quality of the cancer registry in the present study was not high enough in terms of hematologic neoplasms: the proportions of death certificate-only incident cases among all hematologic neoplasms and acute myeloid leukemias were 15% and 4%, respectively. However, the results obtained after the exclusion of the death certificate-only incident cases did not largely alter the overall results. Moreover, the accuracy of our cancer registry is the highest compared to those of previous reports [7, 8]. Eighth, the number of cases of hematologic neoplasms in this cohort was modest. However, this is the largest prospective study that has reported an association between green tea and hematologic neoplasms.

In conclusion, the present cohort study suggests a protective effect of green tea against hematologic neoplasms, especially acute myeloid leukemias.

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Compliance with ethical standards

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

Appendix: study group membership list

Current members of the JACC Study Group include: Dr. Akiko Tamakoshi (present chairperson of the study group), Hokkaido University Graduate School of Medicine; Dr. Mitsuru Mori, Sapporo Medical University School of Medicine; Dr. Yoshihiro Kaneko, Akita University Graduate School of Medicine; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine; Dr. Yosikazu Nakamura, Jichi Medical School; Dr. Hiroyasu Iso, Osaka University School of Medicine; Dr. Kazumasa Yamagishi, Faculty of Medicine, University of Tsukuba; Dr. Haruo Mikami, Chiba Cancer Center; Dr. Michiko Kurosawa, Juntendo University School of Medicine; Dr. Yoshiharu Hoshiyama, Yokohama Soei University; Dr. Naohito Tanabe, University of Niigata Prefecture; Dr. Koji Tamakoshi, Nagoya University Graduate School of Health Science; Dr. Kenji Wakai, Nagoya University Graduate School of Medicine; Dr. Shinkan Tokudome, National Institute of Health and Nutrition; Dr. Koji Suzuki, Fujita Health University School of Health Sciences; Drs. Shuji Hashimoto and Hiroshi Yatsuya, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine; Dr. Yasuhiko Wada, Faculty of Nutrition, University of Kochi; Dr. Takashi Kawamura, Kyoto University Health Service; Dr. Yoshiyuki Watanabe, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Kotaro Ozasa, Radiation Effects Research Foundation; Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Chigusa Date, School of Human Science and Environment, University of Hyogo; Dr. Kiyomi Sakata, Iwate Medical University; Dr. Yoichi Kurozawa, Tottori University Faculty of Medicine; Drs. Takesumi Yoshimura and Yoshihisa Fujino, University of Occupational and Environmental Health; Dr. Akira Shibata, Kurume University; Dr. Naoyuki Okamoto, Kanagawa Cancer Center; and Dr. Hideo Shio, Long-Term Care Health Facility Caretown Minamikusatu, Shiga.

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