

RESEARCH ARTICLE

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# Association of Green Tea Consumption and the Risk of Liver Cancer Incidence among Japanese Adults

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## Abstract

**Background:** The association between green tea consumption and the risk of liver cancer has been reported inconsistently. This study aimed to investigate this association in a large, prospective cohort study of Japanese adults. **Methods:** The Japan Collaborative Cohort (JACC) Study included 41,999 participants (18,205 men and 23,794 women) aged 40–79 years, free from liver cancer at baseline between 1988 and 1990. Validated self-administered questionnaires were used to assess individual socio-demographics, medical history, and lifestyles. Participants were then followed for liver cancer incidence until the end of 2009. Cox proportional hazard models were utilized to calculate hazard ratios (HRs) with 95% confidence intervals (95% CIs) of liver cancer based on the frequency of green tea consumption of <1 cup (reference), 2–4, 5–6, and  $\geq 7$  cups/day, after adjusting for potential confounding factors, including age, sex, study area, education, histories of diabetes, liver diseases, and gallbladder disease, body mass index, drinking status, smoking status, coffee consumption, sports participation, and walking. Major confounders, including coffee consumption, drinking status, and a history of liver disease, were further stratified in the analysis. Population-attributable fractions (PAFs) of liver cancer was also calculated based on green tea consumption. **Results:** Green tea consumption was associated with a trend of lower risk of liver cancer with the multivariable HR (95% CI) of 0.87 (0.61–1.23) for 2–4 cups/day, 0.87 (0.61–1.25) for 5–6 cups/day, and 0.61 (0.40–0.95) for  $\geq 7$  cups/day, compared to <1 cup/day ( $p$  for trend = 0.029). The inverse association was statistically significant for men, people without a history of liver diseases other than cancer, and current drinkers. The multivariable PAF (95%CI) for  $\geq 7$  cups/day was 7.1% (0.9–11.4). **Conclusion:** Green tea consumption was associated with a lower risk of liver cancer in Japanese adults in a dose-response manner, ranging from <1 cup/day to  $\geq 7$  cups/day.

**Keywords:** Green Tea- Liver Cancer; Alcohol Drinking; Liver Diseases; Cohort Studies

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## Introduction

Liver cancer is the sixth most prevalent cancer and the third leading cause of cancer-related deaths globally in 2020 [1]. It is the eighth most prevalent cancer in Asia [2] and caused the seventh most incident cases and the fifth most death cases in Japan in 2022 [3].

Hepatitis virus (mainly B and C) infection is established as a causal factor of liver cancer; however, the contribution of dietary habits has been largely unknown, except for the adverse effects of aflatoxin-contaminated foods, heavy drinking, and a potential protective effect of coffee consumption [4]. Green tea exhibits strong antioxidant properties, primarily through polyphenols, particularly green tea catechins, as well as manganese and several vitamins, which may protect against liver cancer

[5, 6] and other types of cancer [7].

A previous meta-analysis of nine prospective cohort studies in Japan, China, and Singapore revealed that green tea intake (high versus low or no intake) was associated with a reduced risk of liver cancer, reporting a summary relative risk of 0.88 (95% confidence interval [CI]: 0.81–0.97) [6]. However, only two out of the nine studies [8, 9] showed a statistically significant association. Furthermore, only one out of the nine studies, the Osaki Cohort study, adjusted for coffee consumption [9], which has been recognized as a potential protective factor for liver disease [4].

The Ohsaki Cohort study of Japanese adults aged 40–79 years, revealing a 40–50% lower risk of liver cancer associated with green tea consumption of  $\geq 5$  cups/day compared with <1 cup/day [9]. Subsequent analysis in a

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previous Japan Collaborative Cohort (JACC) study that investigated the association between dietary manganese intake and the risk of liver cancer revealed no association between green tea consumption and liver cancer when using the daily intake categories of <1, 1–4, and ≥5 cups/day [10]. However, these results were derived from a preliminary investigation, emphasizing the need for further study on green tea intake as a significant component of the Japanese diet. In particular, the inconsistent results related to potential confounders or effect modification, sex difference, coffee consumption, drinking behavior, and a history of liver diseases [4] should be considered. Thus, we made extensive adjustments for potential confounders, including socioeconomic factors (educational attainment), comorbidities (diabetes and gallbladder disease), body mass index (BMI), and lifestyle factors (participation in sports and walking). Furthermore, we categorized the high green tea intake into 5–6 and ≥7 cups/day and investigated their associations with liver cancer risk, stratified by potential confounders that could modify the associations.

## Materials and Methods

### Study design

This investigation is embedded in the JACC study for cancer risk evaluation. The methodology of the JACC study has been reported elsewhere [11]. In brief, the JACC study is a large community-based cohort study that enrolled 110,585 individuals aged 40–79 years (46,395

men and 64,190 women) from 45 areas across Japan between 1988 and 1990. Participants were instructed to complete a validated, self-administered questionnaire to gather comprehensive information on individual socio-demographics (e.g., education, occupation), medical history (e.g., complications, treatment, surgery), anthropometrics (e.g., height, weight), lifestyle (e.g., smoking, drinking, physical activity), and dietary intake. We first included 53,094 participants who lived in the 22 areas where a cancer surveillance registry was available. We then excluded 933 subjects who reported a history of any cancer and 10,162 subjects who did not provide valid information on green tea intake. Eventually, 41,999 participants were involved at the baseline. They were followed up for cancer incidence until the end of 2000 and 2003 in two areas and until the end of 1997 in four areas, 2002 in eight areas, 2006 in two areas, 2008 in two areas, and 2009 in four areas (Figure 1).

The institutional review boards of Hokkaido University (approval number 14-044) and the University of Osaka (approval number 14285) approved this study, which was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Informed consent was obtained from participants or their community leaders asking their will to participate to the JACC study.

### Assessment of green tea consumption

Participants were instructed to report their frequency of green tea drinking based on the selection of “never,”

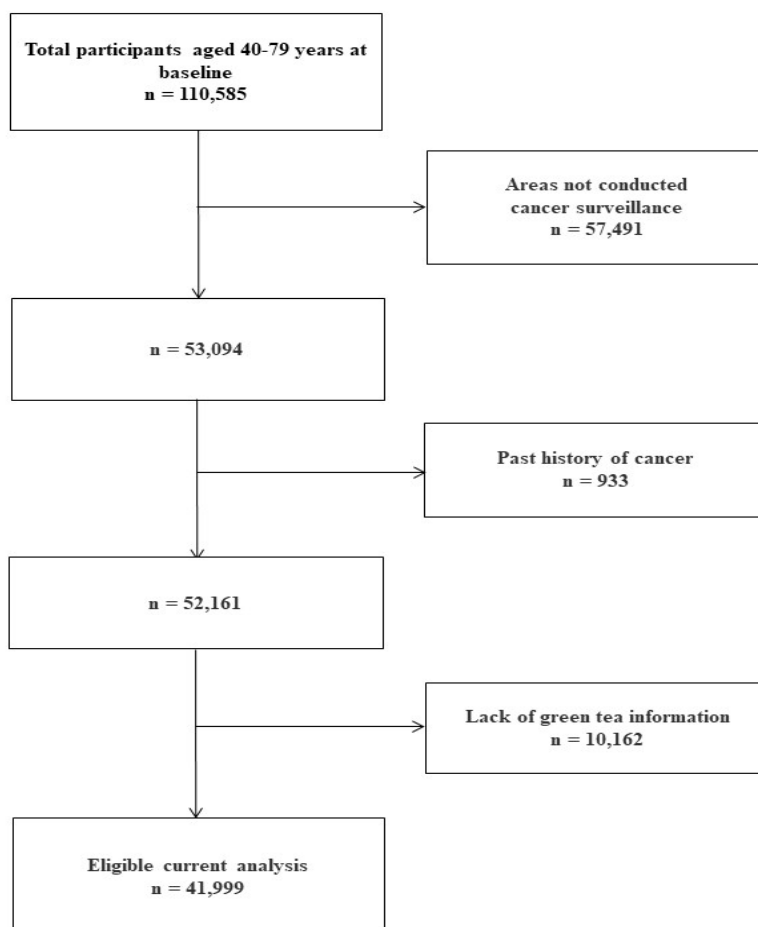


Figure 1. Flow Chart of Participant Recruitment

“1–2 cups per month,” “1–2 cups per week,” “3–4 cups per week,” and “almost every day.” Those who responded “almost every day” were further asked about the amount they consumed daily. More than half of the participants consumed green tea daily; therefore, we defined the lowest intake category as 0–1 cup/day. To examine the threshold of green tea intake associated with a significant benefit, we further categorized the high intake into 5–6 and  $\geq 7$  cups/day. In comparison, the  $\geq 5$  cups/day cutoff was used in the Ohsaki study [9] and JACC study [10]. The final categories of green tea intake were 0–1, 2–4, 5–6, and  $\geq 7$  cups/day. According to a 1-year follow-up survey of 85 participants, the Spearman correlation coefficient for green tea intake between the baseline and 1-year follow-up questionnaires was 0.62, indicating good reproducibility of the dietary assessment for green tea consumption [12].

#### *Follow-up and assessment of liver cancer*

Each regional research center conducted a systematic review of population-based cancer registries, hospital records, and death certificates, with permission from the relevant municipalities, to monitor cancer incidence among participants on an annual basis. Furthermore, the investigators, in collaboration with the local government office, verified the move-out date from the study areas annually or biannually. The outcome includes the incidence of liver cancer coded as C22 according to the 10th Revision of the International Statistical Classification of Diseases (ICD-10) and Related Health Problems, including malignant neoplasm of the liver and intrahepatic bile ducts. Individual person-years of follow-up were calculated from the return date of the baseline questionnaire to the date of a liver cancer diagnosis, death, moving out of the community, or loss to follow-up, or the end of the study, whichever came first.

#### *Confounding variables*

Potential confounding variables were assessed in the baseline survey, including age, sex, study areas, educational status (the age when attaining the highest diploma:  $<16$  versus  $\geq 16$  years), histories of diabetes (no or yes), liver diseases, and gallbladder disease (no or yes), BMI categories ( $<18.5$ ,  $18.5$ – $22.9$ ,  $23.0$ – $24.9$ , and  $\geq 25.0$  kg/m<sup>2</sup>), drinking status (never, former, and current), smoking status (never, former, and current), coffee consumption ( $<1$  cup/month, 1 cup/month to 4 cups/week, and  $\geq 5$  cups/week), frequencies of sport participation ( $<3$  versus  $\geq 3$  h/week) and walking ( $<30$  versus  $\geq 30$  min/day).

#### *Statistical analysis*

Baseline characteristics according to green tea consumption categories were presented as the mean for continuous variables or proportions for categorical variables. The Cox proportional hazard model calculated the hazard ratio (HR) and its 95% CI of incident liver cancer based on green tea consumption, referencing the lowest intake. Apart from the age- and sex-adjusted model, the multivariable model was further adjusted for study areas, education, histories of diabetes, liver diseases, and gallbladder disease, BMI, drinking habits,

smoking status, coffee consumption, and frequencies of sports participation and walking. Because the proportion of missing values in all selected covariates were generally small (all  $\leq 9\%$ ), a dummy variable was employed for each covariate to address its missing value, including in the analysis models using the indicator method [13]. We assessed the p-for-linearities by presenting the median green tea consumption for each category and included these means in the models as a continuous variable, and then tested their statistical significance for the trend. We conducted the stratified analysis by factors that may modify the association between green tea intake and the risk of liver cancer, such as sex (men or women), a history of liver diseases (no or yes), coffee consumption ( $<1$  cup per month,  $\geq 1$  cup/month to 4 cups/week, or  $\geq 5$  cups/week), and drinking status (never, former, or current). The interaction was assessed using the cross-product terms of the green tea categories and the stratified variables. We calculated the population-attributable fraction (PAF) of liver cancer according to green tea consumption [14]. Furthermore, we conducted a step-by-step validation to determine which methodological differences contributed to the discrepancies between our results and those of the previous JACC study [10]. The data underlying the findings of the current study are not publicly available. Requests for data availability should be directed to the JACC study committee.

SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for data analyses. Two-tailed p-values of  $<0.05$  indicated statistical significance for statistical tests.

## **Results**

Table 1 presents the baseline characteristics according to the green tea consumption category. As the frequency of green tea consumption was higher, participants tended to be older and more likely to engage in sports and walk more frequently. The frequency of green tea consumption was not correlated with education, a history of gallbladder disease, drinking status, smoking status, coffee consumption, or frequency of sports participation. During a median of 17.8 years of follow-up, 251 liver cancer cases (151 men and 100 women) were recorded.

Table 2 presents the HRs (95% CIs) of liver cancer according to the green tea consumption category. The frequency of green tea consumption was inversely associated with the risk of liver cancer in a dose-response fashion. The multivariable HRs were 0.87 (0.61–1.23) for 2–4 cups/day, 0.87 (0.61–1.25) for 5–6 cups/day, and 0.61 (0.40–0.95) for  $\geq 7$  cups/day compared to less than 1 cup/day (p for trend = 0.029).

As shown in Table 3, an inverse association between green tea consumption and liver cancer risk was observed among men, people without a history of liver diseases, and current drinkers, but not among women, people with a history of liver diseases, and non-current drinkers, albeit with no significant interaction. The higher HR in the multivariable model for former drinkers who consumed 2–4 cups of green tea per day was partly due to the higher proportion of a history of liver diseases: 14.4% in former versus 4.5% in never drinkers and 5.4% in current drinkers

Table 1. Baseline Characteristics According to Green Tea Consumption

	Green tea consumption (cups/day)				Total
	0-1	2-4	5-6	≥7	
No. at risk	9,675 (23.0)	13,275 (31.6)	11,879 (28.3)	7,170 (17.1)	41,999 (100.0)
Mean green tea intake, cups/day	0.2 (0.4)	2.9 (0.7)	5.4 (0.5)	9.2 (1.2)	4.1 (3.1)
Age, years (SD)	55.0 (10.3)	55.5 (10.3)	57.8 (10.0)	58.5 (9.7)	56.5 (10.2)
Men, n (%)	4,130 (42.7)	5,729 (43.2)	5,020 (42.3)	3,326 (46.4)	18,205 (43.4)
Education, n (%)					
< 16 years	2,940 (30.4)	3,980 (30.0)	4,007 (33.7)	2,334 (32.6)	13,261 (31.6)
≥ 16 years	5,248 (54.2)	8,327 (62.7)	7,083 (59.6)	4,312 (60.1)	24,970 (59.5)
Missing	1,487 (15.4)	968 (7.3)	789 (6.6)	524 (7.3)	3,768 (9.0)
History of diabetes, n (%)	402 (4.2)	506 (3.8)	467 (3.9)	272 (3.8)	1,647 (3.9)
History of liver diseases, n (%)	591 (6.1)	607 (4.6)	539 (4.5)	330 (4.6)	2,067 (4.9)
History of gallbladder diseases, n (%)	395 (4.1)	476 (3.6)	459 (3.9)	308 (4.3)	1,638 (3.9)
Body mass index (kg/m <sup>2</sup> ), n (%)					
<18.5	554 (5.7)	728 (5.5)	637 (5.4)	423 (5.9)	2,342 (5.6)
18.5-24.9	6,632 (68.6)	9,466 (71.3)	8,362 (70.4)	5,075 (70.8)	29,535 (70.3)
≥25.0	2,007 (20.7)	2,401 (18.1)	2,287 (19.3)	1,355 (18.9)	8,050 (19.2)
Missing	482 (5.0)	680 (5.1)	593 (5.0)	317 (4.4)	2,072 (4.9)
Drinking status, n (%)					
Never	4,646 (48.0)	6,472 (48.8)	6,040 (50.9)	3,425 (47.8)	20,583 (49.0)
Former	380 (3.9)	384 (2.9)	373 (3.1)	270 (3.8)	1,407 (3.4)
Current	4,128 (42.7)	5,837 (44.0)	4,921 (41.4)	3,052 (42.6)	17,938 (42.7)
Missing	521 (5.4)	582 (4.4)	545 (4.6)	423 (5.9)	2,071 (4.9)
Smoking status, n (%)					
Never	5,658 (58.5)	7,969 (60.0)	7,118 (59.9)	3,888 (54.2)	24,633 (58.7)
Former	963 (10.0)	1,430 (10.8)	1,309 (11.0)	867 (12.1)	4,569 (10.9)
Current	2,517 (26.0)	3,208 (24.2)	2,825 (23.8)	1,990 (27.8)	10,540 (25.1)
Missing	537 (5.6)	668 (5.0)	627 (5.3)	425 (5.9)	2,257 (5.4)
Coffee consumption category, n (%)					
<1 cup/month	1,784 (18.4)	1,747 (13.2)	1,925 (16.2)	1,264 (17.6)	6,720 (16.0)
≥1 cup/month to 4 cups/week	1,799 (18.6)	2,115 (15.9)	2,220 (18.7)	1,305 (18.2)	7,439 (17.7)
≥5 cups/week	5,967 (61.7)	9,293 (70.0)	7,646 (64.4)	4,532 (63.2)	27,438 (65.3)
Missing	125 (1.3)	120 (0.9)	88 (0.7)	69 (1.0)	402 (1.0)
Sports frequency, n (%)					
Almost never	7,020 (72.6)	8,885 (66.9)	7,973 (67.1)	4,839 (67.5)	28,717 (68.4)
< 3 hours/week	1,300 (13.4)	2,239 (16.9)	1,841 (15.5)	1,045 (14.6)	6,425 (15.3)
≥ 3 hours/week	889 (9.2)	1,458 (11.0)	1,392 (11.7)	816 (11.4)	4,555 (10.9)
Missing	466 (4.8)	693 (5.2)	673 (5.7)	470 (6.6)	2,302 (5.5)
Walking frequency, n (%)					
< 30 minutes/day	2,512 (26.0)	3,925 (29.6)	3,237 (27.3)	1,754 (24.5)	11,428 (27.2)
≥ 30 minutes/day	5,893 (60.9)	8,778 (66.1)	8,073 (68.0)	5,014 (69.9)	27,758 (66.1)
Missing	1,270 (13.1)	572 (4.3)	569 (4.8)	402 (5.6)	2,813 (6.7)

Continuous and categorical variables were presented by mean (SD) and actual number (percentage, %), respectively

(not shown in the Table).

Table 4 indicates the PAF (95% CI) of liver cancer according to green tea consumption, stratified by sex, a history of liver diseases, drinking status, and coffee consumption. The PAF for the total participants attributable to green tea consumption of ≥7 cups/day compared to 0–1 cup/day was 7.1% (0.9-11.4). A significant PAF

was observed for men, individuals without a history of liver disease, and current drinkers, with PAFs of 8.5% (0.4 -13.9), 10.7% (1.9-15.6), and 10.9% (1.7-15.8), respectively.

The discrepancies between our results and the findings of the previous JACC study [10] were primarily explained by the different categorizations of green tea consumption

Table 2. Associations between Green Tea Consumption and the Risk of Liver Cancer Incidence

	Green tea consumption (cups/day)				p for trend*
	0-1	2-4	5-6	≥7	
No. of participants, n	9,675	13,275	11,879	7,170	
Person-years	145,319	193,347	169,144	103,960	
Liver cancer, n	74	73	70	34	
Age, sex-adjusted HR (95% CI)	Ref	0.72 (0.52-0.99)	0.70 (0.51-0.98)	0.52 (0.35-0.78)	0.002
Multivariable HR (95% CI) <sup>a</sup>	Ref	0.87 (0.61-1.23)	0.87 (0.61-1.25)	0.61 (0.40-0.95)	0.029

<sup>a</sup>, Adjusted further for study area, education, histories of diabetes, liver diseases, and gallbladder disease, body mass index, drinking status, smoking status, coffee consumption, and frequency of sports participation and walking. \*p for trend was calculated using the median values of green tea intake for each category.

Table 3. Associations between Green Tea Consumption and the Risk of Liver Cancer Incidence, Stratified by Sex, a History of Liver Diseases, Drinking Status, and Coffee Consumption

	Green tea consumption (cups/day)				p for trend*	p for interaction
	0-1	2-4	5-6	≥7		
<b>Sex</b>						
<b>Men (n = 18,205)</b>						
No. of participants, n	4,130	5,729	5,020	3,326		
Person-years	60,323	82,425	69,762	47,073		
No. of liver cancer, n	47	45	37	22		
Age-adjusted HR (95% CI)	Ref	0.70 (0.46-1.05)	0.60 (0.39-0.92)	0.51 (0.31-0.85)	0.006	0.384
Multivariable HR (95% CI) <sup>a</sup>	Ref	0.82 (0.52-1.27)	0.72 (0.45-1.15)	0.57 (0.33-0.98)	0.034	0.396
<b>Women (n = 23,794)</b>						
No. of participants, n	5,545	7,546	6,859	3,844		
Person-years	84,996	110,922	99,382	56,887		
No. of liver cancer, n	27	28	33	12		
Age-adjusted HR (95% CI)	Ref	0.75 (0.44-1.27)	0.87 (0.52-1.46)	0.54 (0.27-1.06)	0.106	
Multivariable HR (95% CI) <sup>a</sup>	Ref	0.92 (0.51-1.64)	1.08 (0.61-1.92)	0.61 (0.29-1.28)	0.246	
<b>History of liver diseases</b>						
<b>History (-) (n = 37,455)</b>						
No. of participants, n	8,235	11,943	10,802	6,475		
Person-years	124,398	174,738	154,994	94,776		
No. of liver cancer, n	33	36	42	12		
Age, sex-adjusted HR (95% CI)	Ref	0.75 (0.47-1.21)	0.89 (0.56-1.42)	0.39 (0.20-0.76)	0.011	0.111
Multivariable HR (95% CI) <sup>a</sup>	Ref	0.89 (0.53-1.47)	1.03 (0.62-1.70)	0.46 (0.22-0.89)	0.035	0.228
<b>History (+) (n = 2,067)</b>						
No. of participants, n	591	607	539	330		
Person-years	8,031	8,163	6,906	4,361		
No. of liver cancer, n	34	34	22	19		
Age, sex-adjusted HR (95% CI)	Ref	1.02 (0.64-1.65)	0.75 (0.44-1.28)	0.90 (0.52-1.59)	0.515	
Multivariable HR (95% CI) <sup>a</sup>	Ref	1.13 (0.67-1.93)	0.80 (0.44-1.44)	1.00 (0.54-1.86)	0.758	
<b>Drinking status</b>						
<b>Never drinkers (n = 20,583)</b>						
No. of participants, n	4,646	6,472	6,040	3,425		
Person-years	69,454	93,737	85,102	50,239		
No. of liver cancer, n	35	20	39	14		
Age, sex-adjusted HR (95% CI)	Ref	0.41 (0.24-0.71)	0.80 (0.51-1.27)	0.47 (0.25-0.87)	0.059	
Multivariable HR (95% CI) <sup>a</sup>	Ref	0.51 (0.28-0.91)	1.00 (0.60-1.67)	0.54 (0.28-1.06)	0.231	
<b>Former drinkers (n = 1,407)</b>						
No. of participants, n	380	384	373	270		
Person-years	4,834	4,886	4,784	3,330		
No. of liver cancer, n	6	10	5	5		
Age, sex-adjusted HR (95% CI)	Ref	1.58 (0.58-4.35)	0.72 (0.22-2.40)	1.06 (0.32-3.49)	0.798	0.071
Multivariable HR (95% CI) <sup>a</sup>	Ref	4.50 (1.02-19.85)	1.43 (0.27-7.72)	1.66 (0.32-8.56)	0.857	0.615

Table 3. Continued

	Green tea consumption (cups/day)				p for interaction	
	0-1	2-4	5-6	≥7	p for trend*	
<b>Current drinkers (n = 17,938)</b>						
No. of participants, n	4,128	5,837	4,921	3,052		
Person-years	63,094	86,306	71,313	44,584		
No. of liver cancer, n	29	33	26	10		
Age, sex-adjusted HR (95% CI)	Ref	0.81 (0.49-1.34)	0.68 (0.40-1.16)	0.39 (0.19-0.80)	0.007	0.434
Multivariable HR (95% CI) <sup>a</sup>	Ref	0.85 (0.50-1.45)	0.75 (0.42-1.34)	0.42 (0.20-0.90)	0.024	0.485
<b>Coffee consumption</b>						
<b>&lt;1 cup/month (n = 6,720)</b>						
No. of participants, n	1,784	1,747	1,925	1,264		
Person-years	24,935	23,979	26,031	17,461		
No. of liver cancer, n	22	13	19	7		
Age, sex-adjusted HR (95% CI)	Ref	0.59 (0.30-1.18)	0.76 (0.41-1.40)	0.39 (0.17-0.91)	0.043	0.29
Multivariable HR (95% CI) <sup>a</sup>	Ref	0.67 (0.30-1.47)	0.94 (0.45-1.94)	0.50 (0.20-1.28)	0.286	0.93
<b>≥1 cup/month to 4 cups/week (n = 7,439)</b>						
No. of participants, n	1,799	2,115	2,220	1,305		
Person-years	26,422	28,648	29,417	17,666		
No. of liver cancer, n	18	19	14	8		
Age, sex-adjusted HR (95% CI)	Ref	1.03 (0.54-1.96)	0.72 (0.36-1.45)	0.59 (0.26-1.37)	0.148	
Multivariable HR (95% CI) <sup>a</sup>	Ref	0.96 (0.47-1.95)	0.62 (0.28-1.37)	0.52 (0.21-1.30)	0.104	
<b>≥5 cups/week (n = 27,438)</b>						
No. of participants, n	5,967	9,293	7,646	4,532		
Person-years	92,141	139,197	112,526	67,857		
No. of liver cancer, n	31	40	36	19		
Age, sex-adjusted HR (95% CI)	Ref	0.81 (0.51-1.30)	0.80 (0.49-1.30)	0.67 (0.37-1.19)	0.168	
Multivariable HR (95% CI) <sup>a</sup>	Ref	0.82 (0.51-1.34)	0.91 (0.55-1.51)	0.71 (0.39-1.29)	0.288	

<sup>a</sup>, Adjusted further for study area, education, histories of diabetes, liver diseases, and gallbladder disease, BMI categories, drinking status, smoking status, coffee consumption, and frequency of sports participation and walking; \*p for trend was calculated using the median values of green tea intake for each category.

and the varying inclusion criteria (Supplemental Table 1).

## Discussion

This extensive prospective cohort study of Japanese adults aged 40–79 years revealed an inverse trend between the frequency of green tea consumption and the risk of liver cancer in a dose-response fashion. This trend reached statistical significance in people who consumed green tea of ≥7 cups/day. Compared with people who consumed 0-1 cup of green tea per day, those who consumed ≥7 cups/day had an approximately 40% lower risk.

Consistent with previous studies that reported a lower relative risk of liver cancer associated with the highest level of green tea intake (0.88 in Asian populations) [6], the current study observed a comparable risk estimate of 0.61. The association between green tea intake and a reduced risk of liver cancer is thought to be related to the anti-carcinogenic effects of its polyphenol content, which has also been linked to a reduced risk of cancers in general [15, 16]. Green tea is rich in tea polyphenols, such as epigallocatechin gallate (EGCG), epigallocatechin, epicatechin, and epicatechin gallate, with EGCG being the predominant constituent (50%–75% of the catechins). Green tea catechins exhibit potent

antioxidant, anti-inflammatory, and anti-proliferative effects; they can scavenge reactive oxygen species (ROS) and enhance endogenous antioxidant defense systems such as superoxide dismutase, catalase, and glutathione peroxidase [16]. The EGCG modulates intracellular signaling pathways, including nuclear factor-kappa B and mitogen-activated protein kinase, thereby suppressing the production of inflammatory cytokines and preventing chronic inflammation and carcinogenesis [16]. In addition, EGCG and other catechins inhibit various enzyme activities and signal transduction, which suppresses tumor cell proliferation, improves cell apoptosis, and inhibits angiogenesis and metastasis [15].

The sufficiency of the bioavailable catechins from green tea of 7 cups/day in preventing carcinogenesis remains unclear. Reportedly, one-third of 620–880 mg of catechins is available from the typical one cup of green tea brewed with 2.5 g of green tea leaves in 250 ml of hot water, reaching the peak blood concentration of <0.5 μM at 1.5–2.0 h after ingestion [15]. Another potential anticarcinogenic nutrient is manganese, a trace mineral, mainly presents in white rice, green tea, and vegetables in the Japanese diet [17]. Further, manganese exhibits antioxidant properties, helping to defend against reactive oxygen species in hepatocellular carcinogenesis [18].

Table 4. Population Attributable Fractions (PAFs) for Liver Cancer Incidence According to Green Tea Consumption, Stratified by Sex, a History of Liver Diseases, and Drinking Status

	Green tea consumption (cups/day)			
	0-1	2-4	5-6	≥7
Total participants (n = 41,999)				
Multivariable PAF (95% CI)*	Ref	4.3% (-6.8 to 14.1)	3.8% (-6.6 to 12.4)	7.1% (0.9 to 11.4)
Sex				
Men (n = 18,205)				
Multivariable PAF (95% CI)	Ref	6.0% (-7.8 to 17.8)	8.4% (-4.0 to 17.9)	8.5% (0.4 to 13.9)
Women (n = 23,794)				
Multivariable PAF (95% CI)	Ref	2.7% (-16.8 to 18.4)	2.3% (-21.0 to 12.7)	6.7% (-4.3 to 13.0)
History of liver diseases				
History (-) (n = 37,455)				
Multivariable PAF (95% CI)	Ref	3.6% (-13.0 to 17.6)	0.9% (-16.8 to 12.3)	10.7% (1.9 to 15.6)
History (+) (n = 2,067)				
Multivariable PAF (95% CI)	Ref	N.A.	5.5% (-10.3 to 17.1)	N.A.
Coffee consumption				
<1 cup/month (n = 6,720)				
Multivariable PAF (95% CI)	Ref	9.4% (-10.9 to 22.2)	1.7% (-21.2 to 18.7)	10.4% (-5.0 to 17.7)
≥1 cup/month to 4 cups/week (n = 7,439)				
Multivariable PAF (95% CI)	Ref	1.1% (-21.3 to 17.7)	12.8% (-9.9 to 27.4)	9.2% (-5.0 to 16.1)
≥5 cups/week (n = 27,438)				
Multivariable PAF (95% CI)	Ref	6.5% (-10.3 to 19.9)	2.6% (-12.4 to 14.3)	5.0% (-4.6 to 11.2)
Drinking status				
Never drinkers (n = 20,583)				
Multivariable PAF (95% CI)	Ref	18.2% (2.9 to 29.3)	N.A.	8.3 (-1.0 to 13.6)
Former drinkers (n = 1,407)				
Multivariable PAF (95% CI)	Ref	N.A.	N.A.	N.A.
Current drinkers (n = 17,938)				
Multivariable PAF (95% CI)	Ref	5.1% (-12.8 to 19.4)	7.4% (-8.5 to 18.9)	10.9% (1.7 to 15.8)

N.A. Not assessed, due to the corresponding hazard ratio being 1.0 or higher; \* Adjusted for age, sex, study area, education, history of diabetes, histories of liver diseases and gallbladder disease, body mass index, drinking status, smoking status, coffee consumption, and frequency of sports participation and walking.

Vitamin C is a water-soluble vitamin and a well-known antioxidant abundant in green tea [19]. However, previous observational studies have reported no association between vitamin C intake and a decreased risk of liver cancer [20]. Further observational and intervention studies in animals and humans are warranted to investigate the effects of frequent consumption of green tea, for example, ≥7 or more cups/day, on cancer prevention.

In the present study, the inverse association between green tea consumption and the risk of liver cancer incidence was observed among people without a history of liver diseases and current drinkers. Chronic liver disease is a progressive condition characterized by ongoing liver tissue inflammation, destruction, and regeneration, ultimately causing cirrhosis [21]. In such circumstances, green tea, which is rich in antioxidants, such as catechins [22], may not effectively regulate the progression from chronic liver disease to hepatocellular carcinoma. Therefore, people without a history of liver diseases, such as chronic hepatitis, could benefit more from green tea consumption because they are not at a higher risk of

liver cancer.

Green tea consumption is expected to be associated with a lower risk of liver cancer in never drinkers but not in former and current drinkers because the never drinkers are at a lower risk of liver cancer, whereas former drinkers are at a higher risk due to alcohol-induced hepatitis and liver cirrhosis [23]. Despite an inverse trend, no significant association among never drinkers was observed in the present study due to the lower number of liver cancers, causing a lower statistical power to detect the expected association. However, the inverse association in current drinkers was unexpected. This may be because many current drinkers do not have liver dysfunctions in the following circumstances. Under the mandatory screening system for adults in Japan [24], people with higher liver enzymes are strongly recommended to quit drinking. This notion is supported by the previous report from the JACC study, indicating that the risk of liver cancer did not differ between never and current drinkers and was substantially higher in former drinkers [25]. This phenomenon is reflected in our study, where 14.4% of individuals with

a history of liver diseases were among former drinkers, which was higher than that among current drinkers (5.4%) and never drinkers (4.5%), which is similar by sex (Supplemental Table 2). Therefore, current drinkers are unlikely to be at a higher risk of liver cancer than former drinkers.

The inconsistent results between the previous JACC study [10] and our study warrant further discussion. The previous study revealed an inverse association between dietary manganese intake and liver cancer risk. However, the sensitivity analysis revealed no significant association between the highest green tea consumption and the risk of liver cancer. Specifically, contrast directions in women (HR [95% CI]: reference for <daily, 1.17 [0.55–2.45] for 1–4 cups/day, 1.35 [0.66–2.76] for  $\geq 5$  cups/day) after multivariable adjustment [9]. In this aspect, the methodological differences between the two studies, primarily in their primary target, explain these contradictory results. First, the reference level for green tea consumption differed, with the previous study using the lowest category for “0 cup/day,” whereas our study used “0–1 cup/day.” Further, the previous study categorized the highest green tea intake as “ $\geq 5$  cups/day,” whereas our study used “ $\geq 7$  cups/day.” Second, the previous study wrongly treated a man and 11 women as having a cancer history, which, however, did not affect the present results. Third, the previous study excluded 5,148 men and 4,746 women for whom dietary manganese intake was not available. In summary, the previous JACC study was optimally designed as the primary target for dietary manganese.

Furthermore, we calculated the PAF of liver cancer attributable to green tea consumption, estimating that 7.1% of liver cancer was potentially preventable by drinking green tea of  $\geq 7$  cups/day. The estimated number of patients with liver cancer in Japan is 34,744 [3], and over 2,000 patients could have been prevented.

The strengths of the current study include its prospective cohort design, adjustment for potential confounding variables, and stratification based on a history of liver diseases, drinking status, and coffee consumption. The limitations warrant discussion. First, dietary habits were self-reported and assessed only once at baseline. Furthermore, changes in green tea consumption during follow-up were not considered. Second, hepatitis B and C virus infections are strong risk factors for liver cancer. However, our study did not investigate the antibody titers for hepatitis virus infection for all participants. Third, we were unable to distinguish the sources of green tea and the preparation methods. The preparation difference, whether bottled, brewed tea or brewed green tea, may have affected the quantity and bioavailability of polyphenols [26]. Fourth, residual confounding from unmeasured potential confounders remained an inherent limitation due to an observational study design. Finally, the results of the present study should be interpreted with caution, as the study focused on a Japanese population aged 40–79 years, in which green tea drinking is common. It is uncertain whether our findings are generalizable to the non-Asian populations.

In conclusion, the present large and long-term cohort

study of Japanese adults found that green tea consumption was associated with a lower risk of liver cancer, with approximately a 40% risk reduction with consuming  $\geq 7$  cups/day. The risk reduction was evident for men, people without a history of liver diseases, and current drinkers.

## Author Contribution Statement

OF had the original idea, and OF, RS, HI, and RK developed the study design. AT was the principal investigator of the study where data was collected. OF performed the statistical analyses, with RS, HI, and RK assisting in interpreting and analyzing the results. OF wrote the first draft of the manuscript, and all authors revised and approved the final version.

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### Competing interest

The authors declare that they have no competing interests

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