TABLE 3 Sex-specific HR and 95% CI for mortality from CVD according to quintiles of IDF and SDF intakes

	Men						Women					
	Q1 (Low)	Q2	Q3	Q4	Q5 (High)	*P*-trend[1]	Q1 (Low)	Q2	Q3	Q4	Q5 (High)	*P*-trend[1]
n	4623	4624	4624	4624	4624		7122	7122	7122	7122	7122	
IDF												
Range, *g/d*	<5.9	5.9–6.9	7.0–7.9	8.0–9.2	>9.2		<6.2	6.2–7.1	7.2–8.0	8.1–9.1	>9.1	
Person-years	56,963	57,598	57,534	57,720	58,702		89,073	89,584	90,918	91854	93220	
Total stroke												
Cases, *n*	81	77	108	144	109		64	137	100	111	72	
Age-adjusted HR (95%CI)	1	0.97 (0.70–1.36)	1.12 (0.82–1.54)	1.03 (0.76–1.39)	0.98 (0.71–1.34)	0.945	1	1.10 (0.82–1.49)	1.20 (0.87–1.64)	1.13 (0.83-1.54)	0.93 (0.67-1.31)	0.344
Multivariable HR (95%CI)[2]	1	1.01 (0.70–1.46)	1.16 (0.79–1.70)	0.98 (0.64–1.52)	0.96 (0.64–1.45)	0.715	1	1.03 (0.70–1.51)	1.18 (0.83–1.69)	1.06 (0.73-1.53)	0.90 (0.63-1.28)	0.128
CHD												
Cases, *n*	44	38	40	61	48		39	44	35	38	35	
Age-adjusted HR (95%CI)	1	0.69 (0.45–1.07)	0.62 (0.40–0.96)	0.68 (0.46–1.01)	0.65 (0.43–0.98)	0.032	1	0.72 (0.46–1.14)	0.66 (0.42–1.05)	0.60 (0.38-0.94)	0.53 (0.34-0.82)	0.003
Multivariable HR (95%CI)[2]	1	0.63 (0.39–1.02)	0.52 (0.30–0.87)	0.46 (0.26–0.84)	0.48 (0.27–0.84)	<0.001	1	0.63 (0.38–1.04)	0.61 (0.36–1.03)	0.56 (0.33-0.98)	0.49 (0.27-0.86)	0.004
Other CVD												
Cases, *n*	48	49	72	92	72		49	88	73	81	51	
Age-adjusted HR (95%CI)	1	1.43 (0.95–2.14)	1.01 (0.70–1.46)	1.13 (0.80–1.61)	1.24 (0.85–1.79)	0.715	1	0.86 (0.60–1.22)	0.94 (0.65–1.36)	1.01 (0.71-1.44)	1.06 (0.71-1.57)	0.325
Multivariable HR (95%CI)[2]	1	1.24 (0.85–2.06)	1.01 (0.68–1.21)	1.06 (0.69–1.49)	1.15 (0.76–1.62)	0.798	1	0.83 (0.48–1.45)	1.09 (0.67–1.77)	1.20 (0.73-1.99)	0.83 (0.51-1.33)	0.698
Total CVD												
Cases, *n*	153	164	220	297	229		152	269	208	230	158	
Age-adjusted HR (95%CI)	1	0.88 (0.72–1.07)	0.99 (0.84–1.17)	0.91 (0.78–1.06)	0.85 (0.68–1.03)	0.061	1	0.84 (0.67–1.04)	0.93 (0.76–1.15)	0.87 (0.71-1.06)	0.84 (0.68-1.03)	0.301
Multivariable HR (95%CI)[2]	1	0.88 (0.68–1.04)	0.97 (0.79–1.08)	0.89 (0.72–1.03)	0.82 (0.65–0.98)	0.042	1	0.78 (0.61–1.00)	0.82 (0.64–1.06)	0.68 (0.51-0.91)	0.69 (0.53-0.91)	0.017
SDF												
Range, *g/d*	<1.3	1.3–1.6	1.7–1.9	2.0–2.3	>2.3		<1.5	1.5–1.8	1.9–2.1	2.2-2.4	>2.4	
Person-years	57,151	57,436	57,798	57,903	58,230		89,551	89,205	90,778	91613	93503	
Total stroke												
Cases, *n*	85	146	107	90	91		78	72	125	107	102	
Age-adjusted HR (95%CI)	1	1.04 (0.77–1.40)	0.95 (0.69–1.29)	1.11 (0.81–1.53)	0.92 (0.67–1.27)	0.991	1	0.81 (0.59–1.12)	0.91 (0.69–1.21)	1.00 (0.75-1.34)	1.07 (0.80-1.44)	0.901
Multivariable HR (95%CI)[2]	1	0.98 (0.66–1.47)	0.91 (0.61–1.34)	1.12 (0.79–1.59)	0.90 (0.61–1.31)	0.790	1	0.80 (0.57–1.12)	0.88 (0.61–1.24)	0.95 (0.67-1.34)	1.02 (0.73-1.42)	0.643
CHD												
Cases, *n*	38	59	46	43	45		39	39	41	38	34	
Age-adjusted HR (95%CI)	1	0.81 (0.53–1.22)	0.83 (0.54–1.19)	0.74 (0.61–1.10)	0.76 (0.49–1.07)	0.092	1	0.98 (0.55–1.14)	0.56 (0.36–0.87)	0.74 (0.44-1.04)	0.69 (0.44-0.97)	0.005
Multivariable HR (95%CI)[2]	1	0.80 (0.44–1.16)	0.81 (0.48–1.17)	0.72 (0.58–1.02)	0.71 (0.41–0.97)	0.043	1	0.86 (0.54–1.18)	0.60 (0.34–1.04)	0.88 (0.54-1.07)	0.72 (0.43-0.99)	0.035
Other CVD												
Cases, *n*	46	96	71	59	61		56	56	88	65	77	
Age-adjusted HR (95%CI)	1	1.43 (1.00–2.04)	1.41 (0.97–2.06)	1.11 (0.87–1.88)	1.12 (0.88–1.69)	0.765	1	0.79 (0.54–1.16)	0.74 (0.53–1.04)	1.18 (0.82-1.89)	0.84 (0.60-1.19)	0.312
Multivariable HR (95%CI)[2]	1	1.09 (0.86–1.75)	1.24 (0.79–1.87)	1.04 (0.88–1.76)	1.08 (0.75–1.64)	0.573	1	0.74 (0.48–1.14)	0.77 (0.46–1.28)	1.32 (0.81-2.15)	0.96 (0.61-1.50)	0.613
Total CVD												
Cases, *n*	149	301	224	192	197		173	167	254	210	213	
Age-adjusted HR (95%CI)	1	1.23 (0.79–1.88)	1.04 (0.72–1.39)	0.75 (0.54–0.97)	0.82 (0.62–1.08)	0.052	1	0.81 (0.67–0.98)	0.84 (0.68–1.04)	0.77 (0.61-0.97)	0.80 (0.56-0.99)	0.021
Multivariable HR (95%CI)[2]	1	1.11 (0.64–1.33)	0.89 (0.69–1.13)	0.74 (0.52–0.98)	0.81 (0.63–1.04)	0.042	1	0.86 (0.68–1.07)	0.85 (0.67–1.09)	0.79 (0.65-0.98)	0.83 (0.53-1.02)	0.043

[1] Based on tests for trend across quintiles of fiber intake by assigning the median value of each quintile.

[2] Cox proportional hazard model adjusted for age, BMI, history of hypertension, history of diabetes, alcohol consumption, smoking, education level, hours of exercise, hours of walking, perceived mental stress, sleep ho fish, SFA, (n-3) fatty acids, sodium, folate, and vitamin E.

TABLE 4 Sex-specific HR and 95% CI for mortality from CHD according to quintiles of cereal, fruit, and vegetable fiber intakes

	Men						Women					
	Q1 (Low)	Q2	Q3	Q4	Q5 (High)	*P*-trend[1]	Q1 (Low)	Q2	Q3	Q4	Q5 (High)	*P*-trend[1]
n	4623	4624	4624	4624	4624		7122	7122	7122	7122	7122	
Cereal fiber												
Range, *g/d*	<1.4	1.4–1.6	1.7–1.8	1.9–2.1	>2.1		<1.1	1.1–1.3	1.4–1.5	1.6–1.7	>1.7	
Person-years	57,289	57,650	57,640	57,651	58,288		90,356	90,793	91,764	90516	91224	
Cases, *n*	45	50	51	40	45		49	33	28	49	32	
Age-adjusted HR (95%CI)	1	0.92 (0.73–1.16)	0.96 (0.71–1.25)	0.81 (0.66–1.03)	0.88 (0.71–1.05)	0.125	1	0.79 (0.52–0.96)	0.74 (0.56–0.95)	1.03 (0.83–1.54)	0.76 (0.57–0.98)	0.044
Multivariable HR (95%CI)[2]	1	0.90 (0.70–1.16)	0.92 (0.69–1.12)	0.77 (0.64–0.98)	0.86 (0.64–0.99)	0.042	1	0.80 (0.53–0.97)	0.73 (0.53–0.97)	1.06 (0.73–1.53)	0.77 (0.59–0.98)	0.031
Multivariable HR (95%CI)[3]	1	0.89 (0.68–1.15)	0.90 (0.68–1.16)	0.74 (0.61–0.99)	0.89 (0.65–1.01)	0.060	1	0.80 (0.53–0.98)	0.74 (0.50–0.89)	1.06 (0.74–1.56)	0.76 (0.59–0.97)	0.044
Fruit fiber												
Range, *g/d*	<0.4	0.4–0.7	0.8–1.0	1.1–1.7	>1.7		<0.7	0.7–1.1	1.2–1.8	1.9–2.2	>2.2	
Person-years	57,199	57,641	57,971	57,891	57,816		90,999	90,362	90,751	90079	92438	
Cases, *n*	62	53	43	36	37		55	39	36	39	22	
Age-adjusted HR (95%CI)	1	0.79 (0.46–1.01)	0.69 (0.54–0.98)	0.54 (0.38–0.82)	0.54 (0.35–0.86)	0.004	1	0.69 (0.45–1.05)	0.67 (0.45–1.01.	0.66 (0.34–0.98)	0.43 (0.26–0.70)	0.003
Multivariable HR (95%CI)[2]	1	0.80 (0.45–1.03)	0.71 (0.53–0.99)	0.54 (0.37–0.86)	0.56 (0.35–0.90)	0.007	1	0.71 (0.43–1.08)	0.70 (0.43–1.02	0.65 (0.31–0.98)	0.40 (0.28–0.78)	0.005
Multivariable HR (95%CI)[3]	1	0.82 (0.45–1.09)	0.75 (0.52–1.02)	0.55 (0.34–0.92)	0.55 (0.32–0.96)	0.032	1	0.73 (0.42–1.10)	0.69 (0.42–1.04)	0.63 (0.33–0.99)	0.42 (0.33–0.81)	0.014
Vegetable fiber												
Range, *g/d*	<2.8	2.8–3.6	3.7–4.3	4.4–5.5	>4.5		<3.1	3.1–3.9	4.0–4.6	4.7–5.6	>5.6	
Person-years	57,636	58,016	57,735	57,989	57,140		89,688	90,396	90,874	91592	92099	
Cases, *n*	40	47	40	48	61		36	34	36	43	42	
Age-adjusted HR (95%CI)	1	1.04 (0.66–1.62)	1.15 (0.75–1.77)	0.77 (0.49–1.21)	0.90 (0.58–1.38)	0.328	1	0.76 (0.46–1.26)	0.92 (0.58–1.47)	0.64 (0.40–1.05)	0.79 (0.51–1.24)	0.460
Multivariable HR (95%CI)[2]	1	1.06 (0.66–1.71)	1.16 (0.72–1.89)	0.76 (0.46–1.28)	0.92 (0.56–1.52)	0.417	1	0.79 (0.47–1.34)	0.96 (0.58–1.60)	0.73 (0.43–1.24)	0.91 (0.55–1.49)	0.983
Multivariable HR (95%CI)[3]	1	1.03 (0.64–1.67)	1.14 (0.70–1.86)	0.75 (0.44–1.26)	0.90 (0.54–1.51)	0.666	1	0.78 (0.46–1.32)	0.93 (0.56–1.55)	0.73 (0.43–1.25)	0.97 (0.58–1.62)	0.917

[1] Based on tests for trend across quintiles of fiber intake by assigning the median value of each quintile.

[2] Cox proportional hazard model adjusted for age, BMI, history of hypertension, history of diabetes, alcohol consumption, smoking, education level, hours of exercise, hours of walking, perceived mental stress, sleep hour fish, SFA, (n-3) fatty acids, sodium, folate, and vitamin E.

[3] Adjusted further for other types of dietary fiber (cereal, fruit, and vegetable fibers).

The present study has several methodological strengths; the evaluation of a large prospective cohort enrolled from the Japanese general population and the exclusion of persons with known cardiovascular or cancer disease at baseline reduce potential for recall bias and bias from dietary changes due to known diseases. Also, the results from a cohort of community residents are more relevant to generalizability than those of occupational employees, hospital-based patients, or volunteers. Close follow-up, comprehensive review of potential events, and centralized judgment reduced the potential for missed or misclassified outcomes.

The mean intake of TDF in our study was 10–11 g/d for both sexes, although this figure may have been underestimated by as much as 40% according to our validation study (19). Thus, the actual mean fiber intake was probably ~15 g/d, which is compatible with data from the Japan National Nutrition Survey (11), yet this figure is much lower than that for Western countries (7–9,23–33). The low dietary fiber content of refined rice, frequently consumed by Japanese, may have resulted in the low intake of fiber compared with Western populations. Sources of dietary fiber differ from one population to another. The major sources of dietary fiber for the participants in this study were miso soup (18%), rice (14%), fruits other than citrus fruit (9%), and green leafy vegetables (7%). In most Western countries, the sources are mainly whole grains, cereals, vegetables, and fruit (3–9,22,23); e.g., sources of fiber reported in the Zutphen Study were bread and other cereal products (29–34%), vegetables (20–28%), and fruits (15–23%) (34), and that of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study was rye bread (33).

Limitations of this study include the lack of multiple measurements of dietary variables. During the long follow-up period, both the participants' diet and food composition may have changed, so multiple evaluations of diet over time are important to reduce measurement errors and to better assess the temporal relationship between dietary fiber intake and mortality from CVD. Moreover, the ratios of mean intakes estimated by the FFQ to those calculated from the DR were 0.60, 0.58, and 0.51 for TDF, IDF, and SDF, respectively, which is probably due to the limited number of foods in the FFQ. However, the rank correlations for fiber intake between the FFQ and DR were fairly good: 0.46 for TDF, 0.47 for IDF, and 0.42 for SDF, which supports the validity of our FFQ. Lastly, the apparent protective effect of fiber on risk of CHD may be due to other health-related habits, such as regular exercise, no smoking, and a high fish intake by persons who consume greater amounts of dietary fiber. Although we made adjustments for all of these potential confounders, some confounding and other unexamined health habits may remain unaccounted for.

In conclusion, our results constitute supporting evidence that higher intake of both insoluble and soluble fiber, especially fruit and cereal fibers may contribute to the prevention of CHD in Japanese men and women.

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REGULAR ARTICLE

History of blood transfusion before 1990 is associated with increased risk for cancer mortality independently of liver disease: a prospective long-term follow-up study

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Abstract
Objectives The aim of this work is to investigate the association between transfusion history and cancer mortality in a prospective follow-up study.
Methods We conducted a prospective cohort study in four areas of Akita Prefecture, Japan, in 10,451 individuals (4,401 men and 6,050 women, aged 40–79 years) without history of cancer. The subjects were followed until 31 December 2003 and the number of deaths from cancer was recorded.
Results After mean follow-up of 12.76 years (140,259 person–years), 520 individuals (333 men and 187 women) died of cancer. History of blood transfusion before 1990 was mildly but significantly associated with overall cancer mortality (hazard ratio = 1.75, 95% confidence interval: 1.32–2.18) and nonliver cancer mortality (HR = 1.68, 95% CI: 1.25–2.26). This significant association remained unchanged after excluding deaths that occurred within 5 years of baseline for overall cancer mortality (HR = 1.47, 95% CI: 1.04–2.09) and for nonliver cancer mortality (HR = 1.43, 95% CI: 1.00–2.04). The significant association for nonliver cancer mortality was confirmed in subjects with no smoking history and/or alcohol consumption (HR = 2.01, 95% CI: 1.35–3.00). Site-specific analysis showed a possible association between transfusion history and death from pancreatic cancer.
Conclusions History of blood transfusion before 1990 was found to be associated with increased risk for cancer mortality and was independent of liver diseases. The mechanism of the association between blood transfusion and cancer mortality warrants further research.

Keywords Cancer · Cohort studies · Residence characteristics · Blood transfusion

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Introduction

Although allogeneic blood transfusion is an established mode of therapy, it has several recognized risks. In this study, we aimed to test the hypothesis of a long-term biological influence of past transfusion on overall cancer mortality. Although many epidemiological studies have suggested that allogeneic blood transfusion is associated with increased risk for postoperative cancer recurrence [1–12], few studies have investigated the association between transfusion history and cancer mortality. One preliminary study has suggested that past transfusion might increase the risk for overall cancer mortality [13]. Therefore, further studies are needed to confirm this association, with adjustment for related lifestyle factors or past medical histories that might confound the association between cancer mortality and transfusion history.

We conducted a 14-year follow-up cohort study of middle-aged and elderly general population in Japan using self-report questionnaires on transfusion history and other factors that might confound analysis of the association between transfusion history and cancer mortality.

Materials and methods

Study cohort

The cohort was established in four areas (areas A–D) in Akita Prefecture as part of the Japan Collaborative Cohort Study for evaluation of Cancer Risk (JACC study), which was ongoing for 14 years (from 1990 to 2003); the details of the study have been described in more detail elsewhere [14, 15]. In brief, a total of 11,631 individuals (4,865 men and 6,766 women, aged 40–79 years) in the four areas participated in municipal health screening examinations between 1988 and 1991, which were conducted in accordance with Japan's law on health services for elderly people. All of the participants completed a self-administered questionnaire. The cohort study was set up in accordance with the ethical standards of the Helsinki Declaration, and the protocol and the data usage for this research was approved by the Research Ethics Committee of Kyoto University.

Follow-up

Date and cause of death were confirmed biannually, with the permission of the Director-General of the Prime Minister's Office (Ministry of Public Management, Home Affairs, Post, and Telecommunications). The date of moving away from the study area was also annually verified by the investigator in each area by reviewing the population register sheets of the cohort members. The time of follow-up for each subject was calculated from the day of enrollment in the study to the day of death from cancer or any other cause, the time of moving away from the study area or the end of 2003, whichever occurred first. By the end of 2003, 14.2% (944 men and 621 women) of the participants had died and 3.4% (131 men and 241 women) were lost to follow-up because they had moved away from the study areas.

Questionnaire

At baseline, all participants completed self-administered questionnaires containing the following items: sex, age, birth date, medical history (transfusion, liver diseases, external injury that required hospitalization, and abdominal surgery), smoking status, alcohol consumption, and history of pregnancy. Medical histories and history of pregnancy were inquired about, using a yes/no question regarding whether the participant had a particular medical or pregnancy history. For example, for transfusion history, participants were asked, "Have you ever been treated with blood transfusion by the time of this survey?" For alcohol consumption, individuals chose their status from three categories: those who had never consumed alcohol, current drinkers or ex-drinkers. For smoking status, individuals chose from three categories: those who had never smoked, current smokers or ex-smokers. Those with unmarked or missing data in the questionnaire were not used in the analyses.

Data retrieval and analysis

We restricted the present analysis to include only those participants who provided information about their age, sex, and transfusion history, and who did not have history of cancer. Of the 11,631 participants, those with history of cancer ($n = 638$) and those with missing questionnaire data about their age, sex or transfusion history ($n = 759$) were not used in this analysis. A total of 1,180 individuals were excluded, and our final dataset comprised data from 10,451 individuals (4,401 men and 6,050 women, aged 40–79 years). For deceased subjects, cause of death was recorded from death certificates and coded according to the International Classification of Diseases and Related Health Problems (ICD) tenth revision for deaths occurred after 1995, or the ninth version for deaths that occurred between baseline and 1994; the latter were then recoded according to the tenth revision. Deaths due to malignant neoplasms were coded as 140–208 according to the ICD ninth revision (for deaths between baseline and 1994) and as C00-C97 according to the tenth revision (for deaths after 1995).

Statistical analysis

The Cox proportional-hazards model was used to calculate the age-adjusted and multivariate hazard ratio (HR) of history of blood transfusion for cancer mortality, along with the 95% confidence interval (CI). The risk of cancer mortality in patients with liver disease was also estimated. All calculations were performed using SAS version 8.2 software (SAS Inc., Cary, NC, USA). Differences at $P < 0.05$ were considered statistically significant.

The multivariate HR of transfusion history for cancer mortality was estimated after adjusting for baseline age, sex, and typical risk factors of total cancer mortality (smoking status and alcohol consumption), and history of external injury, abdominal surgery, liver disease, and pregnancy, which were factors related to transfusion, or factors showing a significant association in age-adjusted univariate analysis.

Results

During average follow-up of 12.76 years (140,259 person–years), a total of 520 individuals (333 men and 187 women)

died of cancer: 26 (15 men and 11 women) from liver cancer and 494 (318 men and 176 women) from nonliver cancer. Baseline characteristics are presented in Table 1. The prevalence of external injury (41.0%), abdominal surgery (73.7%), and liver disease (8.2%) among subjects with history of blood transfusion was more than twice that of those without history of transfusion (17.6%, 29.6%, and 2.9%, respectively) ($P < 0.001$, χ^2 test). On the other hand, there was no significant difference in smoking status or alcohol intake between those with and those without history of blood transfusion.

Table 1 Demographic and clinical data of the study cohort

	History of transfusion	
	Yes (n = 972)	No (n = 9,479)
Age		
Mean (SD), years	56.7 (9.5)	58.1 (9.3)
	n (%)	*n* (%)
Area		
A	221 (22.7)	1,826 (19.3)
B	247 (25.4)	1,834 (19.3)
C	202 (20.8)	2,827 (29.8)
D	302 (31.1)	2,992 (31.6)
Number		
Men	352 (36.2)	4,049 (42.7)
Women	620 (63.8)	5,430 (57.3)
Smoking status		
Never	555 (57.1)	5,433 (57.3)
Smoker	183 (18.8)	2,086 (22.0)
Ex-smoker	103 (10.6)	726 (7.7)
Unknown	131 (13.5)	1,234 (13.0)
Alcohol intake		
Never	433 (44.5)	4,246 (44.8)
Drinker	396 (40.7)	4,278 (45.1)
Ex-drinker	64 (6.6)	287 (3.0)
Unknown	79 (8.1)	667 (7.0)
History of external injury		
Yes	399 (41.0)	1,673 (17.7)
No	495 (50.9)	7,497 (79.1)
Unknown	78 (8.0)	308 (3.2)
History of abdominal surgery		
Yes	716 (73.7)	2,805 (29.6)
No	229 (23.6)	6,588 (69.5)
Unknown	27 (2.8)	85 (0.9)
History of liver disease		
Yes	80 (8.2)	272 (2.9)
No	821 (84.5)	8,777 (92.6)
Unknown	71 (7.3)	429 (4.5)
History of pregnancy[a]		
Yes	565 (98.8)	5,055 (99.3)
No	7 (1.2)	37 (0.7)

People with history of cancer before participation in the cohort were excluded from this analysis

SD standard derivation

[a] Females only

Table 2 shows the age-adjusted HRs for cancer mortality for the sex-specific and sex-stratified analyses. Generally, history of blood transfusion was significantly associated with increased risk of cancer death, regardless of whether death was associated with liver cancer or nonliver cancer. Smoking status was also significantly associated with increased risk of cancer death. Current smoking and ex-smoking statuses were, respectively, associated with cancer mortality, for overall cancer and nonliver cancer. History of liver disease was significantly associated with increased risk for liver cancer mortality, although this association was not confirmed for mortality due to other cancers. In women, ex-drinking habit and history of external injury were also significantly associated with increased risk of cancer mortality. History of abdominal surgery and pregnancy were not significantly associated with cancer mortality.

On multivariate analysis, the significant association between cancer mortality and history of transfusion remained unchanged (Table 3). We also tested this association after excluding deaths in the first 5 years (totally 511 cases were excluded, including 120 cancer deaths), because such deaths might have resulted from unidentified factors that engendered a spurious association between transfusion and cancer mortality risk. Even after excluding deaths in the first 5 years, the significant association remained unchanged; the HR (95% CI) was 1.47 (1.04–2.09) for overall cancer mortality and 1.43 (1.00–2.04) for nonliver cancer mortality. Furthermore, we confirmed the significant associations between history of transfusion and risk for cancer mortality in subjects with no history of smoking and/or drinking; the HR (95% CI) was 2.04 (1.39–3.00) for overall cancer mortality and 2.01 (1.35–3.00) for nonliver cancer mortality.

Based on the site-specific analysis, we found a significant association between transfusion history and mortality due to cancer in the stomach, liver, and pancreas. After excluding deaths in the first 5 years, there remained significant associations for cancer in liver (HR = 1.75, 95% CI: 1.32–2.33) and pancreas (3.20, 1.02–10.07).

Discussion

We found that history of blood transfusion before 1990 was mildly but significantly associated with elevated cancer mortality risk among middle-aged and elderly general

Table 2 Age-adjusted analysis for factors associated with cancer mortality: all cancers, nonliver cancers, and liver cancers

	Men			Women			All	
	n	HR (95% CI)	*P* value	*n*	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Cancer (all)								
Smoking status								
Never	61	1.00		147	1.00		1.00	
Smoker	194	2.01 (1.51–2.69)	<0.0001	8	1.75 (0.86–3.57)	0.12	1.97 (1.51–2.57)	<0.0001
Ex-smoker	71	1.43 (1.09–1.89)	0.0107	2	1.61 (0.33–7.74)	0.55	1.44 (1.10–1.89)	0.0089
Alcohol intake								
Never	59	1.00		124	1.00		1.00	
Drinker	243	0.77 (0.52–1.13)	0.18	49	0.60 (0.28–1.26)	0.18	0.74 (0.53–1.05)	0.0888
Ex-drinker	29	1.16 (0.75–1.82)	0.51	8	2.23 (1.09–4.56)	0.0279	1.36 (0.92–2.02)	0.12
History of external injury								
No	256	1.00		140	1.00		1.00	
Yes	72	0.87 (0.67–1.13)	0.3	49	1.42 (1.02–1.96)	0.0369	1.04 (0.85–1.27)	0.72
History of abdominal surgery								
No	250	1.00		113	1.00		1.00	
Yes	90	1.08 (0.85–1.37)	0.55	82	1.09 (0.82–1.45)	0.55	1.08 (0.90–1.30)	0.41
History of liver disease								
No	308	1.00		177	1.00		1.00	
Yes	17	1.28 (0.79–2.09)	0.32	8	1.47 (0.72–2.99)	0.29	1.34 (0.89–2.00)	0.16
History of blood transfusion								
No	296	1.00		153	1.00		1.00	
Yes	37	1.33 (0.94–1.87)	0.11	34	1.91 (1.32–2.77)	0.0007	1.55 (1.20–1.99)	0.0006
History of pregnancy								
No				5	1.00			
Yes				169	0.42 (0.17–1.02)	0.0562		
Cancer (nonliver)								
Smoking status								
Never	58	1.00		137	1.00		1.00	
Smoker	185	2.02 (1.50–2.71)	<0.0001	8	1.88 (0.92–3.84)	0.0827	2.00 (1.52–2.62)	<0.0001
Ex-smoker	68	1.44 (1.08–1.91)	0.0116	2	1.61 (0.33–7.74)	0.55	1.44 (1.09–1.90)	0.0096
Alcohol intake								
Never	58	1.00		116	1.00		1.00	
Drinker	233	0.86 (0.56–1.30)	0.46	48	0.67 (0.30–1.48)	0.32	0.83 (0.57–1.20)	0.31
Ex-drinker	25	1.02 (0.64–1.63)	0.95	7	2.09 (0.98–4.49)	0.0575	1.21 (0.80–1.82)	0.37
History of external injury								
No	249	1.00		133	1.00		1.00	
Yes	64	0.80 (0.60–1.05)	0.1	45	1.37 (0.97–1.92)	0.0711	0.97 (0.78–1.20)	0.77
History of abdominal surgery								
No	239	1.00		108	1.00		1.00	
Yes	86	1.08 (0.84–1.38)	0.56	74	1.03 (0.77–1.39)	0.85	1.06 (0.87–1.28)	0.57
History of liver disease								
No	297	1.00		168	1.00		1.00	
Yes	13	1.02 (0.58–1.77)	0.96	6	1.16 (0.52–2.63)	0.72	1.06 (0.67–1.68)	0.81
History of blood transfusion								
No	286	1.00		144	1.00		1.00	
Yes	32	1.19 (0.82–1.71)	0.36	32	1.91 (1.30–2.80)	0.0009	1.46 (1.12–1.90)	0.005

Table 2 continued

	Men			Women			All	
	n	HR (95% CI)	*P* value	*n*	HR (95% CI)	*P* value	HR (95% CI)	*P* value
History of pregnancy								
No				4	1.00			
Yes				159	0.49 (0.18–1.33)	0.1615		
Cancer (liver)								
History of liver disease								
No	11	1.00		9	1.00		1.00	
Yes	4	8.27 (2.63–26.05)	0.0003	2	7.21 (1.55–33.51)	0.0117	7.93 (3.18–19.81)	<0.0001
History of blood transfusion								
No	10	1.00		9	1.00		1.00	
Yes	5	5.41 (1.84–15.88)	0.0021	2	1.88 (0.41–8.70)	0.42	3.56 (1.49–8.50)	0.0042

People with history of cancer before participation in the cohort were excluded from this analysis

HR hazard ratio, *CI* confidence interval

population in Japan who had no history of cancer. These significant associations were maintained even after excluding deaths in the first 5 years, and in subjects who reported no history of smoking and/or drinking.

Site-specific analysis showed a significant association between transfusion history and death from pancreatic cancer. Pancreatic cancer has an extremely low survival rate [16] and is the fifth leading cause of cancer death in Japan [17]. Its incidence and mortality have increased markedly over the past four decades in Japan [18]. Nevertheless, few epidemiological studies have been conducted to identify the environmental/genetic risk factors that contribute to the development of pancreatic cancer, and its etiology remains unclear. Consistent evidence of an association with pancreatic cancer mortality has so far been limited to cigarette smoking [19]. The association between transfusion history and pancreatic cancer in this study needs to be assessed in future studies containing a larger number of cases.

Although this investigation had some limitations, as described below, two main possibilities should be considered if we assume that transfusion history per se leads to an increase in cancer mortality. First, the oncogenic potential of infectious agents transmitted by transfusion is possible. For example, transfusion-transmitted hepatitis virus infection may carry an increased risk for developing a wide range of tumors [20, 21]. Second, the white blood cells and platelets in allogeneic blood transfusion have been suggested to cause transfusion-related immunomodulation (TRIM) [22, 23]. In Japan, until 1988, blood transfusion was performed without filtration or irradiation of white blood cells, or screening for bacterial or viral infections. Whole blood or packed red blood cells were used after matching the allogeneic antigens [24].

In terms of the oncogenic potential of infectious agents, previous studies have suggested that hepatitis C virus (HCV) might have an oncogenic role in a wide range of cancers [21]. Therefore, an association between history of liver disease and cancer mortality might be an important indicator of whether infectious agents are responsible for the significant association between transfusion history and cancer mortality, because blood transfusion is an important transmission route for HCV in Japan [25, 26]. We found that history of liver disease was associated with history of transfusion, and was significantly associated with increased risk for liver cancer mortality. On the other hand, overall cancer and nonliver cancer mortality were not significantly associated with history of liver disease, but were associated with history of transfusion. This suggests that the increased risk for overall cancer mortality was associated with phenomena induced by pathogens other than infectious agents, which occurs in liver disease.

In terms of the second possibility, TRIM might be directly or indirectly associated with the incidence or promotion of fatal cancer. Clinical and experimental results have shown that allogeneic blood transfusion leads to immunomodulation in the recipient [27–29]. There is epidemiological evidence that TRIM facilitates the recurrence of malignancy or the occurrence of postoperative infections [30–32], although an association with fatal cancer occurrence has not been demonstrated. This condition might be similar to the phenomenon that high-dose immunosuppressive regimens, such as cyclosporine, in transplant recipients lead to a higher frequency of cancer mortality [33]. Therefore, further evidence of the immunosuppressive effect of transfusion on cancer mortality is needed in other populations.

The present study has several limitations. We could not determine the incidence of diseases or other events that

Table 3 Multivariate analyses for the association between history of transfusion or liver disease and cancer mortality: cancer (specific site), all cancer, and nonliver cancer

	History of transfusion			History of liver disease		
	n	Adjusted HR (95% CI)	*P* value	*n*	Adjusted HR (95% CI)	*P* value
Cancer (all)						
All	71	1.75 (1.32–2.33)	0.0001	25	1.26 (0.83–1.91)	0.27
Men	37	1.47 (1.00–2.18)	0.0522	17	1.26 (0.76–2.09)	0.38
Women	34	2.18 (1.39–3.43)	0.0007	8	1.39 (0.67–2.84)	0.37
Cancer (nonliver)						
All	64	1.68 (1.25–2.26)	0.0007	19	1.00 (0.62–1.61)	0.99
Men	32	1.33 (0.87–2.02)	0.18	13	1.01 (0.56–1.81)	0.98
Women	32	2.20 (1.38–3.51)	0.0009	6	1.08 (0.47–2.45)	0.86
Cancer (specific site)						
Lung						
All	12	1.54 (0.78–3.06)	0.22	4	1.06 (0.39–2.91)	0.91
Men	7	1.12 (0.46–2.75)	0.8	3	1.09 (0.34–3.50)	0.88
Women	5	2.87 (0.90–9.14)	0.07	1	1.31 (0.17–10.18)	0.79
Stomach						
All	13	1.99 (1.01–3.91)	0.0462	4	1.17 (0.42–3.23)	0.76
Men	7	1.35 (0.55–3.34)	0.51	3	0.78 (0.19–3.22)	0.73
Women	6	3.24 (0.91–11.52)	0.0698	1	2.32 (0.53–10.11)	0.26
Colorectum						
All	6	1.27 (0.46–3.46)	0.65	1	0.68 (0.09–5.02)	0.71
Men	1	n/a	n/a	1	2.40 (0.31–18.60)	0.4
Women	5	1.25 (0.34–4.59)	0.7334	0	n/a	n/a
Liver						
All	7	3.07 (1.14–8.31)	0.0269	6	6.57 (2.51–17.23)	0.0001
Men	5	3.94 (1.19–13.08)	0.025	4	5.45 (1.65–17.93)	0.0053
Women	2	2.15 (0.35–11.89)	0.4259	2	9.04 (1.80–45.40)	0.0075
Pancreas						
All	7	3.34 (1.28–8.72)	0.014	0	n/a	n/a
Men	4	4.10 (1.12–14.98)	0.0328	0	n/a	n/a
Women	3	2.57 (0.63–10.60)	0.1905	0	n/a	n/a
Other						
All	26	1.47 (0.89–2.42)	0.13	9	1.26 (0.61–2.59)	0.53
Men	13	1.32 (0.67–2.57)	0.42	6	1.12 (0.45–2.77)	0.81
Women	13	1.70 (0.80–3.61)	0.16	3	1.58 (0.49–5.13)	0.45

Adjusted HR for cancer mortality was estimated after adjustment for age, sex, and typical risk factors for overall cancer mortality [smoking status (never smokers, current smokers or ex-smokers) and alcohol consumption (never drinkers, current drinkers or ex–drinkers)], history of pregnancy (yes or no), and other factors that may have been related to transfusion or that showed a significant association in the age-adjusted univariate analysis (history of external injury, abdominal surgery, and liver disease). People with history of cancer before participation in the cohort were excluded from this analysis. Each specific site of cancer was defined from ICD, tenth revision, as lung (C34), stomach (C16), colorectum (C18), liver (C22), pancreas (C25)

n/a not applicable

might have been related to cancer mortality following entry to the study, and therefore it is possible that unrecognized confounding factors might be related to the association between history of transfusion and cancer mortality.

Another limitation is that this survey collected self-reported transfusion history, which may have reduced the objectivity of the study. It is also possible that some cancer deaths were not recorded in the cohort, specifically those who left their original communities to undergo long-term hospitalization. These factors may have hindered accurate calculation of the association between transfusion history and cancer mortality. On the other hand, we could not use background information on the transfusion procedure. Therefore, the possibility of biased selection of persons

receiving blood transfusions cannot be ignored. Finally, because this study contained relatively small numbers of cancer mortality for each site, it is possible that statistical errors may have had an adverse influence on the results.

In this study, we found that history of blood transfusion prior to 1990 in middle-aged and elderly general population in Japan was mildly but significantly associated with cancer mortality, in terms of overall cancer and nonliver cancer. The strength of our study was that we tested and confirmed the association between transfusion history and overall or site-specific cancer mortality, by conducting a long-term follow-up cohort study. In addition, the significant association remained even after adjusting for known major cancer mortality factors such as alcohol intake and smoking, and after excluding early deaths, which might have been related to unidentified factors that may engender a spurious association between transfusion history and cancer mortality, and our results showed that this association seemed to be independent from the oncogenic action induced by infectious agents from transfusion. Since 1990, the system and procedures used for transfusion in Japan have evolved dramatically; therefore, we need to evaluate whether current regimens have reduced the risk for major disease such as cancer.

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Coffee, green tea, black tea and oolong tea consumption and risk of mortality from cardiovascular disease in Japanese men and women

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ABSTRACT

Background The effects of coffee and green, black and oolong teas and caffeine intake on cardiovascular disease (CVD) mortality have not been well defined in Asian countries.

Methods To examine the relationship between the consumption of these beverages and risk of mortality from CVD, 76 979 individuals aged 40–79 years free of stroke, coronary heart disease (CHD) and cancer at entry were prospectively followed. The daily consumption of beverages was assessed by questionnaires.

Results 1362 deaths were documented from strokes and 650 deaths from CHD after 1 010 787 person-years of follow-up. Compared with non-drinkers of coffee, the multivariable HR and 95% CI for those drinking 1–6 cups/week, 1–2 cups/day and ≥3 cups/day were 0.78 (0.50 to 1.20), 0.67 (0.47 to 0.96) and 0.45 (0.17 to 0.87) for strokes among men (p=0.009 for trend). Compared with non-drinkers of green tea, the multivariable HR for those drinking 1–6 cups/week, 1–2 cups/day, 3–5 cups/day and ≥6 cups/day were 0.34 (0.06–1.75), 0.28 (0.07–1.11), 0.39 (0.18–0.85) and 0.42 (0.17–0.88) for CHD among women (p=0.038 for trend). As for oolong tea, the multivariable HR of those drinking 1–6 cups/week and ≥1 cups/day were 1.00 (0.65–1.55) and 0.39 (0.17–0.88) for total CVD among men (p=0.049 for trend). Risk reduction for total CVD across categories of caffeine intake was most prominently observed in the second highest quintile, with a 38% lower risk among men and 22% among women.

Conclusions Consumption of coffee, green tea and oolong tea and total caffeine intake was associated with a reduced risk of mortality from CVD.

Both coffee and tea are one of the most frequently consumed beverages worldwide. They are rich in caffeine and polyphenols, which have potent antioxidant properties and have been observed to play a protective role against cardiovascular disease (CVD).[1 2] Although the relationship between coffee consumption and CVD has been extensively studied,[3–7] few studies have examined the relationship between tea consumption and CVD.[8–11] Instead, most studies have examined the association between coffee consumption and CVD and have focused on coronary heart disease (CHD) in which the association of coffee consumption with stroke remains unclear. In addition, most studies on the link between coffee consumption and CVD have been conducted in western countries, and only a few studies have been undertaken in Asian countries. The purpose of the present study was thus to examine comprehensively the relationship of the consumption of coffee, green, black and oolong tea with mortality from CVD among Japanese men and women in a large prospective cohort study with 1 010 787 person-years of follow-up. We also examined whether caffeine can be used to explain the effects of these beverages.

METHODS

Study population

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) started between 1988 and 1990. Details of our research methods have been published elsewhere.[12] The study consisted of 110 792 individuals (46 465 men and 64 327 women) who were 40–79 years of age and living in 45 communities across Japan. Among them, data on the consumption of all beverages (coffee, green tea, black tea and oolong tea) were available for 36 332 men and 50 925 women. A total of 1977 men and 2615 women was then excluded from the study because of a history of stroke, CHD, or cancer at baseline. Therefore, 34 345 men and 48 310 women were involved in the present study. The ethical committees at Nagoya University and the University of Tsukuba approved the study.

Assessment of cardiovascular disease

For mortality surveillance in each community, investigators conducted a systematic review for death certificates, all of which were forwarded to the public health centre in the area of residency.[13] Mortality data were sent centrally to the Ministry of Health and Welfare, and the underlying causes of death were coded according to the International Classification of Diseases, 9th revision, from 1988 to 1994 and the 10th revision from 1995 to 2003 for the National Vital Statistics. In Japan, registration of death is required by the Family Registration Law and is believed to be followed across Japan. Therefore, all deaths that occurred in the cohort were ascertained by death certificates from a public health centre, except for subjects who died after they had moved from their original community, in which case subjects were treated as censored cases.

The follow-up was conducted until the end of 2003, and the average follow-up for the participants was 13.1 years. Cause-specific mortality was determined by total CVD (International Classification of Disease, 9th revision codes 390–459, 10th revision codes I01–I99), total CHD (codes 410–414 and I20–I25) and total stroke (430–438 and I60–I69), separately.

Assessment of consumption of coffee and caffeine intake

At baseline, consumption of coffee and teas was assessed using a self-administered dietary questionnaire as described previously.[14] Briefly, participants were asked to state their average consumption of coffee, green, black and oolong teas during the previous year. They could select any of four frequency responses: 'less than once a week', 'about one to two times a week', 'about three to four times a week' and 'almost every day'. Participants who selected the response of 'almost every day' were also asked to state their average consumption of these beverages in numbers of cups per day. The consumption of decaffeinated coffee or tea was not recorded because these products were not commercially available in Japan in the early 1990s. The estimated caffeine content was 153 mg per cup (170 ml) of coffee, 30 mg per cup (200 ml) of green tea, 51 mg per cup (170 ml) of black tea and 38 mg per cup (190 ml) of oolong tea. The mean caffeine intake was 287 mg/day for men and 254 mg/day for women. Relative proportions of caffeine intake by beverage were 45–49% from coffee, 47–48% from green tea, 1–2% from black tea and 3–6% from oolong tea.

The reproducibility and validity of this dietary questionnaire was reported previously.[15] Briefly, the Spearman correlation coefficients between the two questionnaires, administered 1 year apart for 85 participants (eight men and 77 women), were 0.87 for coffee, 0.79 for green tea, 0.77 for black tea and 0.56 for oolong tea.[15] The coefficients between the average of two questionnaires and four 3-day dietary records and four 1-week dietary records were 0.79 (8.0 cups and 7.1 cups per week) for coffee, 0.47 (25.4 cups and 30.1 cups per week) for green tea, 0.70 (1.4 cups and 1.6 cups per week) for black tea and 0.55 (1.8 cups and 1.2 cups per week) for oolong tea. When we restricted the data to the 77 women, the results were essentially the same.

Statistical analysis

We presented baseline characteristics according to the frequency of consumption of each beverage. Tests for trends were conducted using the median values of confounding variables in each category of beverage. The linear regression model was used for continuous variables and the logistic regression model was used for categorical variables.

The HR and 95% CI for CVD were calculated in each category of beverage and in each quartile of caffeine intake; less than one cup per week or the lowest quartile was used as the reference category. We estimated age and body mass index (BMI)-adjusted HR and multivariable HR using the Cox proportional hazards model, adjusting for age (in years), sex-specific quintiles of BMI (weight in kilograms divided by the square of height in meters), smoking status (never, former, or current (one to 19, 20–29, or ≥30 cigarettes/day)), alcohol intake (never, former, or current (one to 22, 23–45, 46–68, or ≥69 g/day)), hours of walking (<0.5, 0.5, 0.6–0.9 and ≥1.0 h/day), hours of participation in sports (<1, 1–2, 3–4 and ≥5 h/week), use of hormone therapy for women, history of hypertension (yes or no), history of diabetes mellitus (yes or no), perceived mental stress (low, medium and high), and educational level (primary school, junior high school, high school and college or higher). Furthermore, we adjusted for the consumption of other beverages, multivitamin use, vitamin E supplement use, consumption of total fruits, total vegetables, total bean products, total meats (continuous variable, servings/week for each food) and daily total energy intake (continuous variable, kcal/day). Sex-specific quintiles of BMI were used to account for different distributions between the sexes. We conducted a test for trend by treating median values of each category of beverage or caffeine intake as continuous variables. We also examined a possible non-linear relationship between mortality from total CVD and caffeine intake, coffee consumption or green tea consumption with cubic spline analysis using SAS macro.[16 17] Four knots were set at quintiles 0.05, 0.35, 0.65 and 0.95.

We examined the association of each beverage consumption and total caffeine intake with the risk for CVD stratified by age group (40–59 years and 60–80 years), smoking status (non or ex-smokers and current smokers), alcohol intake (non or ex-drinkers and current drinkers), history of hypertension (yes and no), history of diabetes (yes and no), BMI (<25.1 kg/m^2 and ≥25.1 kg/m^2), educational level (before college and college or higher), total fruit intake (<3 servings/week and ≥3 servings/week), total vegetable intake (<3 servings/week and ≥3 servings/week) and total bean intake (<3 servings/week and ≥3 servings/week). The interactions with these stratified variables were tested by using cross-product terms of caffeine intake and the stratified variables. All analyses were conducted using the SAS statistical package, version 8.2. p Values for statistical tests were two-tailed, and 95% CI were estimated.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

The baseline characteristics of the study cohort according to beverage consumptions are given in table 1 and table 2. During the 13.1-year follow-up of 34 345 men and 48 310 women aged 40–79 years (mean age of 57.1 years), we documented 1807 deaths from total CVD (404 total CHD and 782 total strokes) among men and 1557 (292 total CHD and 704 total strokes) among women. Age was associated with higher consumption of green tea and black tea and lower consumption of coffee and oolong tea for both men and women. BMI was positively associated with the consumption of oolong tea for men and women but were inversely associated with the consumption of coffee for men and women, green tea for men and black tea for women. A history of hypertension was inversely associated with the consumption of coffee and black tea, but it was not associated with the consumption of green tea and oolong tea. A history of diabetes was inversely associated with the consumption of coffee, green tea and black tea, but it was inversely associated with oolong tea consumption. Higher stress, higher vitamin E intake, higher multivitamin intake and less walking time were associated with a higher consumption of coffee, black tea and oolong tea and lower consumption of green tea. Achieving a higher educational level was associated with a higher consumption of coffee, black tea and oolong tea, but it was not associated with green tea consumption. In general, the consumption of vegetables, fruits and beans were positively associated with the consumption of teas but were inversely associated with coffee in both men and women. The association of current smoking and alcohol drinking with the consumption of the beverages varies among each beverage and among men and women.

A U-shaped association was found between coffee consumption and mortality from total CVD (table 3). In men, compared

Table 1 Baseline characteristics of men according to the consumption of coffee, green tea, black tea, and oolong tea: Japan Collaborative Cohort (JACC) Study, Japan, 1988

Variable	Men													
	Participants, n	Age, years	BMI, kg/m^2	History of HT, %	History of DM, %	Current smoker, %	Current drinker, %	Vitamin E use, %	Multivitamin use, %	Hormone use, %	High mental stress, %	College or higher education, %	Walking >0.5 h/day, %	Sports participation >3 h/week, %
Coffee														
<1 cup/week	11 680	59.5	22.6	20.6	8.9	46.7	75.3	2.7	12.5	–	17.4	13.4	71.8	15.1
1–6 cups/week	8837	57.4	22.8	21.3	7.0	51.3	78.7	3.3	16.1	–	19.0	15.6	70.4	14.7
1–2 cups/day	8012	55.5	22.7	16.6	6.0	58.9	76.1	3.6	16.4	–	27.1	20.5	68.2	14.5
≥3 cups/day	3061	51.7	22.6	10.7	5.5	76.8	67.4	3.9	16.7	–	34.2	22.4	66.2	13.2
p for trend		<0.001	0.026	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	–	<0.001	<0.001	<0.001	0.014
Green tea														
<1 cup/week	3076	56.7	22.6	21.4	8.4	51.2	71.7	3.5	12.9	–	25.2	14.7	68.1	12.9
1–6 cups/week	3415	55.3	22.9	18.8	7.3	52.8	79.4	3.6	15.2	–	24.3	17.7	67.3	13.0
1–2 cups/day	4510	55.4	22.6	18.8	6.3	55.6	77.4	3.4	15.6	–	27.1	20.5	67.9	14.7
3–5 cups/day	12 151	57.0	22.6	19.5	6.9	54.0	76.8	3.4	15.1	–	23.9	19.1	68.4	14.9
≥6 cups/day	8115	58.7	22.5	20.2	6.1	55.2	73.3	2.7	13.3	–	19.1	17.1	73.7	15.1
p for trend		<0.001	<0.001	0.936	<0.001	<0.001	0.115	0.009	0.431	–	<0.001	0.234	<0.001	<0.001
Black tea														
<1 cup/week	30 459	56.9	22.6	20.2	6.6	54.5	75.8	3.0	14.1	–	22.7	17.0	69.2	13.8
1–6 cups/week	3363	56.3	27.1	17.9	6.0	49.9	74.3	5.2	18.5	–	28.0	28.0	67.4	17.0
≥1 cups/day	523	57.1	22.4	17.1	6.3	45.2	72.0	5.5	17.3	–	29.6	31.7	65.2	16.2
p for trend		<0.001	0.098	0.001	0.266	<0.001	0.007	<0.001	<0.001	–	<0.001	<0.001	0.007	<0.001
Oolong tea														
<1 cup/week	26 973	57.1	22.5	20.0	6.2	53.9	75.4	2.8	13.7	–	22.4	17.5	69.4	13.9
1–6 cups/week	3273	54.4	23.3	18.3	6.9	55.1	77.2	4.9	19.6	–	28.7	22.9	66.8	16.1
≥1 cups/day	1611	54.9	23.4	19.8	10.8	51.1	74.0	6.9	17.2	–	30.0	22.3	65.9	16.3
p for trend		<0.001	<0.001	0.170	<0.001	0.294	0.944	<0.001	<0.001	–	<0.001	<0.001	<0.001	<0.001

Variable	Men					
	Total vegetables, servings/week	Total fruits, servings/week	Total beans, servings/week	Total fish, servings/week	Total meat, servings/week	Total energy intake, kcal/day
Coffee						
<1 cup/week	2.83	2.42	2.37	2.49	1.03	1773
1–6 cups/week	2.7	2.4	2.36	2.47	1.12	1785
1–2 cups/day	2.61	2.91	2.21	2.31	1.11	1697
≥3 cups/day	2.44	2.77	2.01	2.15	1.13	1691
p for trend	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Continued

Table 1 Continued

Variable	Men						
	Total vegetables, servings/week	Total fruits, servings/week	Total beans, servings/week	Total fish, servings/week	Total meat, servings/week	Total energy intake, kcal/day
Green tea						
<1 cup/week	2.49	2.40	2.22	2.23	0.98	1653
1–6 cups/week	2.52	2.39	2.18	2.27	1.02	1712
1–2 cups/day	2.66	2.78	2.22	2.32	1.11	1680
3–5 cups/day	2.70	2.87	2.30	2.38	1.10	1721
≥6 cups/day	2.95	3.02	2.47	2.60	1.14	1842
p for trend	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Black tea						
<1 cup/week	2.71	2.71	2.31	2.40	1.07	1743
1–6 cups/week	2.95	3.35	2.51	2.49	1.27	1750
≥1 cups/day	2.89	3.33	2.40	2.37	1.19	1627
p for trend	<0.001	<0.001	<0.001	0.024	<0.001	0.079
Oolong tea						
<1 cup/week	2.70	2.71	2.29	2.39	1.07	1746
1–6 cups/week	2.84	3.12	2.39	2.40	1.17	1716
≥1 cups/day	2.91	3.21	2.53	2.49	1.16	1649
p for trend	<0.001	<0.001	<0.001	0.012	<0.001	<0.001

with those who drank less than one cup per week, the multivariable HR for total CVD among those drinking one to six cups a week, one to two cups a day and three or more cups a day were 0.71 (95% CI 0.53 to 0.96), 0.84 (95% CI 0.64 to 0.99) and 1.17 (95% CI 0.77 to 1.76). The corresponding data for women were 0.87 (95% CI 0.62 to 1.23), 0.77 (95% CI 0.55 to 0.99) and 2.30 (95% CI 1.31 to 4.02). The non-linear relationship was confirmed by cubic spline analysis (figure 1; non-linear $p<0.001$ for both men and women). On the other hand, coffee consumption was associated with linear risk reduction for mortality from stroke in men: the multivariable HR across categories of coffee consumption were 1.0, 0.78 (95% CI 0.50 to 1.20), 0.67 (95% CI 0.47 to 0.96), 0.45 (95% CI 0.17 to 0.87, $p=0.009$ for trend). The inverse association was more prominently observed among men, although interaction with sex was not statistically significant ($p=0.204$). We found no significant association of coffee consumption with CHD for either men or women.

We found that green tea consumption was associated with a lower risk of mortality from total CVD (table 4). In women, the multivariable HR of mortality due to total CVD based on green tea consumption compared with non-drinkers were 1.13 (95% CI 0.66 to 1.93) for one to six cups a week, 0.77 (95% CI 0.48 to 1.26) for one to two cups a day, 0.81 (95% CI 0.56 to 1.18) for three to five cups a day and 0.62 (95% CI 0.40 to 0.98) for six or more cups a day ($p=0.031$ for trend). The inverse association was not observed in men ($p=0.047$ for interaction). The corresponding data for CHD among women were 0.34 (95% CI 0.06 to 1.75), 0.33 (95% CI 0.07 to 1.11), 0.39 (95% CI 0.18 to 0.85) and 0.42 (95% CI 0.15 to 0.92, $p=0.038$ for trend).

Black tea consumption showed no association with CHD, stroke or total CVD either among men and women (see supplementary table 1 (available online only), $p=0.467$ for interaction with sex). Oolong tea consumption of one or more cups per day was associated with a reduced risk of mortality from total CVD. Compared with those who drank less than one cup a week, the multivariable HR for total CVD among those drinking one to six cups a week and one or more cups per day were 1.00 (95% CI 0.65 to 1.55) and 0.39 (95% CI 0.17 to 0.88) in men (see supplementary table 2 (available online only), $p=0.049$ for trend). The inverse association was more strongly observed in men, although the interaction was not significant ($p=0.261$).

The relationship between caffeine intake and the risk of mortality from total CVD and stroke was U-shaped, in which the highest risk reduction was observed among persons with the second highest quintile (table 5). In men, the HR for mortality from total CVD across categories of caffeine intake were 1.0, 0.83 (95% CI 0.61 to 1.13), 0.70 (95% CI 0.50 to 0.98), 0.62 (95% CI 0.43 to 0.92) and 0.95 (95% CI 0.86 to 1.05; $p=0.083$ for trend). The inverse association was more pronounced in men than women ($p=0.040$ for interaction). A U-shaped association was also observed between caffeine intake and stroke. The multivariable HR for those with the second highest quintile for caffeine intake compared with those with the lowest quintile was 0.65 (95% CI 0.37 to 1.13) for men and 0.50 (95% CI 0.26 to 0.94) for women. The non-linear relationship was confirmed by cubic spline analyses (figure 1; non-linear $p<0.001$ for both men and women). No significant association was observed between caffeine intake and CHD.

We conducted stratified analyses to evaluate whether the association between CVD and caffeine intake or the consumption of coffee or teas varied according to age, smoking status, alcohol intake, history of hypertension, history of diabetes, BMI, educational level, total fruit intake, total vegetable intake and

Table 2 Baseline characteristics of women according to the consumption of coffee, green tea, black tea, and oolong tea: Japan Collaborative Cohort (JACC) Study, Japan, 1988

Variable	Women													
	Participants, n	Age, years	BMI, kg/m^2	History of HT, %	History of DM, %	Current smoker, %	Current drinker, %	Vitamin E use, %	Multivitamin use, %	Hormone use, %	High mental stress, %	College or higher education, %	Walking >0.5 h/day, %	Sports participation >3 h/week, %
Coffee														
<1 cup/week	18 214	60.2	23	28.1	5.5	3.5	17.7	7.2	11.5	4.1	17.8	7.6	73.6	11.0
1–6 cups/week	11 966	56.9	23.1	22.0	3.2	3.8	26.9	9.1	13.5	4.5	18.5	9.9	74.8	11.2
1–2 cups/day	12 477	55.3	22.8	18.3	3.2	6.5	30.5	9.3	14.0	5.1	22.3	11.4	72.1	9.8
≥3 cups/day	2732	50.9	22.7	12.1	2.5	18.3	34.3	9.1	13.2	5.8	28.3	13.8	71.0	8.2
p for trend		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Green tea														
<1 cup/week	5118	56.9	22.9	23.4	5.4	6.5	22.6	8.0	11.8	5.3	21.6	8.6	69.7	8.7
1–6 cups/week	5017	55.6	23.1	20.9	4.0	5.7	28.2	10.1	12.8	5.0	21.8	9.2	71.0	9.4
1–2 cups/day	5424	55.9	22.8	19.5	3.8	6.3	26.5	8.6	13.2	5.0	22.3	11.4	71.0	9.7
3–5 cups/day	17 665	57.6	22.8	21.9	3.8	4.7	23.3	7.8	12.7	4.7	19.9	10.9	72.5	10.6
≥6 cups/day	10 288	58.5	23.0	21.7	3.7	5.3	22.1	7.3	12.1	5.0	17.9	10.1	75.1	10.1
p for trend		<0.001	0.605	0.592	<0.001	<0.001	<0.001	<0.001	0.918	0.307	<0.001	0.004	<0.001	0.001
Black tea														
<1 cup/week	41 605	57.3	22.9	22.6	4.1	5.1	22.5	7.5	11.8	4.5	20.0	9.2	72.0	9.6
1–6 cups/week	5761	56.1	22.7	19.4	2.8	4.0	27.3	11.3	16.4	7.0	21.7	17.0	71.8	12.3
≥1 cups/day	944	57.4	22.2	21.5	4.0	7.0	30.6	11.9	18.7	8.3	25.3	23.0	69.3	10.2
p for trend		<0.001	<0.001	<0.001	0.002	0.298	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.165	<0.001
Oolong tea														
<1 cup/week	35 575	57.6	22.8	22.1	3.7	4.7	21.8	6.7	11.8	4.4	19.7	9.6	72.4	9.7
1–6 cups/week	4760	55.0	23.5	21.7	4.5	6.2	29.4	11.6	15.9	6.2	23.8	14.0	70.6	11.3
≥1 cups/day	3694	55.5	23.6	22.8	4.9	8.1	29.8	14.4	15.8	7.4	23.3	14.5	70.3	10.2
p for trend		<0.001	<0.001	0.581	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.0

Variable	Women				
	Total vegetables, servings/week	Total fruits, servings/week	Total beans, servings/week	Total fish, servings/week	Total meat, servings/week	Total energy intake, kcal/day
Coffee						
<1 cup/week	3.29	3.11	2.68	2.65	1.04	1636
1–6 cups/week	3.21	3.35	2.59	2.68	1.14	1674
1–2 cups/day	3.06	3.73	2.5	2.52	1.17	1621
≥3 cups/day	2.95	3.56	2.27	2.41	1.23	1665
p for trend	<0.001	<0.001	<0.001	<0.001	<0.001	0.325

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Table 2 Continued

Variable	Women						
	Total vegetables, servings/week	Total fruits, servings/week	Total beans, servings/week	Total fish, servings/week	Total meat, servings/week	Total energy intake, kcal/day
Green tea						
<1 cup/week	2.99	3.08	2.42	2.42	1.00	1365
1–6 cups/week	3.08	3.21	2.49	2.49	1.07	1402
1–2 cups/day	3.10	3.57	2.57	2.53	1.12	1389
3–5 cups/day	3.17	3.63	2.60	2.61	1.13	1440
≥6 cups/day	3.37	3.73	2.77	2.77	1.15	1503
p for trend	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Black tea						
<1 cup/week	3.17	3.41	2.61	2.60	1.08	1435
1–6 cups/week	3.39	4.09	2.80	2.74	1.30	1461
≥1 cups/day	3.31	4.13	2.69	2.55	1.23	1382
p for trend	<0.001	<0.001	<0.001	<0.001	<0.001	0.118
Oolong tea						
<1 cup/week	3.12	3.43	2.57	2.58	1.09	1445
1–6 cups/week	3.44	3.88	2.84	2.75	1.21	1431
≥1 cups/day	3.43	3.79	2.78	2.67	1.15	1372
p for trend	<0.001	<0.001	0.098	0.266	<0.001	<0.001

total bean intake. Effect modification was observed for a history of hypertension and BMI in coffee consumption and caffeine intake (figure 1). The inverse association was more clearly observed for individuals with a history of hypertension (p=0.015 for coffee consumption and p=0.018 for caffeine intake) and non-obese individuals with a BMI less than 25 kg/m^2 (p=0.003 for coffee consumption and p=0.006 for caffeine intake). No significant effect modification was observed for any variables in the consumption of teas.

DISCUSSION

In the present large prospective study, we observed that the consumption of coffee, green tea and oolong tea and caffeine intake was associated with a lower risk of mortality from CVD for Japanese men and women. A U-shaped relationship was observed between the risk of mortality from total CVD and coffee consumption or caffeine intake. Moderate coffee consumption (one to two cups a day) was associated with a 16–23% lower risk of mortality from total CVD among men and women. The second highest quintile of caffeine intake was associated with a 22–38% lower risk of mortality from total CVD compared with a 4–5% lower risk in the highest quintile. In contrast to the U-shaped relationship between coffee consumption or caffeine intake and mortality from CVD, a higher amount of green tea consumption consistently decreased the risk of mortality from CVD. The inverse association was primarily observed among women, who had a 38% lower risk of mortality for those who drank six or more cups per day. Oolong tea consumption of one or more cups per day was associated with a 61% lower risk of mortality from total CVD among men. In contrast to the inverse association of green tea and oolong tea with mortality from CVD, black tea consumption did not show any association.

The U-shaped relationship between coffee consumption and CVD was consistent with recent epidemiological studies.[3 5 6 18] Andersen *et al*[5] reported in the Iowa Women's Health Study that moderate coffee consumption (one to three cups a day) was associated with the highest (29%) risk reduction of mortality from CVD. Similar observations were obtained in the Nurses' Health Study consisting of 83 076 women. In that study, participants who consume two to three cups a day of coffee had the lowest incidence of stroke. It should be noted that frequent coffee consumption (three or more cups per day) for women was associated with a 130% higher risk of mortality from total CVD compared with a 23% lower risk for moderate coffee consumption (one to two cups a day), showing a J-shaped relationship. In the CARDIO2000 case–control study consisting of 848 case subjects and 1078 control subjects,[19] Panagiotakos *et al*[19] reported a J-shaped association between coffee consumption and the risk of developing acute coronary syndrome. Compared with non-drinkers, those who consume more than four cups per day of coffee had a 3.24 times higher risk of developing acute coronary syndrome. In the present study, there were only a few individuals who drank four or more cups of coffee per day and, therefore, we could not examine the effect of excessive coffee intake among men. There thus remains the possibility that excessive coffee consumption might increase the risk of mortality from CVD in men as well as in women. In the stratified analysis, effect modification by history of hypertension was observed. Taking into account that a history of hypertension and smoking status showed opposite trends according to coffee consumption, one might suspect that a U or J-shaped relationship could be influenced by a history of hypertension and smoking status. However, a U or J-shaped relationship was also

Table 3 HR for mortality from CVD according to coffee consumption: JACC Study, Japan, 1988–2003 (n=82 655)

	Coffee consumption				
	<1 cup/week	1–6 cups/week	1–2 cups/day	≥3 cups/day	p for trend
Men					
Person-years	145 683	116 260	102 867	39 378	
Total CVD					
N	822	450	326	83	
Age and BMI-adjusted HR	1	0.88 (0.84–0.94)	0.80 (0.71–0.90)	0.75 (0.66–0.86)	<0.001
Multivariable HR	1	0.71 (0.53–0.96)	0.84 (0.64–0.99)	1.17 (0.77–1.76)	0.065*
CHD					
N	160	99	92	25	
Age and BMI-adjusted HR	1	0.88 (0.68–1.14)	1.11 (0.85–1.46)	1.20 (0.77–1.87)	0.482
Multivariable HR	1	0.85 (0.46–1.58)	0.92 (0.50–1.66)	1.29 (0.59–2.84)	0.906
Stroke					
N	384	194	127	17	
Age and BMI-adjusted HR	1	0.73 (0.61–0.87)	0.61 (0.49–0.76)	0.34 (0.21–0.57)	<0.001
Multivariable HR	1	0.78 (0.50–1.20)	0.67 (0.47–0.96)	0.45 (0.17–0.87)	0.009
Women					
Person-years	239 297	164 307	166 699	36 295	
Total CVD					
N	850	307	233	46	
Age and BMI-adjusted HR	1	0.76 (0.66–0.88)	0.65 (0.55–0.76)	1.25 (0.91–1.70)	<0.001
Multivariable HR	1	0.87 (0.62–1.23)	0.77 (0.55–0.99)	2.30 (1.31–4.02)	0.966
CHD					
N	155	73	39	7	
Age and BMI-adjusted HR	1	0.95 (0.69–1.30)	0.65 (0.44–0.95)	1.30 (0.60–2.83)	0.102
Multivariable HR	1	0.63 (0.23–1.67)	0.89 (0.42–1.87)	0.57 (0.06–4.94)	0.409
Stroke					
N	374	122	124	20	
Age and BMI-adjusted HR	1	0.67 (0.54–0.84)	0.73 (0.58–0.92)	1.16 (0.72–1.86)	0.011
Multivariable HR	1	0.87 (0.53–1.44)	0.68 (0.41–1.03)	3.17 (1.50–6.69)	0.967

Multivariable HR was adjusted for body mass index (BMI), history of hypertension, history of diabetes, smoking status, alcohol intake, education, walking hours, hours of sports participation, perceived mental stress, multivitamin use, vitamin E supplement use, consumption of total fruits, total vegetable, total beans, total meat, total fish and seaweeds and total daily energy intake.
*Non-linear p (cubic spline) <0.001.
CHD, coronary heart disease; CVD, cardiovascular disease.

observed in non-smokers without a history of hypertension, indicating that smoking status and hypertension is unlikely to influence the non-linear relationship.

The inverse association between mortality from CVD and the consumption of green tea was consistent with previous studies.[9 10 20–22] In the study by Kuriyama *et al*[9] using 40 530 Japanese men and women, the inverse association was most pronounced for stroke but not for CHD, as shown in our study. The reason for the discrepancy between the studies is unclear. One possibility is a different classification of green tea consumption employed in each study (less than one cup a day, one to two cups a day, three to four cups a day, more than five cups a day in the study by Kuriyama *et al*;[9] less than one cup a week, one to six cups a week, one to two cups a day, three to five cups a day and more than six cups a day in the present study). We thus employed the classification of green tea consumption used in the study by Kuriyama *et al*,[9] but the results remained substantially the same after changing the classification (data not shown). Another possible explanation for the discrepancy is misclassification of the consumption of green tea. Because consumption of green tea was self-reported on the questionnaire in both studies, some misclassification of exposure was inevitable. Such misclassification might have yielded the null results in the relationship between mortality from stroke or CHD and green tea consumption.

The inverse association of oolong tea and CVD mortality was not previously noted. This may be partly because oolong tea was not so popular before the 1980s in Asian countries and it is not consumed worldwide. In contrast to the inverse association of green tea and oolong tea, black tea did not show any association with mortality from CVD, although an inverse association was shown in western populations.[23 24] The null association of black tea with CVD mortality may be partly because black tea contains less antioxidant compounds such as caffeine or cathechin compared with other teas. Besides, most of the catechins in black tea are oxidised by fermentation to thearubigens and theaflavins, which have less antioxidant properties. Compared with the green tea that is not fermented, oolong tea (medium fermented) and black tea (fully fermented) have lower antioxidant properties (green tea>oolong tea>black tea).[25] In our study population, only 1.5–2.0% consumed one or more cups of black tea. Therefore, the smaller amount of consumption might partly contribute to the lack of association.

The inverse association for the consumption of coffee and caffeine intake was more pronounced in stroke among men, whereas the inverse association for green tea consumption was more pronounced in CHD among women. Similar observations have previously been reported. Sesso *et al*[26] showed the reduced risk of myocardial infarction by drinking tea (although black tea) but not by drinking coffee. Arts *et al*[23] reported that tea consumption was associated with a reduced risk of CHD but not stroke. One possible explanation for the distinct properties between coffee and green tea might be that caffeine plays a major role in the inverse association between coffee and CVD mortality, whereas another compound in green tea such as catechin has more impact on CVD mortality than caffeine.

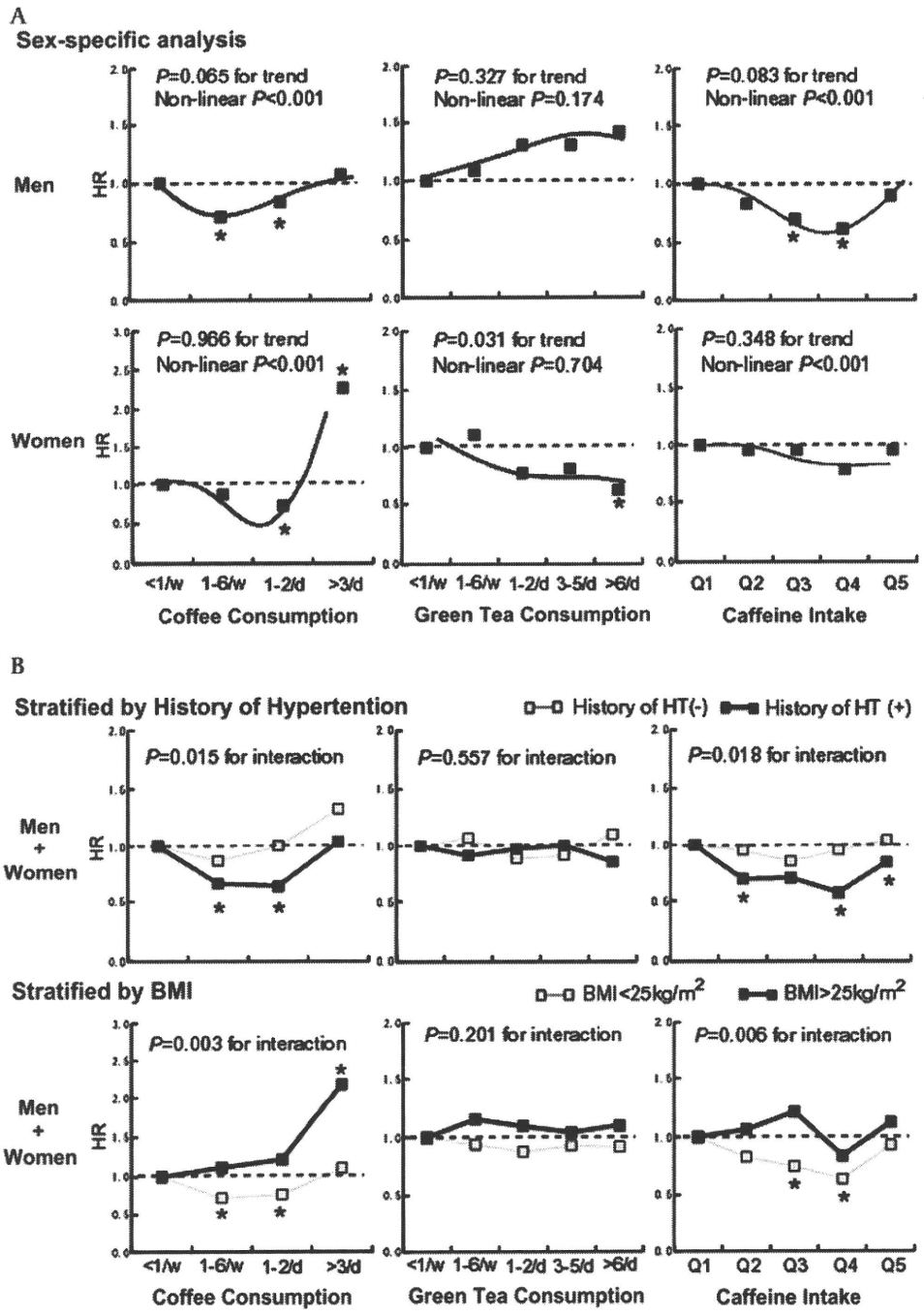

Figure 1 Multivariable HR for mortality from cardiovascular disease according to the consumption of coffee and green tea and caffeine intake, adjusted for body mass index (BMI), history of hypertension (HT), history of diabetes, smoking status, alcohol intake, education, walking hours, hours of sports participation, perceived mental stress, multivitamin use, vitamin E supplement use, consumption of total fruits, total vegetable, total beans, total meat, total fish and seaweeds and total daily energy intake in the JACC Study, Japan, 1988–2003 (n=82 655). *Indicates $p<0.05$. (A) Sex-specific HR curves and non-linear p values were drawn by cubic spline analyses with four knots at quintiles 0.05, 0.35, 0.65 and 0.95. Dots represent multivariable adjusted HR calculated by Cox proportional hazards model. (B) Sex-stratified HR was obtained in the stratified analysis by a history of hypertension and BMI.

In the stratified analysis, an inverse association of caffeine intake or coffee consumption and mortality from CVD was predominantly observed among non-obese participants with a BMI less than 25 kg/m^2 or among participants with a history of hypertension. There are two interesting reports that explain the relationship between BMI, hypertension, coffee and caffeine. It has been reported that the metabolic rate of caffeine is significantly lower (higher absorption, lower elimination and longer half-life) in obese individuals than lean ones.[27] Interestingly, it has also been reported that coffee consumption was associated with an increased risk of hypertension for individuals with slow caffeine metabolism, whereas it was associated with a decreased risk of hypertension for individuals with faster caffeine metabolism.[28] Taking into account that hypertension is an important risk factor for CVD, coffee consumption might increase the risk of CVD by inducing or worsening hypertension for obese individuals, whereas it will decrease the risk of CVD by improving hypertension for non-obese individuals. The BMI of women is significantly higher than that of men in our cohort, which might help to explain how the inverse association of coffee consumption or caffeine intake with fatal CVD is more clearly observed among men. In fact, the metabolic rate of caffeine was reported to be significantly slower in women than in men in several ethnicities.[29 30] Coffee thus shows similar characteristics to those of caffeine (ie, an inverse association is prominently observed in stroke among men, non-obese individuals and individuals with a history of hypertension), indicating that caffeine intake mostly accounts for the inverse association of coffee with mortality from CVD. On the other hand, green tea shows distinct properties from coffee or caffeine, supporting the idea that the main compound in green tea that works against CVD is different from caffeine.