Table 1
Baseline characteristics of the Ohsaki Study subjects in 1995, Japan

	Non-participants	Study participants	*P*-value[a]	Overweight/Obesity[b]		Hypertension[c]		Hyperglycemia[d]		Dyslipidemia[e]	
				(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)
N	38,915	12,340		8152	4188	7158	5182	11,292	1048	6790	5550
Age (year) (SD)	61.0 (10.6)	61.1 (9.4)	0.25	61.2 (9.6)	61.0 (8.9)	59.1 (9.7)	63.9 (8.2)	60.8 (8.3)	64.0 (8.3)	60.5 (9.8)	61.8 (8.9)
Male (%)	49.4	43.0	<0.0001	45.5	38.2	41.7	44.8	41.6	58.2	47.1	38.0
Current smoker (%)	30.0	22.3	<0.0001	24.7	17.7	23.0	21.3	21.6	30.3	23.9	20.4
Current drinker (%)	42.1	42.6	<0.0001	43.6	40.8	41.3	44.4	42.0	49.6	47.9	36.2
Overweight/obesity (%)	28.7[f]	28.8[f]	0.75	0.0[b]	100.0[b]	27.8[b]	42.5[b]	33.7[b]	36.1[b]	27.9[b]	41.4[b]
Hypertension (%)	27.5[g]	23.8[g]	<0.0001	36.6[c]	52.5[c]	0.0[c]	100.0[c]	41.0[c]	52.5[c]	39.5[c]	45.1[c]
Hyperglycemia (%)	7.2[h]	4.7[h]	<0.0001	8.2[d]	9.0[d]	7.0[d]	10.6[d]	0.0[d]	100.0[d]	7.9[d]	9.2[d]
Dyslipidemia (%)	–	–		39.9[e]	54.9[e]	42.6[e]	48.3[e]	44.6[e]	48.9[e]	0.0[e]	100.0[e]

SD denotes standard deviation.
[a] Variables were compared between study participants and non-participants by the *t*-test or the χ^2 test, as appropriate.
[b] Measured Body Mass Index ≥25.0.
[c] Blood pressure ≥140/90 mm Hg or self-report of taking antihypertensive medication.
[d] Casual blood glucose ≥150 mg/dl or self-reported history of diabetes.
[e] Casual serum cholesterol ≥220 mg/dl, or HDL <40 mg/dl, or self-report of taking lipid-lowering medication.
[f] Body Mass Index calculated by self-reported weight/(height*height) ≥25.0.
[g] Self-reported history of hypertension.
[h] Self-reported history of diabetes.

Of the 12,340 study participants, 12,054 (97.7%), 4215 (34.2%), and 12,047 (97.6%) used total, inpatient, and outpatient medical care and had more than zero costs for the 6-year period. During the follow-up, 584 subjects (4.7%) died and 921 (7.5%) were lost to follow-up. Table 1 shows the baseline characteristics of the subjects in terms of presence/absence of overweight/obesity, hypertension, hyperglycemia, and dyslipidemia. Cardiovascular risk factors were often present together in the same individual. Among the study participants, 39.1% had no risk factor, 39.3% had a single risk factor, and 21.6% had two or more risk factors. In comparison with those without overweight/obesity, those with overweight/obesity had a higher prevalence of the other three cardiovascular risk factors and were less likely to be current smokers or current drinkers. Also, hypertension, hyperglycemia, and dyslipidemia were associated with a higher prevalence of the other three cardiovascular risk factors.

Table 2 shows the adjusted monthly medical costs of the subjects in terms of presence/absence of these cardiovascular risk factors. The adjusted mean total and outpatient medical costs among overweight/obese subjects were significantly higher than those among subjects who were not overweight/obese (P=0.013, 0.030, respectively). The mean inpatient cost among overweight/obese subjects was higher than that among subjects who were not overweight/obese, but the difference was not significant (P=0.068). The adjusted mean total, inpatient, and outpatient medical costs among subjects with hypertension were significantly higher than among subjects without hypertension (P <0.0001, 0.0008, <0.0001). The adjusted mean total, inpatient, and outpatient medical costs among subjects with hyperglycemia were significantly higher than among subjects without hyperglycemia (P <0.0001, 0.0004, <0.0001). There was no difference in total, inpatient, and outpatient medical costs between subjects with and without dyslipidemia (P=0.74, 0.50, 0.55).

Table 2
Adjusted monthly medical costs by the presence/absence of the cardiovascular risk factors in the Ohsaki Study, Japan, 1996–2001

		N	Adjusted inpatient cost[a], $		Adjusted outpatient cost[a], $		Adjusted total cost[a], $		Increasing rate (%)
			(95%CI)	*P*-value	(95%CI)	*P*-value	(95%CI)	*P*-value	
Overweight/obesity[b]	(−)	8152	87.1 (78.8–95.5)	(Referent)	139.5 (135.4–143.6)	(Referent)	226.6 (216.9–236.3)	(Referent)	(Referent)
	(+)	4188	100.6 (88.9–112.3)	0.068	147.4 (141.6–153.2)	0.030	248.0 (234.4–261.6)	0.013	9.4
Hypertension[c]	(−)	7158	81.5 (72.5–90.5)	(Referent)	122.0 (117.6–126.4)	(Referent)	203.5 (193.0–213.9)	(Referent)	(Referent)
	(+)	5182	105.8 (95.1–116.4)	0.0008	170.1 (164.8–175.3)	<0.0001	275.9 (263.5–288.2)	<0.0001	35.6
Hyperglycemia[d]	(−)	11,292	88.0 (80.9–95.0)	(Referent)	137.8 (134.3–141.3)	(Referent)	225.8 (217.6–234.0)	(Referent)	(Referent)
	(+)	1048	131.8 (108.4–155.1)	0.0004	189.4 (177.9–200.9)	<0.0001	321.1 (294.0–348.2)	<0.0001	42.2
Dyslipidemia[e]	(−)	6790	93.8 (84.7–103.0)	(Referent)	141.3 (136.7–145.8)	(Referent)	235.1 (224.5–245.7)	(Referent)	(Referent)
	(+)	5550	89.1 (79.0–99.2)	0.50	143.3 (138.3–148.3)	0.55	232.4 (220.6–244.2)	0.74	−1.1

CI denotes confidence interval. The plus (+) denotes the presence of each of the index risk factors. The minus (−) denotes the absence of each of the index risk factors.
[a] Tested by analysis of covariance (ANCOVA) using non-log-transformed data on charges adjusted by age at baseline (continuous variable), sex, smoking (current smoker, past smoker, or never smoker), alcohol drinking (current drinker, past drinker, or never drinker), and comorbid condition of other three cardiovascular risk factors.
[b] Body Mass Index ≥25.0.
[c] Blood pressure ≥140/90 mm Hg or self-report of taking antihypertensive medication.
[d] Casual blood glucose ≥150 mg/dl or self-reported history of diabetes.
[e] Casual serum cholesterol ≥220 mg/dl, or HDL <40 mg/dl, or self-report of taking lipid-lowering medication.

Table 3
The joint impact of cardiovascular risk factors upon medical costs in the Ohsaki Study, Japan, 1996–2001

No. of risks	*N*	Person-months	Inpatient costs						Outpatient costs	
			Adjusted cost[a], $				Risk-attributable costs[b], $	RAC%[c] (%)	Adjusted cost[a], $	
				(95%CI)	*P*-value	Increasing rate (%)				(95%CI)
0	4821	323,036	76.2	(65.3–87.1)	(Referent)	(Referent)			117.2	(111.9–122.6)
1										
Overweight/obesity[d]	1839	123,039	82.8	(65.2–100.4)	0.99	8.7	812,054	1.1	120.4	(111.8–129.0)
Hypretension[e]	2661	177,066	95.3	(80.6–110.0)	0.47	25.1	3,381,967	4.5	161.9	(154.7–169.1)
Hyperglycemia[f]	349	23,080	126.7	(86.6–166.8)	0.25	66.3	1,165,524	1.5	160.2	(140.5–179.9)
2										
Overweight/obesity[d]+ Hypretension[e]	1971	131,829	111.1	(94.2–128.1)	0.017	45.8	4,600,825	6.1	170.1	(161.8–178.4)
Overweight/obesity[d]+ Hyperglycemia[f]	149	10,117	105.4	(44.2–166.7)	0.98	38.3	295,418	0.4	173.4	(143.4–203.5)
Hypretension[e]+ Hyperglycemia[f]	321	20,718	134.7	(92.7–176.7)	0.13	75.8	1,211,976	1.6	223.5	(202.9–244.1)
3										
Overweight/obesity[d]+ Hypretension[e]+ Hyperglycemia[f]	229	15,173	158.2	(108.7–207.7)	0.034	107.6	1,244,169	1.6	211.2	(186.9–235.5)
Total	12,340	824,056					12,711,934	16.8		

CI denotes confidence interval. RAC% denotes percentage of risk-attributable medical costs.

[a] Tested by analysis of covariance (ANCOVA) adjusted by age at baseline (continuous variable), sex, smoking (current smoker, past smoker, or never smoker), and alcohol drinking (current drinker, past drinker, or never drinker).

[b] The increment in medical costs attribute to cardiovascular risk factors were calculated by multiplying the adjusted excess costs by the number of person-months observed.

[c] The proportion of medical costs in the entire cohort that would not occur if no one had cardiovascular risk factors, which were calculated by dividing the risk-attributable medical costs by the total medical costs for entire cohort during the 6-years of observation period.

[d] Body Mass Index ≥25.

[e] Blood pressure ≥140/90 mm Hg or self-report of taking antihypertensive medication.

[f] Casual blood glucose ≥150 mg/dl or self-reported history of diabetes.

Table 3 lists the monthly mean medical costs according to the combination of cardiovascular risk factors. Medical costs increased significantly as the number of risk factors increased. Subjects without any of overweight/obesity, hypertension, and hyperglycemia (the 'no-risk-factor' group) had an adjusted mean total medical cost of $193.4 per month. Relative to this group, among subjects who had one risk factor, the presence of overweight/obesity alone was associated with a 5.1% increase in total medical costs, but this was not statistically significant; the presence of hypertension alone was associated with a 33.0% significant increase in total medical costs, and the presence of hyperglycemia alone was associated with a 48.3% significant increase. The combinations of overweight/obesity+hypertension, overweight/obesity+hyperglycemia, and hypertension+hyperglycemia were associated with 45.4%, 44.2%, and 85.2% increases in total medical costs, respectively. Subjects who had all three risk factors had total medical costs that were 91.0% higher than those of the no-risk-factor group.

During the 6-year observation period, the whole study population consumed medical costs totaling $192.6 million (824,056 person-months). Risk-attributable medical costs for each risk category were estimated by multiplying the excess cost and the person-months for each risk category observed. For example, the risk-attributable total medical cost for overweight/obesity alone was estimated by multiplying the adjusted total excess cost per individual who had the single risk factor of overweight/obesity ($9.8) by the associated person-months (123,039 person-months). By multiplying these values, it was estimated that a medical cost of $1.2 million (0.6%) was attributable to this risk factor. Although the degree of increase in medical cost per individual was greater among subjects with hyperglycemia alone than among subjects with hypertension alone, the RAC% for hyperglycemia alone was smaller than that for hypertension because of its lower prevalence. Total RAC% was 17.2%. RAC% for inpatient medical care was 16.8%, and that for outpatient care was 17.5%. There was no notable interaction between risk categories and age or sex in adjusted mean total cost.

For sensitivity analysis, we redefined overweight/obesity, hypertension, hyperglycemia, and dyslipidemia and re-estimated the economic impact of these factors (Table 4). Among subjects who had BP ≥140/90 mm Hg, 42.2% reported taking antihypertensive medication. Among subjects who had a casual blood glucose level of ≥150 mg/dl, 32.0% reported a history of diabetes. Among subjects who had a casual serum cholesterol level of ≥220 mg/dl or HDL <40 mg/dl, 4.0% reported taking lipid-lowering medication. Self-reporting of antihypertensive medication and a self-reported history of diabetes, and a BMI of ≥30 were associated with significantly increased total medical cost (P <0.0001, <0.0001, 0.0030, respectively). Subjects who self-reported taking lipid-lowering

				Total costs					
		Risk-attributable costs[b], $	RAC%[c] (%)	Adjusted cost[a], $				Risk-attributable total costs[b], $	RAC%[c] (%)
P-value	Increasing rate (%)				(95%CI)	*P*-value	Increasing rate (%)		
(Referent)	(Referent)			193.4	(180.8–206.0)	(Referent)	(Referent)		
0.99	2.7	393,723	1.3	203.2	(182.8–223.6)	0.99	5.1	1,204,956	0.6
0.0010	38.1	7,914,864	6.8	257.2	(240.1–274.3)	<0.0001	33.0	11,298,260	5.9
<0.0001	36.7	992,427	0.8	286.9	(240.3–333.5)	0.038	48.3	2,157,869	1.1
0.0074	45.1	6,973,743	6.0	281.2	(261.5–300.9)	<0.0001	45.4	11,575,527	6.0
0.0003	48.0	568,579	0.5	278.9	(207.7–350.0)	0.28	44.2	864,735	0.4
<0.0001	90.7	2,202,274	1.9	358.3	(309.5–407.0)	<0.0001	85.2	3,415,376	1.8
<0.0001	80.2	1,426,243	1.2	369.4	(311.9–426.9)	<0.0001	91.0	2,670,227	1.4
		20,471,853	17.5					33,186,950	17.2

medication had a higher mean cost than those with a serum cholesterol level of <220 mg/dl and HDL ≥40 mg/dl and who did not self-report taking lipid-lowering medication, but the difference was not significant ($P=0.76$). Among subjects who did not self-report a history of diabetes, those who had a blood glucose level of ≥150 mg/dl and <200 mg/dl had a significantly higher mean total cost than those who had a blood glucose level of <150 mg/dl ($P=0.017$).

Discussion

Mean medical cost among subjects who were overweight/obese, hypertensive, and hyperglycemic was 91.0% higher than that among subjects without any of these three risk factors, after adjustment for a variety of potential confounders. In this cohort, 17.2% of the total medical cost was attributable to these three cardiovascular risk factors.

One cohort study in Korea (Jee et al., 2001) and one cohort study in the U.S. (Anderson et al., 2000) have estimated RAC % for combination of cardiovascular risk factors in terms of total medical costs. Anderson et al., based on a prospective observation of a large employee cohort in the U.S., reported the RAC% for obesity, hyperglycemia, and hypertension of 6.3% (Anderson et al., 2000). In their study, dyslipidemia was not associated with any increase in medical cost. Jee et al. (2001) found that the RAC% for obesity, hyperglycemia, and hypertension was 10.4% for men and 5.5% for women, using a large employee cohort in Korea. In the present study, the RAC% for overweight/obesity, hyperglycemia, and hypertension was 17.2%, and was thus higher than in the previous studies. This may have been partly due to the fact that the previous studies were based on observations of healthy young workers; the impact of cardiovascular risk factors upon medical costs would become larger with age. In addition, as these previous studies excluded subjects who became too ill to work during the follow-up, they would have underestimated the impact of cardiovascular risks upon medical costs.

The result of sensitivity analysis (Table 4) showed that being on treatment at the baseline rather than having a raised level of risk factors without treatment was associated with higher cost. Especially in hyperglycemia, most of the costs associated with hyperglycemia were attributable to diabetes rather than prediabetic hyperglycemia.

Study limitations and strengths

The present study had a number of strengths. First, we followed up a large population-based cohort retaining the elderly and those who became ill during follow-up. In our cohort, only 921 subjects (7.5%) withdrew from the NHI and were thus lost to follow-up because of emigration. Second,

Table 4
Adjusted monthly medical costs by the cardiovascular risk status in the Ohsaki Study, Japan, 1996–2001

		N	Adjusted cost[a], $ (95%CI)	P-value	Increasing rate (%)
Overweight/Obesity	Body Mass Index <25	8152	226.6 (216.8–236.3)	(Referent)	(Referent)
	Body Mass Index ≥25 and <30	3747	242.3 (228.0–256.7)	0.17	7.0
	Body Mass Index ≥30	421	299.9 (257.2–342.5)	0.0030	32.4
Hypertension	Without self-report of taking antihypertensive medication				
	Systolic BP <140 mm Hg and diastolic BP <90 mm Hg	7158	202.9 (192.5–213.3)	(Referent)	(Referent)
	Systolic BP ≥140 mm Hg or diastolic BP ≥91 mm Hg	2247	223.0 (204.6–241.4)	0.15	9.9
	Self-report of taking antihypertensive medication	2935	317.7 (301.3–334.1)	<0.0001	56.6
Hyperglycemia	Without self-reported history of diabetes				
	Casual blood glucose <150 mg/dl	11,292	225.8 (217.6–234.0)	(Referent)	(Referent)
	Casual blood glucose ≥150 mg/dl and <200 mg/dl	354	296.6 (250.2–343.0)	0.017	31.4
	Casual blood glucose ≥200 mg/dl	111	255.9 (173.2–338.6)	0.89	13.3
	Self-reported history of diabetes	583	348.5 (312.2–384.8)	<0.0001	54.4
Dyslipidemia	Without self-report of taking lipid-lowering medication				
	Casual serum cholesterol <220 mg/dl and HDL ≥40 mg/dl	6790	235.1 (224.5–245.7)	(Referent)	(Referent)
	Casual serum cholesterol ≥220 mg/dl or HDL <40 mg/dl	5328	231.4 (219.4–243.4)	0.9	−1.6
	Self-report of taking lipid-lowering medication	222	256.5 (198.0–315.1)	0.76	9.1

CI denotes confidence interval. BP denotes blood pressure. HDL denotes high-density lipoprotein.

[a] Tested by analysis of covariance (ANCOVA) using non-log-transformed data on charges adjusted by age at baseline (continuous variable), sex, smoking (current smoker, past smoker, or never smoker), alcohol drinking (current drinker, past drinker, or never drinker), and comorbid condition of other three cardiovascular risk factors.

because NHI claim files were obtained directly from the local NHI Association and included almost all available medical treatment, our charge calculation was accurate. Third, in this study, the joint impact of cardiovascular risk factors was analyzed after adjustment for a variety of potential confounders.

Our study also had some limitations. Among all this study population, participation rate in the annual health check-up was as low as 33.3%. However, the participation rate in the annual health check-up was similar to that for Japan as a whole. According to the Ministry of Health, Labour and Welfare, the participation rate in the annual health check-up in Japan was 36.5% in 1995. Second, only 24.1% of the study population participated in the annual health check-up and had no prior history of cancer, stroke, or myocardial infarction and were available for the present study. The present study subjects were less likely to be hypertensive and hyperglycemic and might have been healthier than the rest of the study population. Therefore, we might have underestimated the RAC% because of the lower prevalence of cardiovascular risk factors in these individuals. Third, the present study does not prove whether prevention of these cardiovascular risk factors can reduce medical costs. Further interventional strategies could reduce these cardiovascular risk factors and potentially lower medical costs. Fourth, we did not identify individual reasons for medical treatment, and thereby we were unable to distinguish treatment costs from comorbid costs. However, each of the cardiovascular risk factors was associated with an increase not only in outpatient medical costs but also inpatient medical cost. In Japan, because hypertension and obesity rarely become main reasons for hospitalization, inpatient costs mainly reflect the costs of comorbidity. Moreover, the fact that RAC% for inpatient care was comparable to RAC% for outpatient care (16.8% vs. 17.5%) implies that overweight/obesity, hypertension, and hyperglycemia are related to not only high prescription costs for treatment of the primary disease but also severe medical events requiring inpatient treatment.

Conclusion

We have demonstrated that 17.2% of medical costs are attributable to overweight/obesity, hypertension, and hyperglycemia. These cardiovascular risk factors could have a large impact on health care resources in rural Japan.

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Attributable Risk Fraction of Prehypertension on Cardiovascular Disease Mortality in the Japanese Population: The Ohsaki Study

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BACKGROUND

Although relative risk of prehypertension (pre-HT) on cardiovascular disease (CVD) mortality is modest, prevalence of pre-HT is large, that is, population attributable fraction (PAF) of pre-HT on CVD mortality might be large. However, no studies have reported the fraction.

METHODS

We followed 12,928 Japanese National Health Insurance (NHI) beneficiaries aged 40–79 years without a history of CVD. On the basis of their blood pressure (BP), the participants were categorized as normal BP, pre-HT, and hypertension (HT) (Seventh Report of the Joint National Committee criteria). Multivariate-adjusted Cox proportional hazards model was used to estimate the hazard ratio (HR) of the BP status vs. CVD mortality.

RESULTS

During 12-years of follow-up, 321 participants died of CVD. As positive relation between BP category and CVD mortality was steeper in middle-aged (40–64 years) than that in elderly (65–79 years), we separately calculated PAF on CVD mortality among middle-aged and elderly. HR (95% confidence interval) for cardiovascular mortality for pre-HT and HT, respectively, was 1.31 (0.59–2.94) and 2.98 (1.39–6.41) in middle-aged, and 1.03 (0.62–1.70) and 1.65 (1.02–2.64) in elderly. Non-normal BP, i.e., pre-HT and HT, accounted for 47 and 26% of the CVD deaths among the middle-aged and elderly participants, respectively. Although the PAF of pre-HT was larger in the middle-aged participants (7%) than that in the elderly ones (0%), neither fraction was considered large.

CONCLUSION

The PAF on CVD mortality in pre-HT was not large compared with that in HT.

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Blood pressure (BP) is known to relate linearly to cardiovascular disease (CVD) mortality or incidence, and there is no threshold BP value for risk increase.[1] Furthermore, high BP is known as a leading cause of global burden of disease.[2] In light of this, the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure introduced a new category of BP patients, designated as prehypertension (pre-HT).[3] The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure reported that pre-HT category is neither a disease category nor candidate for drug therapy.[3] It also stated that individuals with pre-HT should be advised to reduce their risk of developing hypertension (HT) in the future through lifestyle modification.[3]

However, Rose reported that a large number of people at a small risk may give rise to more cases of disease than the small number who are at a high risk;[4] individuals with modest risk, such as pre-HT, might have greater impact on CVD mortality or incidence. Furthermore, an intervention study revealed the benefits and feasibility of drug treatment for subjects with pre-HT on HT incidence, indicating a possibility that drug treatment may reduce the risk of CVD mortality/incidence in subjects with pre-HT.[5] Thus, if population attributable fraction (PAF) of pre-HT on CVD were large, individuals with pre-HT should be treated appropriately. The PAF is an indicator of how much of the disease burden in a population could be eliminated if the effects of specific causal factors were eliminated from that population. However, to our knowledge, no studies calculated the excess deaths due to elevated BP and PAF among pre-HT. Therefore, we investigated the relation of BP categories with CVD mortality and estimate PAF.

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METHODS

Study setting and design. The setting and design of the Ohsaki Cohort Study have already been reported in detail.[6–8] In brief, this prospective cohort study started in 1994, when we delivered a self-administered questionnaire on various health-related lifestyles to all National Health Insurance (NHI) beneficiaries aged 40–79 years living in the catchment areas of Ohsaki Public Health Center, Miyagi Prefecture, Japan. NHI in Japan is used by farmers, the self-employed, pensioners, and their dependents. Ohsaki Public Health Center, which is a local government agency, provides preventive health services for the residents of 14 municipalities. The questionnaires were delivered to and collected from the subjects' residences by public health officials in each municipality. This procedure yielded a high response rate of 94.6% (N = 52,029). We excluded 776 subjects because they had withdrawn from the NHI before 1 January 1995, when we started the prospective collection of NHI claim files. Thus, 51,253 subjects formed the study cohort. Among the participants of the Ohsaki NHI Cohort Study, 16,515 (32.2%) had undergone an annual health checkup between April and December 1995, and they provided their consent for analysis of their results in this study. Among them, 280 participants were withdrawn before undergoing a health checkup. We also excluded those with no history of CVD (N = 502), as well as those in whom BP (N = 31), and other important confounding factors, such as total cholesterol (N = 154), glucose (N = 2,617) and body mass index (BMI) (N = 3) were not measured. Consequently, we analyzed 12,928 Japanese men and women in this study. The participants who had undergone an annual health checkup were slightly younger than those who had not (mean age: 60.8 years vs. 61.5 years, $P < 0.001$). The proportion of women was higher among the participants who underwent the annual checkup than those who did not (57.7% vs. 49.4%).

This study was approved by the ethics committee of the Tohoku University School of Medicine. The participants who had completed the self-administered questionnaires and had signed them were considered to have consented to participate in this study.

Exposure data. Data on the risk factors for CVD in the participants were obtained from results of the annual health checkup that had been organized by the local municipalities and conducted by physicians in 1995. This annual health checkup is provided free, or at low charge, to all people aged ≥40 years in Japan. The checkups include an interview; weight, height, and BP measurements; a physical examination; and blood chemistry tests to determine the serum total cholesterol, plasma glucose, and other parameters. The subjects were not instructed to fast prior to the blood chemistry tests.[8] A single BP measurement was obtained by trained nurses using automated devices after a rest for few minutes, which is standard procedure in annual health checkups in Japan.

We categorized our study participants into three groups according to the criteria provided in the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criteria.[2] Participants with a systolic BP of ≥140 mm Hg and/or a diastolic BP of ≥90 mm Hg and/or those who were taking antihypertensive medication were regarded as HT; those who did not satisfy the HT criteria and those with a systolic BP of ≥120 mm Hg and/or a diastolic BP of ≥80 mm Hg were regarded as pre-HT; and those who did not satisfy either the HT or pre-HT criteria were regarded as normal BP. We defined hyperglycemia as either a self-reported history of diabetes or a casual plasma glucose level of ≥140 mg/dl.[9] The BMI of the participants was calculated as the ratio of the body weight (kg) to the height $(m)^2$. We defined underweight and overweight/obesity as a BMI of <18.5 kg/m^2 and ≥25 kg/m^2, respectively.[10]

Follow-up. We prospectively collected NHI claim files from the local NHI Association for all individuals in the cohort for the period from date when they received annual health check up between April 1995 and December 1995, to the date of withdrawal from the NHI because of death or emigration, or until 31 December 2006. When a beneficiary withdraws from the NHI, the date and reason are entered in the NHI withdrawal files. Both the NHI claim and withdrawal files were linked to our baseline survey data and the annual health checkup data by using each beneficiary's identification number as the key code. For decedents identified as described herein, we investigated the cause of death by reviewing the death certificates filed at Ohsaki Public Health Center. Cause of death was coded by trained physicians according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. We identified deaths from CVD according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes I00–I99. None of the participants died of unknown causes. Because the Family Registration Law in Japan requires registration of death, death certificates confirmed all deaths that occurred in the study area, except participants who died after emigration from the area.

Statistical analysis. We described baseline characteristics according to BP categories using means for continuous variable and percentages for dichotomous variables. P for trends was calculated by Pearson's correlation for continuous variable and by logistic regression model for categorized variable. We estimated the age–sex or multivariate-adjusted hazard ratios (HRs) and the 95% confidence intervals for the relation of BP categories with CVD and all-cause mortality using Cox proportional hazard models. We treated participants with normal BP as a reference group. The multivariate-adjusted model included the following possible confounding factors: age, sex, BMI category (underweight, normal, and overweight/obesity), hyperglycemia, total cholesterol, and smoking (never, past, and current). We also tested the interaction of age group, i.e., middle-aged (years 40–64) and elderly (years ≥65), or sex with BP category for CVD mortality. The numbers of excess CVD or all-cause deaths due to non-normal BP were calculated as (number of cases exposed to the BP category) × (multiple adjusted HR − 1)/multiple adjusted HR, and the percentage of

excess CVD or all-cause deaths due to non-normal BP (PAF) was calculated as follows: $P \times$ (multiple adjusted HR − 1)/ multiple adjusted HR, where P = proportion of cases exposed to the BP category.[11]

RESULTS

Baseline characteristics

The mean age of the study participants was 61.2 years (s.d. 9.4 years). The prevalence of pre-HT and HT was 41.8% and 40.1%, respectively. **Table 1** shows the baseline characteristics of the study participants according to the BP categories. Higher BP categories related to older age, lower prevalence of current smoking, higher prevalence of hyperglycemia, higher total cholesterol level, and higher BMI. The proportion of women in the high-BP categories was low.

Follow-up data

There were 130,782 person-years of follow-up (up to 11.7 years per person), corresponding to a follow-up rate of 88.3%. During the follow-up period, 1,227 participants died and 321 participants of them died due to CVD.

Overall, a positive relation was observed between the BP status and CVD mortality (**Table 2**). Since relation between BP categories and CVD mortality in middle-aged was stronger than that in elderly (**Table 2**, P for interaction = 0.07), we analyzed middle-aged and elderly separately. Whereas, since no sex interaction between sex and BP category for CVD mortality was observed in both age groups, we combined men and women together ($P \geq 0.18$).

Among the middle-aged patients, 8, 24, and 48 of them in the normal BP, pre-HT, and HT categories, respectively, died of CVD. Among the elderly patients, 20, 64 and 157 died of CVD in these respective categories. Thus, 30% (24/80) and 27% (64/241) of CVD deaths were observed from pre-HT categories.

PAF

The number of excess CVD deaths due to high BP was 5.7 and 31.9 in middle-aged participants with pre-HT and HT, respectively, and the corresponding PAF for CVD mortality was 7.1% and 39.9%, respectively (**Figure 1**). Non-normal BP explained 47.0% of CVD deaths among middle-aged. The PAF for CVD mortality in the elderly participants with pre-HT and HT was 0.1% and 25.7%, respectively (**Figure 1**). The sum of the excess CVD deaths (PAF) due to pre-HT and HT was 7.6 (2.4%) and 93.7 (29.2%),

Table 1 | Baseline characteristics of study participants according to blood pressure (BP) category: the Ohsaki study 1995

		Total				Age 40–64				Age ≥65			
		Normal BP	Pre-HT	HT	*P* for trend	Normal BP	Pre-HT	HT	*P* for trend	Normal BP	Pre-HT	HT	*P* for trend
Numbers of participants		2,350	5,398	5,180		1,723	3,648	2,637		627	1,750	2,543	
Age (years)	mean (s.d)	57.9 (9.8)	60.0 (9.5)	64.0 (8.2)	<0.01	53.6 (7.6)	55.1 (7.2)	57.9 (6.2)	<0.01	69.7 (3.4)	70.2 (3.8)	70.5 (3.9)	<0.01
Women	*N* (%)	1,528 (65.0%)	3,013 (55.8%)	2,869 (55.4%)	<0.01	1,169 (67.9%)	2,104 (57.7%)	1,497 (56.8%)	<0.01	359 (57.3%)	909 (51.9%)	1,372 (54.0%)	0.54
Current smoking	*N* (%)	543 (26.5%)	1,222 (26.4%)	1,085 (25.0%)	0.02	401 (26.2%)	824 (25.9%)	589 (26.0%)	0.49	142 (27.6%)	398 (27.4%)	496 (23.8%)	0.01
Past smoking	*N* (%)	216 (10.6%)	695 (15.0%)	729 (16.8%)	<0.01	123 (8.0%)	380 (12.0%)	279 (12.3%)	<0.01	93 (18.1%)	315 (21.7%)	450 (21.6%)	0.22
Never smoker	*N* (%)	1,287 (62.9%)	2,718 (58.6%)	2,534 (58.3%)	<0.01	1,008 (65.8%)	1,977 (62.2%)	1,394 (61.6%)	<0.01	279 (54.3%)	741 (51.0%)	1,140 (54.7%)	0.42
Hyperglycemia	*N* (%)	175 (7.5%)	503 (9.3%)	682 (13.2%)	<0.01	112 (6.5%)	285 (7.8%)	292 (11.1%)	<0.01	63 (10.1%)	218 (12.5%)	390 (15.3%)	<0.01
Total cholesterol (mg/dl)	mean (s.d)	200.6 (34.7)	204.1 (34.6)	207.3 (36.1)	<0.01	200.0 (34.5)	204.2 (34.6)	208.7 (36.8)	<0.01	202.1 (35.3)	203.8 (34.7)	205.9 (35.2)	<0.01
Body mass index (kg/m^2)	mean (s.d)	22.9 (2.8)	23.7 (2.9)	24.6 (3.2)	<0.01	23.0 (2.8)	23.9 (2.9)	24.9 (3.1)	<0.01	22.6 (3.0)	23.2 (2.9)	24.3 (3.3)	<0.01
Systolic BP (mm Hg)	mean (s.d)	108.9 (6.5)	128.0 (7.2)	145.6 (16.1)	<0.01	108.6 (6.6)	127.4 (7.3)	144.9 (15.7)	<0.01	109.4 (6.3)	129.3 (6.9)	146.4 (16.5)	<0.01
Diastolic BP (mm Hg)	mean (s.d)	67.7 (6.9)	78.4 (7.7)	85.7 (10.3)	<0.01	67.9 (6.7)	79.0 (7.4)	87.8 (9.5)	<0.01	67.0 (7.3)	77.1 (8.2)	83.5 (10.5)	<0.01
Antihypertensive medication	*N* (%)	0	0	2,548 (49.2%)	<0.01	0	0	1,154 (43.8%)	<0.01	0	0	1,394 (54.8%)	<0.01

BP, blood pressure; *N*, numbers of participants.
Clinic BP category: HT, hypertension (systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg and/or taking antihypertensive medication); Pre-HT, prehypertension (BP level less than HT and systolic BP ≥120 mm Hg and/or diastolic BP ≥80 mm Hg); Normal BP, BP level less than pre-HT.

Table 2 | Relation of blood pressure category with cardiovascular disease and all-cause mortality, the Ohsaki study, 1995–2006

		Total			Age 40–64			Age ≥65		
		Normal BP	Pre-HT	HT	Normal BP	Pre-HT	HT	Normal BP	Pre-HT	HT
	Numbers of participants	2,350	5,398	5,180	1,723	3,648	2,637	627	1,750	2,543
	Person-years	23,709	55,040	52,033	17,413	37,611	26,886	6,296	17,429	25,146
CVD death	Numbers of CVD deaths	28	88	205	8	24	48	20	64	157
	CVD mortality rate (/1,000 person-years)	1.2	1.6	3.9	0.5	0.6	1.8	3.2	3.7	6.2
	Age–sex adjusted HR	1	1.07 (0.70–1.64)	1.93 (1.29–2.87)	1	1.18 (0.53–2.64)	2.71 (1.27–5.78)	1	1.02 (0.61–1.68)	1.70 (1.06–2.71)
	Multiple adjusted HR[a]	1	1.10 (0.72–1.69)	1.91 (1.28–2.85)	1	1.31 (0.59–2.94)	2.98 (1.39–6.41)	1	1.03 (0.62–1.70)	1.65 (1.02–2.64)
All-cause death	Numbers of all-cause deaths	153	417	657	48	126	164	105	291	493
	All-cause mortality rate (/1,000 person-years)	6.5	7.6	12.6	2.8	3.4	6.1	16.7	16.7	19.6
	Age–sex adjusted HR	1	0.93 (0.77–1.12)	1.16 (0.97–1.38)	1	1.02 (0.73–1.42)	1.52 (1.10–2.10)	1	0.89 (0.71–1.11)	1.04 (0.85–1.29)
	Multiple adjusted HR[a]	1	0.97 (0.80–1.17)	1.20 (0.995–1.43)	1	1.06 (0.76–1.49)	1.53 (1.10–2.13)	1	0.93 (0.75–1.17)	1.09 (0.88–1.35)

Clinic BP category: HT, hypertension (systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg and/or taking antihypertensive medication); Pre-HT, prehypertension (BP level less than HT and systolic BP ≥120 mm Hg and/or diastolic BP ≥80 mm Hg); Normal BP, BP level less than pre-HT.
[a]Adjusted for age, sex, smoking (current, past, never), hyperglycemia, total cholesterol, BMI (underweight, normal, overweight).

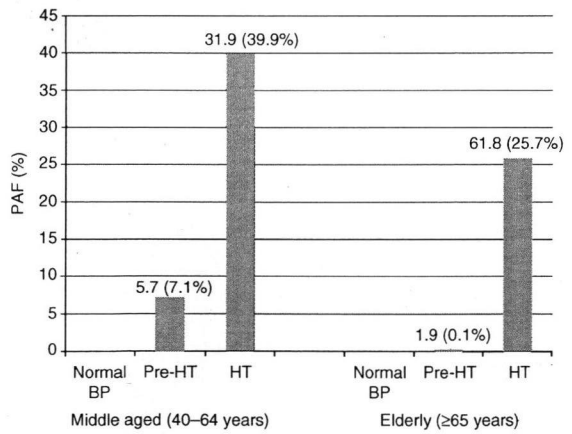

Figure 1 | Population attributable fraction (PAF) for cardiovascular diseases (CVDs) mortality in each blood pressure (BP) category. Excess CVD deaths (PAF) are shown at the top of the bars. The excess CVD mortality due to non-normal BP was calculated as (HR – 1)/HR × number of CVD deaths observed for each BP category. The PAF was calculated as the excess of CVD deaths for each BP category divided by the total number of CVD deaths. Pre-HT, prehypertension; HT, hypertension.

respectively, i.e., non-normal BP accounted for 31.6% of the CVD deaths in this Japanese population. These values remained essentially unchanged when PAF was calculated using age–sex adjusted HR instead of multiple adjusted HR (4.6% and 37.9% for middle-aged participants with pre-HT and HT and 0.5% and 26.8% for elderly participants with pre-HT and HT).

All-cause mortality

We also analyzed the relation between BP categories and all-cause mortality, and we estimated the PAF for all-cause mortality. Among middle-aged, positive relation between BP category and all-cause mortality was observed (**Table 2**). The relation was modest in elderly (**Table 2**). The excess all-cause deaths due to high BP (PAF) in middle-aged were 7.1 (2.1%) for pre-HT and 56.8 (16.8%) for HT. Similarly, the excess all-cause deaths (PAF) due to pre-HT and HT in elderly were 0 (0%) and 40.7 (4.6%), respectively. Thus, non-normal BP explained 18.9 and 4.6% of all-cause deaths among middle-aged and elderly, respectively.

DISCUSSION

In this study, based on 130,000 person-years of follow-up, we calculated the attributable risk fraction of pre-HT on CVD mortality in Japanese population. Although 25–30% CVD deaths were observed from pre-HT category, relative risk in pre-HT was modest and PAF of pre-HT on CVD mortality was not large, i.e., 7, 0, and 2% of CVD deaths were explained by pre-HT categories in middle-aged, elderly, and overall, respectively.

Our results indicate that a high BP is positively related with CVD mortality.[1,3] In addition, we found that the relation between the BP categories and CVD mortality was stronger among younger participants. These results were consistent with those from many previous studies.[1,12–14]

In our study, prevalences of pre-HT were 45.5% in middle-aged and 35.6% in elderly and 30 and 27% of CVD deaths were

observed from this category. That is, pre-HT category can be considered as one category with "large number of people at a low risk".[4] In the National Health and Nutrition Examination Survey that was conducted in 1999–2000, the prevalence of pre-HT was found to be 34.7% in the population aged 40–59 years and 23.1% in that aged 60 years and more.[15] Thus, the proportion of pre-HT is reported to be high in the United States.

In our study, the HR for CVD mortality among the middle-aged subjects with pre-HT was 1.31 (95% confidence interval: 0.59–2.94). Previous studies have reported this value to range from 1.08 to 1.80 among the pre-HT individuals.[16–20] Although the point estimate determined in this study was relatively lower than that reported previously, we considered that the HR determined here is largely consistent with that determined in previous studies. Although the risk of CVD mortality showed no increase (HR = 1.03; 95% confidence interval: 0.62–1.70) among the elderly pre-HT patients, this finding was also consistent with the results of the follow-up survey performed by National Health and Nutrition Examination Survey III.[19] Gu *et al.* reported that the risk of CVD mortality did not increase among pre-HT subjects aged 65–74 years and ≥75 years.

We investigated the PAF of high BP with regard to CVD mortality. Non-normal BP, i.e., combination of pre-HT and HT, explained 47% of CVD deaths in middle-aged and 26% of CVD deaths in elderly. This proportion was similar to the previous reports from Japan. Sairenchi *et al.* reported that PAF of non-normal BP was 60, 28, 15, and 7% of in middle-aged men, elderly men, middle-aged women, and elderly women, respectively.[14] Our findings that the PAF of non-normal BP for all-cause mortality was higher in middle-aged than that in elderly were also consistent with those of a recent report describing that the PAF of non-normal BP for all-cause mortality was higher in the 50s or 60s age group than in the 70s or 80s.[21] However, to the best of our knowledge, no study reported the fraction specific to pre-HT category. The PAF of pre-HT on CVD mortality was 7, 0, and 2% in the middle-aged, elderly, and total study population, respectively. We do not consider this proportion to be very large.

In recent years, the effects of drug treatment for prehypertensive patients to avoid progression to HT have been reported. Participants with repeated measurements of systolic pressure of 130–139 mm Hg and diastolic pressure of ≤89 mm Hg, or systolic pressure of ≤139 mm Hg, and diastolic pressure of 85–89 mm Hg were randomly assigned to receive 2 years of candesartan (N = 409) or placebo (N = 400), and followed by 2 years of placebo for all.[5] The result revealed that pre-HT patients tolerated treatment with candesartan well and that the risk of incident HT (relative risk = 0.58) reduced during the study period. Therefore, it was concluded that candesartan treatment is feasible and effective for pre-HT patients. After this trial, the topic whether pre-HT should be treated or not was debated.[22,23] However, as we have shown in this study, population impact of treatment pre-HT should not be large and HT categories explained a large proportion of excess CVD death. Furthermore, only a quarter of hypertensive is known to be well controlled, i.e., a half of hypertensives were treated and a half of treated hypertensives were well controlled at best.[3,24–27] Thus, we believe that the primary target population that should receive antihypertensive medication is that of HT patients. Further researches also should be required to estimate the burden in other population.

Our study has some limitations. First, the study population consisted of participants who underwent an annual health checkup. As this population was likely to be health conscious, the distribution of pre-HT may have been overestimated. Second, as most of Japanese annual health checkups, single measurement of BP was used for analyses. Due to regression dilution effect, relative risks might be underestimated.[28] Finally, our data were based on mortality data but not morbidity data. Although the relationship between BP categories and CVD mortality might be similar to that between BP categories and CVD morbidity, risk profiles of morbid and mortal events sometimes differ. Thus, further studies using morbidity data might be required to corroborate our findings.

In conclusion, large amount of CVD deaths were accounted for non-normal BP categories in this Japanese population. We found that the PAF of pre-HT with regard to CVD mortality was not high, while that of HT was high. Therefore, we concluded that the primary target population that should receive antihypertensive medication is that of HT patients.

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Original Contribution

Green Tea Consumption and Hematologic Malignancies in Japan

The Ohsaki Study

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Several biologic studies have reported that green tea constituents have antitumor effects on hematologic malignancies. However, the effects in humans are uncertain. The authors used data from the Ohsaki National Health Insurance Cohort Study in Japan to evaluate the association between green tea consumption and the risk of hematologic malignancies. Study participants were 41,761 Japanese adults aged 40–79 years without a history of cancer at baseline who answered a food frequency questionnaire survey in 1994. During 9 years of follow-up beginning in 1995, the authors documented 157 hematologic malignancies, including 119 cases of lymphoid neoplasms and 36 cases of myeloid neoplasms. Hazard ratios were calculated by using the Cox proportional hazards regression model. Risk of hematologic malignancies was inversely associated with green tea consumption. The multivariate-adjusted hazard ratio of hematologic malignancies for 5 cups/day or more compared with less than 1 cup/day of green tea was 0.58 (95% confidence interval: 0.37, 0.89). The corresponding risk estimate was 0.52 (95% confidence interval: 0.31, 0.87) for lymphoid neoplasms and 0.76 (95% confidence interval: 0.32, 1.78) for myeloid neoplasms. This inverse association was consistent across sex and body mass index strata. In conclusion, green tea consumption was associated with a lower risk of hematologic malignancies.

catechin; cohort studies; hematologic neoplasms; Japan; risk; tea

Abbreviations: EGCG, (-)-epigallocatechin-3-gallate; FFQ, food frequency questionnaire; ICD-O-3, *International Classification of Diseases for Oncology*, Third Edition; NHI, National Health Insurance.

Hematologic malignancies are known to have a wide geographic distribution; incidence rates are relatively high in Western countries and low throughout Asia, including Japan and developing countries (1). According to "Global Cancer Statistics, 2002" by Parkin et al. (1), age-standardized incidence rates per 100,000 for non-Hodgkin lymphoma were higher than 10.0 for men and 6.5 for women in North America and in western, northern, and southern Europe, while they were lower than 6.5 for men and 4.0 for women in eastern and southern Asia, including Japan. Similarly, the rates of Hodgkin lymphoma were higher than 2.0 in North and Central America and in Europe and lower than 1.0 in southeastern Asia (1). The reasons for this discrepancy are still unclear. Many epidemiologic studies have explored the risk factors for hematologic malignancies. Cigarette smoking (2–5), high alcohol consumption (5), obesity (6–9), height (6), occupational exposures (10), infection with some viruses, and immunodeficiency (11–13) are thought to induce some types of hematologic malignancies. However, preventive factors for hematologic malignancies are not well known and are a public health concern because the incidence of hematologic malignancies has been increasing worldwide (1).

Currently, there is extensive interest in the health benefits of green tea. Thus, green tea and its major constituent, tea polyphenols, have been widely studied as preventive factors for various diseases, including cancers (14–20). Several biologic studies have reported that green tea constituents, such

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as (-)-epigallocatechin-3-gallate (EGCG), exert antitumor effects against hematologic malignancies by inducing apoptosis and/or suppressing angiogenesis (21–25). However, epidemiologic studies on this topic have been few; to our knowledge, only 3 case-control studies have been conducted (26–28). Two reported that green tea intake was associated with a lower risk of leukemia (26, 28), and another study reported that higher intake of tea flavonoids was inversely associated with the risk of non-Hodgkin lymphoma (27).

This evidence may help explain the low incidence of hematologic malignancies in Asian countries, where consumption of green tea is the highest in the world. However, further evidence from cohort studies or intervention trials is needed to obtain some consensus on this issue. We therefore designed this population-based cohort study to investigate the association between green tea consumption and the risk of hematologic malignancies in a rural area of Japan, where green tea is widely consumed.

MATERIALS AND METHODS

Study cohort

We conducted a population-based cohort study based on data from the Ohsaki National Health Insurance (NHI) Cohort, the details of which have been described previously (29–31). In brief, from October through December 1994, we delivered self-administered questionnaires, including items on dietary intake, to all NHI beneficiaries aged 40–79 years living in the catchment area of the Ohsaki Public Health Center, Miyagi Prefecture, in northeastern Japan. The Ohsaki Public Health Center, a local government agency, provides preventive health services for residents of 14 municipalities in the northern part of Miyagi Prefecture. The study area is a typical rural area of Japan, where the main industry is agriculture.

Of 54,996 eligible individuals, 52,029 returned usable questionnaires; the response rate was 94.6%. We started prospective collection of the NHI withdrawal history files on January 1, 1995, to ascertain the date of and reason for withdrawal from NHI. We excluded 776 participants who had withdrawn from NHI before the baseline questionnaire survey. Thus, 51,253 participants (24,573 men and 26,680 women) were finally entered into the study as our cohort participants. The ethics committee of Tohoku University School of Medicine reviewed and approved the study protocol. We considered the return of self-administered questionnaires signed by the participants to imply their consent to take part in the study.

For the current analysis, we excluded 7 participants (1 man and 6 women) who had incomplete data in the cancer incidence registry, as well as 3,148 participants (1,557 men and 1,591 women) who, as ascertained from self-reports and the cancer registry, had been diagnosed as having cancer before the baseline survey was conducted. We also excluded 6,337 participants (3,266 men and 3,071 women) who had provided incomplete responses regarding frequency of green tea consumption. Consequently, we entered data for 41,761 eligible participants (19,749 men and 22,012 women) into our analysis.

Dietary assessment

We assessed dietary intake of participants at the baseline survey by using the self-administered questionnaire, which included a food frequency questionnaire (FFQ). In this FFQ, we asked participants to report their frequency of recent consumption of 36 food items and 4 beverages, including green tea. The FFQ provided 5 categories of response to describe participants' frequency of green tea consumption: never, occasionally, 1–2 cups/day, 3–4 cups/day, and 5 cups/day or more. The volume of a typical cup of green tea was 100 mL in the study region (19). The questionnaire also consisted of items on personal and family history of disease, physical status, drinking and smoking habits, and occupational and educational status.

We conducted a validation study of the FFQ, as reported previously (32). Spearman's rank coefficient for the correlation between green tea consumption as assessed by the FFQ and four 3-day food records was 0.71 for men and 0.53 for women, and the correlation between consumption measured by 2 FFQs administered 1 year apart was 0.63 for men and 0.64 for women. We examined the total energy intake of each participant from the FFQ responses by converting the selected frequency category for each food to daily intake, using portion sizes based on the median values observed in the validation study (32).

Ascertainment of cases and follow-up

The endpoint of our analysis was the incidence of all hematologic malignancies defined by morphology codes 9590/3–9989/3 in accordance with the *International Classification of Diseases for Oncology*, Third Edition (ICD-O-3) (33). Hematologic malignancies included the following diseases: Hodgkin and non-Hodgkin lymphomas (ICD-O-3 codes 9590/3–9729/3), plasma cell tumors (ICD-O-3 codes 9731/3–9734/3), mast cell tumors (ICD-O-3 codes 9740/1–9742/3), neoplasms of histiocytes and accessory lymphoid cells (ICD-O-3 codes 9750/3–9758/3), immunoproliferative diseases (ICD-O-3 codes 9760/3–9769/1), leukemias (ICD-O-3 codes 9800/3–9948/3), chronic myeloproliferative disorders (ICD-O-3 codes 9950/3–9964/3), other hematologic disorders (ICD-O-3 codes 9970/1 and 9975/1), and myelodysplastic syndromes (ICD-O-3 codes 9980/3–9989/3). Cases were further categorized as follows: lymphoid neoplasms including Hodgkin and non-Hodgkin lymphomas (ICD-O-3 codes 9590/3–9729/3), plasma cell tumors (ICD-O-3 codes 9731/3–9734/3), lymphoid leukemias (ICD-O-3 codes 9820/3–9837/3), hairy cell leukemia (ICD-O-3 codes 9940/3), aggressive NK-cell leukemia (ICD-O-3 codes 9948/3), and lymphoproliferative disorder not otherwise specified (ICD-O-3 codes 9970/1); and myeloid neoplasms including myeloid leukemias (ICD-O-3 codes 9840/3–9931/3), chronic myelomonocytic leukemia not otherwise specified (ICD-O-3 codes 9945/3), juvenile myelomonocytic leukemia (ICD-O-3 codes 9946/3), chronic myeloproliferative disorders (ICD-O-3 codes 9950/3–9964/3), myeloproliferative disease not otherwise specified (ICD-O-3 codes 9975/1), and myelodysplastic syndromes (ICD-O-3 codes 9980/3–9989/3) according to

ICD-O-3 and the *World Health Organization Classification of Tumors* (34).

We ascertained the incidence of cancer through computerized record linkage to the Miyagi Prefecture Cancer Registry, one of the oldest and most accurate population-based cancer registries in Japan (35). Between 1993 and 1997, the percentages registered by death certificates only were, for lymphoma, 23% for men and 21% for women and, for leukemia, 36% for men and 37% for women (35).

We prospectively counted person-years of follow-up for each of the participants from January 1, 1995, until the date of diagnosis of hematologic malignancies, the date of withdrawal from NHI, the date of death, or the end of the follow-up period (December 31, 2003), whichever occurred first. For follow-up, we periodically reviewed the NHI withdrawal history files. When a participant in this study withdrew from the NHI system because of death, emigration, or occupational change, the date of withdrawal and the reason were coded in the files. Follow-up of participants who had withdrawn from the NHI system was discontinued because we were unable to obtain subsequent information on them. During the study period, 5,427 participants (2,147 men and 3,280 women: 13.0% of the total) were lost to follow-up.

Statistical analysis

We combined the lower 2 categories of green tea consumption (never, occasionally) into the single category "less than 1 cup/day" for the purpose of this analysis because of the small number of participants and cases in each category. We used the Cox proportional hazards regression model to estimate hazard ratios and 95% confidence intervals for the incidence of hematologic malignancies according to levels of green tea consumption and to adjust for potential confounding variables, using SAS version 9.1 statistical software (SAS Institute, Inc., Cary, North Carolina). We calculated incidence rates of hematologic malignancies by dividing the number of incident cases by the number of person-years in each stratum of green tea consumption. The hazard ratio was computed as the incidence rate among participants in each green tea consumption stratum divided by the rate among participants in the lowest intake stratum (less than 1 cup/day), which was chosen as the reference group. All hazard ratios were calculated as age and sex adjusted and as multivariate adjusted. The P values for the test of linear trends were calculated by scoring the green tea consumption category as an ordinal variable (less than 1 cup/day = 1–5 cups/day or more = 4). All reported P values were 2-sided, and the estimates with $P < 0.05$ were considered statistically significant. We also conducted additional analyses after categorizing hematologic malignancies as lymphoid neoplasms and myeloid neoplasms.

We evaluated and compared the risk across sex and body mass index strata to assess whether any impact of green tea consumption on the risk of hematologic malignancies differed across sex and/or obesity status. To avoid any possible bias resulting from the influence of undiagnosed cancers present at baseline, we repeated the analysis after excluding participants who had been given a diagnosis of cancer within the first 3 years of follow-up and started follow-up from January 1, 1998, 3 years from the baseline date.

We considered the following variables to be potential confounders prior to the analyses: age (continuous variable, years), sex, family history of leukemia (yes or no), history of blood transfusion (yes or no), job status (nonfarmers or farmers, including former farmers), educational level (less than high school, high school, some college or higher), height (≤155, 155–164, ≥165 cm), body mass index (<18.5, 18.5–24.9, ≥25.0 kg/m^2), cigarette smoking (never smoked, former smoker, current smoker of <20 cigarettes/day, current smoker of ≥20 cigarettes/day), alcohol drinking (never drank, former drinker, current drinker of <45.6 g ethanol/day, current drinker of ≥45.6 g ethanol/day), fish consumption (≤2 times/week, 3–4 times/week, every day), soybean products consumption (≤2 times/week, 3–4 times/week, every day), daily miso soup consumption (yes or no), coffee consumption (never, occasionally, ≥1 cup/day), and total caloric intake (continuous variable, kcal/day). To avoid overfitting a model, we included these variables apart from age and sex in our final multivariate-adjusted model as confounders only if each variable met both of the following criteria: 1) it was associated with both green tea consumption and risk of hematologic malignancies (i.e., the probabilities of being exposed and diseased varied more than 5% among the strata of a potential confounder); and 2) after adding the variable into the age- and sex-adjusted model, the hazard ratio point estimate changed more than 1%. In the FFQ, alcohol consumption was classified in terms of "go," a traditional Japanese unit for measuring the amount of alcoholic beverages equal to approximately 180 mL of sake, containing 22.8 g of ethanol.

RESULTS

Participants who consumed more green tea than others tended to be older and were more likely to consume fish and soybean products, the typical sources of protein in the Japanese traditional daily diet (Table 1). Meat consumption was not associated with green tea consumption (data not shown). Men, but not women, who consumed more green tea were less likely to be heavy alcohol drinkers and obese. Furthermore, participants who consumed more green tea were more likely to smoke less, but this association was not obvious when we stratified them by sex.

During 326,012 person-years of follow-up (154,348 person-years for men and 171,664 person-years for women; mean = 7.8, maximum = 9.0 years), we documented 157 hematologic malignancies (in 88 men and 69 women); included were 119 cases of lymphoid neoplasms (66 men and 53 women) and 36 cases of myeloid neoplasms (20 men and 16 women). We found a significant inverse association between green tea consumption and the risk of hematologic malignancies in our participants (Table 2). The multivariate-adjusted hazard ratios for the incidence of hematologic malignancies were 0.88 (95% confidence interval: 0.57, 1.38) for 1–2 cups/day, 0.90 (95% confidence interval: 0.59, 1.39) for 3–4 cups/day, and 0.58 (95% confidence interval: 0.37, 0.89) for 5 cups/day or more (P for trend = 0.02) compared with less than 1 cup/day of green tea consumption. After

Table 1. Characteristics of Subjects (n = 41,761) According to Green Tea Consumption at Baseline, the Ohsaki Cohort, Japan, 1995–2003[a]

Characteristic	Green Tea Consumption, Cups/Day							
	Men (n = 19,749)				Women (n = 22,012)			
	<1 (n = 6,039)	1–2 (n = 4,479)	3–4 (n = 4,008)	≥5 (n = 5,223)	<1 (n = 5,054)	1–2 (n = 4,567)	3–4 (n = 5,046)	≥5 (n = 7,345)
Age in years, mean (SD)	57.9 (10.7)	58.1 (10.8)	60.5 (10.4)	61.9 (9.8)	59.3 (10.9)	60.4 (10.6)	61.8 (9.7)	62.8 (9.2)
Educational level								
Less than high school	62.4	56.9	58.6	61.7	59.4	54.8	54.2	58.3
High school	30.7	34.8	32.4	30.3	33.2	36.5	37.1	33.4
Some college or higher	6.9	8.4	9.0	8.0	7.4	8.7	8.7	8.3
Body mass index, kg/m^2								
<18.5	3.3	3.1	2.7	3.5	4.7	3.6	4.0	3.5
18.5–24.9	69.7	70.9	71.7	71.3	64.0	65.0	65.2	62.9
≥25.0	27.0	26.0	25.6	25.2	31.3	31.4	30.8	33.7
Cigarette smoking, cigarettes/day								
Never	20.7	19.1	19.1	16.8	86.8	90.9	92.2	88.2
Former	24.5	24.1	27.6	27.9	3.0	2.4	2.3	2.7
Current, <20	20.6	21.6	21.0	22.5	6.8	4.7	4.4	6.6
Current, ≥20	34.2	35.2	32.3	32.9	3.3	2.1	1.1	2.5
Alcohol drinking, g of ethanol/day								
Never	16.3	14.6	15.1	18.3	70.8	73.0	75.2	72.3
Former	10.6	9.8	10.3	11.6	5.5	4.0	3.8	4.3
Current, <45.6	59.9	63.2	63.0	59.5	22.7	22.3	20.6	22.9
Current, ≥45.6	13.2	12.4	11.6	10.6	1.0	0.6	0.4	0.6
Fish consumption,[b] times/week								
≤2	31.3	28.3	23.9	19.1	29.1	25.3	20.1	17.0
3–4	34.5	36.1	37.7	35.1	36.7	37.8	40.0	36.7
Every day	34.2	35.6	38.4	45.9	34.2	36.9	39.9	46.3
Soybean products consumption, times/week								
≤2	27.2	21.7	18.3	14.2	21.2	15.1	10.8	10.3
3–4	33.5	33.2	33.5	29.7	30.1	28.2	27.9	24.9
Every day	39.3	45.2	48.3	56.1	48.7	56.7	61.2	64.8

Abbreviation: SD, standard deviation.
[a] All values except those for age are expressed as percentages.
[b] Maximum intake of fresh fish, boiled fish paste, and dried fish.

dividing all hematologic malignancies into lymphoid neoplasms and myeloid neoplasms, we observed similar trends in the former, but not the latter, group.

We observed associations similar to those in our primary analysis across the strata of sex and body mass index (Table 3). Furthermore, the likelihood ratio tests between the models with and without interaction were not statistically significant for both sex and body mass index; the P values were 0.80 and 0.99, respectively. Because the numbers of participants and cases in the body mass index stratum of less than 18.5 kg/m^2 were very small, we integrated it and the stratum of 18.5–24.9 kg/m^2 into a new stratum of less than 25.0 kg/m^2 in this stratified analysis.

The risks did not change considerably after we started follow-up 3 years after the baseline date (data not shown).

DISCUSSION

We observed a significant inverse association between green tea consumption and the risk of hematologic

Table 2. Hazard Ratios and 95% Confidence Intervals for the Incidence of Hematologic Malignancies According to Green Tea Consumption, the Ohsaki Cohort, Japan, 1995–2003

	Green Tea Consumption, Cups/Day				*P* for Trend[a]
	<1 (n = 11,093)[b]	1–2 (n = 9,046)	3–4 (n = 9,054)	≥5 (n = 12,568)	
All hematologic malignancies					
No. of person-years	85,080	70,127	71,075	99,730	
No. of cases (n = 157)	46	34	39	38	
Age- and sex-adjusted hazard ratio	1.00	0.88	0.93	0.62	0.04
95% confidence interval		0.57, 1.38	0.61, 1.43	0.40, 0.95	
Multivariate-adjusted hazard ratio[c]	1.00	0.88	0.90	0.58	0.02
95% confidence interval		0.57, 1.38	0.59, 1.39	0.37, 0.89	
Lymphoid neoplasms					
No. of person-years	85,100	70,143	71,099	99,759	
No. of cases (n = 119)	34	29	30	26	
Age- and sex-adjusted hazard ratio	1.00	1.02	0.97	0.57	0.03
95% confidence interval		0.62, 1.67	0.59, 1.58	0.34, 0.96	
Multivariate-adjusted hazard ratio[c]	1.00	1.00	0.92	0.52	0.01
95% confidence interval		0.61, 1.65	0.56, 1.52	0.31, 0.87	
Myeloid neoplasms					
No. of person-years	85,151	70,205	71,180	99,773	
No. of cases (n = 36)	11	5	9	11	
Age- and sex-adjusted hazard ratio	1.00	0.54	0.89	0.74	0.67
95% confidence interval		0.19, 1.56	0.37, 2.15	0.32, 1.71	
Multivariate-adjusted hazard ratio[c]	1.00	0.57	0.91	0.76	0.70
95% confidence interval		0.20, 1.64	0.37, 2.23	0.32, 1.78	

[a] *P* values for trend were calculated by treating the green tea consumption categories as an ordinal variable and as 2-sided.

[b] Less than 1 cup/day was chosen as the reference group.

[c] Adjusted for age (continuous variable, years), sex, educational level (<high school, high school, ≥college), cigarette smoking (never smoked, former smoker, current smoker of <20 cigarettes/day, current smoker of ≥20 cigarettes/day), alcohol drinking (never drank, former drinker, current drinker of <45.6 g ethanol/day, current drinker of ≥45.6 g ethanol/day), fish consumption (≤2 times/week, 3–4 times/week, every day), and soybean products consumption (≤2 times/week, 3–4 times/week, every day).

malignancies during 9 years of follow-up in a large population-based cohort of Japanese that included 157 cases of hematologic malignancies. This association was more apparent for lymphoid neoplasms after we categorized hematologic malignancies as lymphoid and myeloid neoplasms. Compared with participants who consumed less than 1 cup/day of green tea, those who consumed 5 cups/day or more had a 42% lower risk of hematologic malignancies and a 48% lower risk of lymphoid neoplasms.

To our knowledge, this population-based cohort study is the first to find an association between green tea consumption and hematologic malignancies; no cohort study and only 3 case-control studies have been known to assess the relation between consumption of green tea or its constituents and hematologic malignancies. In a study from China, longer duration, higher quantity, and frequency of green tea intake were associated with a reduced risk for 107 leukemia cases and 110 controls (26). A study from the United States reported that higher intake of epicatechins, one of the flavonoids present richly in green tea, was associated with lower risk of non-Hodgkin lymphoma in 466 cases and 390 controls (27). The most recent case-control study of 252 leukemia cases and 637 controls from Taiwan reported an inverse association between green tea consumption and the risk of leukemia for individuals aged 16–29 years (28). These results were consistent with those of our study; however, case-control studies are not free from selection bias or recall bias related to retrospective measurement of exposure and other possible confounding factors after a diagnosis of disease.

Table 3. Hazard Ratios and 95% Confidence Intervals for the Incidence of Hematologic Malignancies According to Green Tea Consumption, Stratified by Sex and Body Mass Index, the Ohsaki Cohort, Japan, 1995–2003

	Green Tea Consumption, Cups/Day				*P* for Trend[a]
	<1[b]	1–2	3–4	≥5	
Sex					
Men (n = 19,749)					
No. of person-years	46,846	34,859	31,310	41,333	
No. of cases (n = 88)	30	17	20	21	
Age-adjusted hazard ratio	1.00	0.75	0.85	0.63	0.15
95% confidence interval		0.41, 1.35	0.48, 1.50	0.36, 1.10	
Multivariate-adjusted hazard ratio[c]	1.00	0.75	0.82	0.57	0.07
95% confidence interval		0.41, 1.35	0.47, 1.46	0.32, 1.00	
Women (n = 22,012)					
No. of person-years	38,235	35,267	39,764	58,398	
No. of cases (n = 69)	16	17	19	17	
Age-adjusted hazard ratio	1.00	1.11	1.05	0.62	0.14
95% confidence interval		0.56, 2.19	0.54, 2.03	0.31, 1.22	
Multivariate-adjusted hazard ratio[c]	1.00	1.09	1.01	0.58	0.10
95% confidence interval		0.55, 2.16	0.52, 1.99	0.29, 1.16	
Body mass index, kg/m^2					
<25.0 (n = 28,162)					
No. of person-years	56,667	47,482	48,601	66,647	
No. of cases (n = 101)	30	20	26	25	
Age- and sex-adjusted hazard ratio	1.00	0.78	0.91	0.60	0.10
95% confidence interval		0.45, 1.38	0.54, 1.55	0.35, 1.03	
Multivariate-adjusted hazard ratio[c]	1.00	0.78	0.89	0.56	0.06
95% confidence interval		0.44, 1.38	0.52, 1.51	0.33, 0.97	
≥25.0 (n = 11,586)					
No. of person-years	23,627	19,316	19,553	29,036	
No. of cases (n = 46)	14	10	11	11	
Age- and sex-adjusted hazard ratio	1.00	0.84	0.86	0.57	0.19
95% confidence interval		0.37, 1.89	0.39, 1.90	0.26, 1.27	
Multivariate-adjusted hazard ratio[c]	1.00	0.80	0.79	0.52	0.12
95% confidence interval		0.35, 1.80	0.36, 1.77	0.23, 1.16	

[a] *P* values for trend were calculated by treating the green tea consumption categories as an ordinal variable and as 2-sided.

[b] Less than 1 cup/day was chosen as the reference group.

[c] Adjusted for age (continuous variable, years), sex, educational level (<high school, high school, ≥college), cigarette smoking (never smoked, former smoker, current smoker of <20 cigarettes/day, current smoker of ≥20 cigarettes/day), alcohol drinking (never drank, former drinker, current drinker of <45.6 g ethanol/day, current drinker of ≥45.6 g ethanol/day), fish consumption (≤2 times/week, 3–4 times/week, every day), and soybean products consumption (≤2 times/week, 3–4 times/week, every day). The model stratified by sex did not include the variable for sex.

Recent animal and in vitro studies have reported that green tea and some of its constituents, especially EGCG, have antitumor activities against several types of hematologic malignancies. For instance, green tea inhibited angiogenesis and induced apoptosis in animal models of human non-Hodgkin lymphoma (21); EGCG suppressed vascular endothelial growth factor production and induced apoptosis in chronic lymphocytic leukemia B cells (22); EGCG induced apoptotic cell death in malignant B cells in vitro (23); EGCG induced apoptotic cell death in human

lymphoblastoid B cells through several pathways, such as production of intracellular reactive oxygen species (24); and EGCG and some of the other green tea catechins inhibited matrix metalloproteinase-9 secretion, thus affecting myeloid cell differentiation and angiogenesis (25). Furthermore, a clinical case report documented antitumor effects of oral green tea extracts in 4 patients with low-grade B-cell malignancies (36). This evidence supports our results and might explain the mechanisms of the observed association of green tea with a reduced incidence of hematologic malignancies.

Our present results indicate that the preventive effect of green tea consumption against hematologic malignancies seems to have a threshold effect rather than a dose-response effect. The lower risks of hematologic malignancies were obvious only in the group consuming 5 cups or more of green tea daily (Tables 2 and 3). This result is inconsistent with recent biologic studies indicating a dose-dependent manner of green tea constituents against hematologic tumor cells (22–25). These discrepancies between animal experiments and our epidemiologic observations might be due to differences in species, metabolism of green tea constituents, accuracy of exposure measurement, degree of confounding and/or bias, and essential differences in study design. Moreover, although we observed that green tea consumption was inversely associated with the incidence of all hematologic malignancies as a whole and lymphoid neoplasms, we were unable to find any significant association with myeloid neoplasms alone. Because the number of cases of myeloid neoplasm in this study was very small, we were unable to conclude whether this lack of association was due to insufficient statistical power or to pathogenetic differences between malignant lymphoid and myeloid cells, such as differences in sensitivity to green tea constituents or in the mechanisms of development, proliferation, and/or differentiation.

Infection with human immunodeficiency virus, human T-cell leukemia virus type-1, and Epstein-Barr virus is an established risk factor for hematologic malignancies (11–13). Although we were unable to acquire any information about such viral infections in our participants, infection with human immunodeficiency virus and human T-cell leukemia virus type-1 is very rare in this region (37, 38); Japan is known to have a relatively high rate of human T-cell leukemia virus type-1 infection, but the endemic area is southern Japan, far from our study area. Epstein-Barr virus is widespread throughout the world, and most adults in any country are seropositive against Epstein-Barr virus antigen (38). We thus considered that our inability to assess infection with such viruses would not substantially distort our result.

Our study had some limitations. First, 13% of all participants were lost to follow-up. Nevertheless, this proportion did not vary across the 4 green tea consumption categories: the proportions of participants lost to follow-up at the lowest to highest green tea consumption levels were 14%, 14%, 13%, and 12%.

Second, the number of cases of hematologic malignancies among our participants was modest in comparison with the Western population. Therefore, we were unable to evaluate the association between green tea consumption and risk of each subtype of hematologic malignancy (e.g., Hodgkin lymphomas, non-Hodgkin lymphomas, lymphoid leukemias, or myeloid leukemias), even though the risk factors probably vary according to subtype.

Third, the quality and completeness of the Miyagi Cancer Registry were not high enough regarding hematologic malignancies: the level of death-certificate-only diagnosed lymphoma and leukemia was higher than 20%. Such a fairly high proportion of death-certificate-only cases might have led to failure to ascertain some individuals who had hematologic malignancies but did not die during the study period.

Fourth, we were unable to obtain enough information related to occupational exposures, ionizing radiation, benzene, and so forth, which may affect the risk of hematologic malignancies (10). Even though we added a variety of potential confounders to our analysis, there were a considerable number of unmeasured confounders.

Finally, we excluded 6,337 participants from our analysis because they provided incomplete answers for, or did not answer the question on, green tea consumption. In this excluded group, 31 cases of hematologic malignancies were diagnosed. Because the distribution of baseline characteristics among those participants was similar to that among participants in the lowest green tea consumption stratum (data not shown), we assumed that they were likely to consume no or less green tea. Using this assumption, we conducted a sensitivity analysis after including those participants in the lowest stratum of green tea consumption. The result of this analysis did not differ from that of our primary analysis: the multivariate-adjusted hazard ratios were 0.86 (95% confidence interval: 0.57, 1.30), 0.90 (95% confidence interval: 0.61, 1.34), and 0.58 (95% confidence interval: 0.39, 0.87) for 1–2, 3–4, and 5 cups/day or more, respectively, compared with less than 1 cup/day.

We previously reported that green tea consumption was not associated with risk of gastric cancer (39, 40), breast cancer (41), colorectal cancer (42), prostate cancer (43), and lung cancer (44). Hematologic malignancies are the first and only malignant tumors for which we have derived a significant inverse association with green tea consumption. The differences in evidence between our previous studies and the present one indicate that hematologic malignancies may have specific characteristics that result in a response to certain green tea components.

We concluded that green tea consumption was inversely associated with the risk of hematologic malignancies in the general rural population of Japan. Our results have implications for not only primary prevention of hematologic malignancies but also treatment and/or recurrence prevention. Further biologic studies and clinical trials are necessary to confirm the role of green tea in prevention and treatment of hematologic malignancies.

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