The prevalence of current smoking in the present study was lower than that reported in the Hirayama study,[13] [males: 54.4% vs. 74.5% (daily); females: 8.1% vs. 9.7% (daily)]. The prevalence of current smokers in the Hirayama study (carried out in 1965, when there were fewer former smokers) was comparable to the prevalence of ever-smokers in the present study (males: 79.5%; females: 10.5%, from the 1980s to the early 1990s). When we compared the estimate of the PAF of ever-smoking for all-cause mortality in the present study with the Hirayama results (current smoking only), the former was larger both for males (27.8% vs. 17.5%) and for females (6.7% vs. 4.4%). Considering the comparable prevalence of ever-smoking in the present study and current smoking in the Hirayama study, the larger PAFs in the present study would appear to be due to the higher relative risks. Indeed, the relative risks for ever-smokers for all-cause mortality in the present study (vs. never-smokers) were higher than the relative risks for current smokers in the Hirayama study (1.5 vs. 1.3 for males and 1.7 vs. 1.3 for females).

Compared with the annual smoking-attributable mortality in the US from 1997 to 2001,[1] our estimates of the male disease-specific PAFs of smoking were smaller for cancers of the lip/oral cavity/pharynx (52.0% vs. 74.1%) and the lung (69.2% vs. 87.9%), for pneumonia (9.4% vs. 22.5%), and for COPD (60.3% vs. over 80%), while our estimate was larger for IHD (44.1% vs. 20.8%). Note that the PAFs in the US were calculated from the numbers of deaths, excluding those from passive smoking. When we compared our estimated relative risks with the results of the CPS-II,[28] upon which the PAF for the US were based, the relative risks for male current smokers (vs. never-smokers) estimated in the present study were lower for all causes [1.6 vs. 2.3 (95% CI: 2.3-2.4)], lung cancer [4.8 vs. 23.2 (95% CI 19.3-27.9)], stroke [1.3 vs. 1.9 (95% CI: 1.6-2.2)], and COPD [3.1 vs. 11.7 (95% CI: 9.1-15.0)]. Given that the prevalence of current smokers among adult males is considerably higher in Japan than in the US (52.8% vs. 25.7%[29]), the smaller PAFs of smoking in the present study were considered to be due to these lower relative risks. In contrast, the relative risks for male current smokers for IHD were similar in the two studies [2.2 vs. 1.9 (1.8: 2.0)]. Thus, the larger male PAF of smoking for IHD recorded in the present study is considered to be due to the higher prevalence of smoking among Japanese males. For females, our estimate of the PAF of smoking was smaller than the US estimates[1] for many diseases, including lung cancer (19.8% vs. 70.9%), stroke (6.2% vs. 8.7%), and COPD (15.6% vs. over 70%). The relative risks for female current smokers were lower in the present study than in the CPS-II[28] for all causes [1.8 vs. 1.9 (95% CI: 1.9-2.0)], lung cancer [3.9 vs. 12.8 (95% CI 11.3-14.7)], and COPD [3.6 vs. 12.8 (95% CI 10.4-15.9)], whereas those for stroke were similar [1.8 vs. 1.8 (95% CI: 1.6-2.1)]. The prevalence of female current smokers is considerably lower in Japan than in the US (13.4% vs. 21.5%[29]). Thus, the lower PAFs of smoking in Japanese females for lung cancer and COPD are considered to be due to both the lower relative risks and the lower prevalence of smokers. In the case of stroke, the lower PAF was thought to be due to the lower smoking prevalence.

The lower relative risks associated with smoking for Japanese populations compared with those for Western populations have been well documented by previous studies for all causes,[6,30] total cancers,[7] and lung cancer.[15,31,32] A commonly proposed reason for this finding is the lower exposure level among Japanese smokers.[15,32] However, the difference in relative risks is reported to remain even after adjustment for duration of smoking and daily cigarette consumption,[15] or stratification by dose of exposure.[30,31] Other proposed reasons include the possibility of a higher level of passive smoking in Japan (i.e., a higher risk for non-smokers), the misclassification of former smokers as never-smokers (causing an apparent increase in the risk to non-smokers) and a lower genetic susceptibility to tobacco smoke among the Japanese. It is also possible that COPD tends to be underreported as a cause of death on death certificates.

There are several limitations to the present study that could have been potential sources of uncertainty in the estimation of the fraction and the number of smoking-attributable deaths. First, the smoking prevalence used for the estimation of the PAFs was obtained from our cohort data, the baseline survey for which was conducted from the 1980s to the early 1990s. The reason for using cohort data was the need to obtain the prevalence among those who died of a given cause of death.[20] There have been recent changes in the prevalence of smoking in Japan, and a decreasing trend for males is becoming evident. Although the pooled smoking prevalence in the present study was comparable to the national representative adult prevalence around the year 1990 (e.g., 53.1% for males and 9.7% for females in 1990),[33] recent corresponding values were lower for males and higher for females (43.3% for males and 12.0% for females in 2004).[34] On the basis of the national representative smoking prevalence data in 2004 and the relative risks for all-cause mortality in the present study, the PAF of ever-smoking was 25.2% for males and 11.0% for females. The corresponding value based on the prevalence data in the present study (i.e., the prevalence among all participants, not among those who died) was 29.1% for males and 7.2% for females. Thus, the PAFs of smoking in recent calendar years for the Japanese population are probably smaller for males and larger for females, as compared with our estimates.

The information on the smoking status of our participants was collected only at the baseline. Smoking cessation or initiation during the follow-up period might have led to an underestimation of the relative risks of current or former smokers and, conversely, smoking re-initiation during the follow-up period might have caused an overestimation of the relative risk of former smokers. A Japanese cohort study that

examined smoking status 5 years after the baseline survey demonstrated that the shift from current to former smokers was considerably more frequent than either the shift from never-smokers to current smokers or the shift from former to current smokers.[35] This suggests the possibility of underestimating the relative risks of current smokers. However, our relative risk estimate of male current smokers for lung cancer was similar to that obtained by pooling the data from Japanese case-control studies,[36] which implies that the possible change in smoking status had only a limited influence, at least on the lung cancer relative risks. It remains possible that the relative risks of current smokers were underestimated for diseases with a risk that decreases more rapidly after smoking cessation compared to lung cancer.

We excluded participants with unknown smoking status (5% of males and 12% of females). In our preliminary analysis, we calculated the lung cancer mortality rate among participants with unknown smoking status; the value was found to be similar to the mortality rate among current smokers for males, whereas for females it was between the mortality rates of former smokers and never-smokers. If the other risk factors of lung cancer were evenly distributed, it can be assumed that most of the males with unknown smoking status were actually smokers, whereas the females with unknown smoking status were not strongly biased toward smokers or never-smokers. Thus, the prevalence of male smokers could have been underestimated by the selective exclusion of smokers. However, the extent of this effect was considered to be small since the proportion of male participants with unknown smoking status was correspondingly small.

Since the relative risks estimated in the present study were adjusted only for age, other potential confounding factors might have influenced our results. One such possible confounding factor was cohort, although this might have been negligible because the HRs adjusted for age and cohort did not differ from those adjusted only for age [e.g., the age- and cohort-adjusted HR of lung cancer for current smokers was 4.8 (95% CI: 3.9-5.9) for males and 3.8 (95% CI: 3.0-4.9) for females]. Our relative risk and PAF estimates for a specific disease might have been overestimated if its risk factors were positively correlated with smoking (i.e., alcohol consumption for esophageal cancer). For several disease groups, the age-adjusted relative risks of current smokers (vs. never-smokers) have been reported to be slightly higher than the multivariate adjusted values (i.e., all causes,[6,30] stomach cancer,[37] and stroke[10,38]), suggesting the existence of risk factors associated with smoking. In contrast, it is possible that the list of tobacco-related diseases might overlook non-established smoking-attributable diseases or disease sub-categories. Thus, our PAF estimates of all-cause mortality calculated using the relative risk of all-cause mortality itself [i.e., equation (1) in the Methods section] might have included overestimates, whereas the PAF calculated by summing the disease-specific PAFs [i.e., equation (2)] might have included underestimates.

For diseases with a relatively long duration (i.e., a time lag from incidence to death), high HRs in former smokers could be due to the "ill-quitter" effect; that is, those individuals who developed these diseases might have quit smoking because of the illness. We analyzed our data excluding deaths within 5 years of follow-up and confirmed that there was no major change in the relative risks of former smokers.

The sample sizes were small for relatively rare diseases, particularly among females. We either could not estimate HRs, or the estimated HRs had a wide CI, for female mortality from cancers in the lip/oral cavity/pharynx, esophagus, larynx, and kidney (except renal pelvis), myeloid leukemia, abdominal aortic aneurysm, COPD, and peptic ulcer. However, since these causes of death accounted for a small proportion of the total number of deaths observed in the present study (2% of the total female deaths), we consider the instability of the HRs to have had only a weak influence on our estimates of the disease distribution of smoking-attributable deaths.

Regarding the generalizability of our PAF estimates, some of the participants in the present study were recruited not from the general population but rather from those undergoing health check-ups (Table 1). Health check-up examinees might have different relative risks to those of the general population to which they belong. For example, a previous study using the JPHC cohort examined the differences in relative risks between health check-up examinees and the entire cohort, and revealed that the relative risk of all-cause mortality for current smokers (vs. never-smokers) was 24% higher for health check-up examinees.[39] These types of difference might have influenced our relative risk estimates.

Another issue regarding generalizability is age. The age distribution of participants in the present study was slightly different to that of the Japanese population as a whole. Compared with the Japanese population aged 40-79 years in 1983-1994, the proportion of those aged 70-79 years was smaller among the participants in the present study (7.5% vs. 10.9% for males and 8.0% vs. 14.4% for females). Generally, the prevalence of current smokers was lower among the group aged 70-79 years than among the younger age groups. We used the age-pooled smoking prevalence to calculate the PAFs, which might have led to the inclusion of slight overestimations.

The reason for the small proportion of individuals aged 70-79 years among the participants in the present study was that this age group was only covered by the 3-pref and JACC cohorts. We analyzed the differences between the groups of cohorts with and without this age group (3-pref + JACC vs. JPHC-I + JPHC-II) in terms of the age-adjusted HR of the current smokers (vs. never-smokers) for all-cause mortality, limiting to the common baseline age groups (40-59 years old). The calculated HRs were similar [males: 1.8 (95% CI:

Appendix. Cause-specific, age-adjusted population attributable fraction according to smoking status, for males and females.

Cause of death	ICD-9	ICD-10	Males						Females					
			Current smokers		Former smokers		Ever-smokers		Current smokers		Former smokers		Ever-smokers	
All-cause	(All)	(All)	21.9%	(20.1% – 23.7%)	5.8%	(4.7% – 7.1%)	27.8%	(25.2% – 30.4%)	5.0%	(4.3% – 5.8%)	1.8%	(1.3% – 2.2%)	6.7%	(5.9% – 7.5%)
All-cause§	(All)	(All)	14.7%	(12.9% – 16.4%)	4.4%	(3.5% – 5.3%)	19.1%	(16.0% – 22.2%)	2.9%	(2.3% – 3.4%)	0.8%	(0.5% – 1.0%)	3.6%	(3.0% – 4.2%)
Total tobacco-related diseases			26.7%	(24.3% – 28.9%)	8.0%	(6.4% – 9.6%)	34.7%	(31.2% – 38.0%)	6.5%	(5.4% – 7.5%)	1.7%	(1.0% – 2.3%)	8.1%	(6.8% – 9.4%)
All cancers	140-208	C00-C97	29.3%	(26.5% – 31.9%)	9.3%	(7.5% – 11.1%)	38.6%	(34.5% – 42.3%)	3.6%	(2.7% – 4.9%)	1.4%	(0.7% – 2.0%)	5.2%	(3.8% – 6.5%)
All cancers§	140-208	C00-C97	26.0%	(22.5% – 29.5%)	7.8%	(6.2% – 9.5%)	33.8%	(27.5% – 40.2%)	3.5%	(2.6% – 4.5%)	1.0%	(0.5% – 1.5%)	4.4%	(3.3% – 5.5%)
Total tobacco-related cancers			35.2%	(32.1% – 38.1%)	10.5%	(8.5% – 12.5%)	45.7%	(41.2% – 49.8%)	6.5%	(4.9% – 8.2%)	1.7%	(0.8% – 2.6%)	8.3%	(6.3% – 10.1%)
Lip, oral cavity, and pharynx*	140-149	C00-C14	39.3%	(19.0% – 54.8%)	12.7%	(0.3% – 23.6%)	52.0%	(19.6% – 71.4%)	6.4%	(-7.2% – 18.2%)	0.6%	(-6.0% – 6.8%)	7.0%	(-8.6% – 20.3%)
Esophagus*	150	C15	47.0%	(35.3% – 56.5%)	13.8%	(6.7% – 20.4%)	60.8%	(43.4% – 72.9%)	5.5%	(-5.3% – 15.2%)	6.7%	(-2.7% – 15.2%)	12.2%	(-2.4% – 24.7%)
Stomach*	151	C16	18.8%	(12.1% – 24.9%)	6.4%	(2.0% – 10.6%)	25.1%	(15.0% – 34.1%)	1.5%	(-1.0% – 4.0%)	1.2%	(-0.4% – 2.8%)	2.7%	(-0.4% – 5.7%)
Liver*	155	C22	25.6%	(18.1% – 32.5%)	11.5%	(6.7% – 16.0%)	37.1%	(25.9% – 46.6%)	4.9%	(0.9% – 8.7%)	0.6%	(-1.5% – 2.6%)	5.4%	(0.9% – 9.8%)
Pancreas*	157	C25	21.2%	(8.3% – 32.3%)	4.4%	(-3.8% – 11.9%)	25.5%	(5.7% – 41.2%)	5.3%	(1.3% – 9.1%)	2.4%	(-0.1% – 4.9%)	7.7%	(2.9% – 12.2%)
Larynx*	161	C32	56.7%	(20.0% – 78.6%)	16.7%	(-4.8% – 33.9%)	73.4%	(-2.1% – 93.1%)	0.0%	– –	0.0%	– –	0.0%	– –
Lung*	162	C33-C34	55.8%	(51.2% – 60.0%)	13.4%	(10.3% – 16.4%)	69.2%	(62.6% – 74.7%)	16.4%	(12.0% – 20.5%)	3.4%	(1.2% – 5.6%)	19.8%	(14.9% – 24.4%)
Cervix uteri*	180	C53	–	– –	–	– –	–	– –	8.6%	(0.4% – 16.2%)	0.0%	(-3.1% – 3.0%)	8.6%	(-0.3% – 16.8%)
Kidney, except renal pelvis*	189.0	C64	19.9%	(-11.0% – 42.2%)	9.7%	(-9.6% – 25.6%)	29.6%	(-21.5% – 59.2%)	-2.9%	(-12.3% – 5.7%)	1.5%	(-7.4% – 9.8%)	-1.4%	(-15.0% – 10.7%)
Renal pelvis, ureter, bladder*	189.1, 189.2, 188	C65-C67	56.9%	(39.5% – 69.3%)	15.4%	(4.2% – 25.4%)	72.3%	(43.1% – 86.5%)	5.8%	(-4.0% – 14.7%)	0.0%	– –	2.9%	(-7.2% – 12.1%)
Renal pelvis	189.1	C65	74.6%	(-13.7% – 94.3%)	-2.8%	(-25.0% – 15.7%)	72.0%	(-87.7% – 95.8%)	0.0%	– –	0.0%	– –	0.0%	– –
Ureter	189.2	C66	33.0%	(-59.1% – 71.8%)	0.3%	(-46.1% – 31.9%)	33.2%	(-141.3% – 81.5%)	19.1%	(-20.7% – 45.8%)	0.0%	– –	16.9%	(-23.9% – 44.3%)
Bladder	188	C67	57.4%	(38.4% – 70.5%)	21.3%	(8.2% – 32.5%)	78.6%	(44.3% – 91.8%)	4.5%	(-6.1% – 14.1%)	0.0%	– –	1.6%	(-9.5% – 11.4%)
Myeloid leukemia*	205	C92	14.8%	(-13.7% – 36.2%)	20.3%	(1.9% – 35.3%)	35.1%	(-12.6% – 62.6%)	-0.3%	(-8.9% – 7.6%)	-0.1%	(-4.8% – 4.4%)	-0.4%	(-10.5% – 8.8%)
All cardiovascular diseases	390-459	I01-I99	18.8%	(15.3% – 22.2%)	4.2%	(1.7% – 6.6%)	23.0%	(17.5% – 28.0%)	6.4%	(5.1% – 7.7%)	1.6%	(0.9% – 2.4%)	8.0%	(6.5% – 9.6%)
All cardiovascular diseases§	390-459	I01-I99	12.4%	(9.9% – 15.9%)	2.9%	(0.9% – 5.0%)	15.3%	(9.6% – 21.0%)	4.5%	(3.3% – 5.6%)	1.1%	(0.5% – 1.7%)	5.8%	(4.2% – 7.0%)
Total tobacco-related cardiovascular diseases			18.7%	(14.3% – 22.8%)	4.5%	(1.5% – 7.4%)	23.1%	(16.4% – 29.3%)	7.0%	(5.3% – 8.7%)	1.8%	(0.8% – 2.7%)	8.8%	(6.8% – 10.7%)
Ischemic heart diseases*	410-414	I20-I25	31.8%	(24.9% – 37.9%)	12.3%	(7.7% – 16.8%)	44.1%	(33.7% – 52.8%)	11.8%	(7.9% – 15.1%)	3.6%	(1.4% – 5.8%)	15.2%	(10.9% – 19.3%)
Total stroke*	430-438	I60-I69	10.6%	(4.8% – 16.0%)	-0.1%	(-4.1% – 3.8%)	10.4%	(1.4% – 18.8%)	5.3%	(3.4% – 7.1%)	1.0%	(-0.1% – 2.0%)	6.2%	(4.1% – 8.4%)
Subarachnoid hemorrhage	430	I60	39.5%	(21.3% – 53.5%)	3.1%	(-6.3% – 11.6%)	42.6%	(15.8% – 60.9%)	11.3%	(6.5% – 15.9%)	0.1%	(-1.7% – 1.9%)	11.5%	(6.2% – 16.4%)
Intracerebral hemorrhage	431	I61	10.8%	(-1.5% – 21.5%)	-2.5%	(-9.8% – 4.3%)	8.3%	(-10.2% – 23.7%)	6.0%	(2.1% – 9.8%)	1.7%	(-0.5% – 4.0%)	7.8%	(3.2% – 12.2%)
Cerebral infarction	433-434	I63	9.5%	(0.6% – 17.5%)	0.5%	(-6.1% – 6.7%)	9.9%	(-4.5% – 22.3%)	3.3%	(0.3% – 6.3%)	0.5%	(-1.2% – 2.3%)	3.9%	(0.3% – 7.3%)
Aortic aneurysm and dissection	441	I71	47.4%	(30.3% – 60.3%)	18.3%	(6.8% – 28.4%)	65.6%	(37.6% – 81.1%)	8.2%	(-1.5% – 17.0%)	5.4%	(-1.7% – 12.0%)	13.6%	(1.4% – 24.3%)
Abdominal aortic aneurysm*	441.3, 441.4	I71.3, I71.4	52.2%	(19.0% – 72.1%)	8.3%	(-11.8% – 24.8%)	60.3%	(-1.3% – 84.5%)	16.5%	(-9.9% – 36.5%)	12.1%	(-8.9% – 29.0%)	28.5%	(-5.6% – 51.6%)
All respiratory diseases	460-519	J00-J99	13.9%	(8.4% – 19.0%)	9.5%	(5.2% – 13.7%)	23.4%	(14.5% – 31.4%)	4.3%	(1.8% – 6.8%)	0.8%	(-0.7% – 2.2%)	5.1%	(2.1% – 8.0%)
All respiratory diseases§	460-519	J00-J99	8.8%	(3.7% – 13.9%)	4.9%	(1.0% – 8.8%)	13.7%	(4.2% – 23.2%)	2.4%	(0.3% – 4.5%)	0.8%	(-0.5% – 2.1%)	3.2%	(0.6% – 5.7%)
Total tobacco-related respiratory diseases			12.4%	(5.8% – 18.5%)	6.9%	(1.8% – 11.8%)	19.2%	(8.4% – 28.7%)	3.6%	(0.5% – 6.6%)	1.2%	(-0.7% – 3.1%)	4.8%	(1.1% – 8.3%)
Pneumonia*	480-486	J12-J18	6.6%	(-0.9% – 13.6%)	2.8%	(-3.2% – 8.5%)	9.4%	(-3.1% – 20.5%)	2.7%	(-0.4% – 5.7%)	1.2%	(-0.8% – 3.2%)	3.9%	(0.2% – 7.5%)
Chronic obstructive pulmonary diseases*	491-492, 496	J41-J44	36.5%	(23.8% – 47.1%)	23.8%	(13.5% – 32.9%)	60.3%	(39.0% – 74.2%)	15.2%	(-1.2% – 29.0%)	0.4%	(-5.8% – 6.3%)	15.6%	(-2.3% – 30.5%)
All digestive diseases	520-579	K00-K93	33.0%	(23.1% – 41.6%)	4.1%	(-1.6% – 9.4%)	37.1%	(22.0% – 48.8%)	7.1%	(3.0% – 11.0%)	2.8%	(0.2% – 5.3%)	9.9%	(5.0% – 14.5%)
All digestive diseases§	520-579	K00-K93	4.6%	(-0.5% – 9.7%)	0.5%	(-0.7% – 1.6%)	5.1%	(-4.0% – 14.2%)	0.2%	(-0.7% – 1.1%)	0.1%	(-0.5% – 0.7%)	0.3%	(-0.9% – 1.4%)
Peptic ulcer*	531-533	K25-K27	66.8%	(33.5% – 85.3%)	7.4%	(-9.9% – 21.9%)	76.0%	(7.5% – 93.8%)	2.6%	(-11.9% – 15.2%)	1.6%	(-8.3% – 10.6%)	4.2%	(-14.1% – 19.6%)

*: Tobacco-related diseases selected from the Surgeon General's Report of 2004 and IARC Monograph volume 83.
§: Population attributable fraction was calculated by summing up attributable fractions estimated for each tobacco-related disease, assuming that the fraction of diseases other than tobacco-related diseases was zero.

1.6-2.0) for 3-pref + JACC, 1.8 (95% CI: 1.6-2.0) for JPHC-I + JPHC-II; females: 1.9 (95% CI: 1.6-2.2) for 3-pref + JACC, 1.8 (95% CI: 1.5-2.1) for JPHC-I + JPHC-II]. The prevalence of current smokers in the two groups of cohorts was not widely different (males: 58.8% for 3-pref + JACC, 54.5% for JPHC-I + JPHC-II; females: 8.8% for 3-pref + JACC, 8.2% for JPHC-I + JPHC-II). Therefore, the influence of using partial data for the group aged 70-79 years was considered to be small.

The generalizability of our PAF estimates to the age groups that were not covered by the present study (i.e., those under 40 or over 79 years old) is limited. We estimated the number of deaths attributable to smoking using the all-age number of deaths in Japan. In this calculation, the influence of the group aged under 40 years was negligible because it accounted for only a small part of the all-age mortality in Japan (2.6% in 2005). The group aged over 79 years was partly covered by the present study in terms of attained age since the follow-up period was on average 10 years. According to a previous study that used the same dataset employed in the present study, the all-cause mortality rate ratios of current smokers vs. never-smokers were similar for the groups aged 40-69 years and 70 years or older (calculated using the attained age).[40] The smoking prevalence among those aged 70-79 years in the present study was not notably different to the national data for those aged 70 years or older (42.5% vs. 38.8% for males and 8.5% vs. 7.2% for females).[33] Thus, we believe that approximating the number of smoking-attributable deaths for all ages based on our PAF estimates is a valid approach.

In conclusion, we used the pooled data from three large-scale cohort studies in Japan to demonstrate that the estimated smoking-attributable fraction of all-cause mortality among individuals aged 40-79 years was 27.8% for males and 6.7% for females. The corresponding values calculated by summing the disease-specific smoking-attributable fractions were 19.1% for males and 3.6% for females. These results confirmed that the health burden of smoking is still large among Japanese males. Considering the high prevalence of male current smokers and the increasing prevalence of young female current smokers, effective tobacco controls and quantitative assessments of the health burden of smoking should be continuously implemented in Japan.

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Original Contribution

Green Tea Consumption and Prostate Cancer Risk in Japanese Men: A Prospective Study

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The incidence of prostate cancer is much lower in Asian than Western populations. Given that environmental factors such as dietary habits may play a major role in the causation of prostate cancer and the high consumption of green tea in Asian populations, this low incidence may be partly due to the effects of green tea. The JPHC Study (Japan Public Health Center-based Prospective Study) was established in 1990 for cohort I and in 1993 for cohort II. The subjects were 49,920 men aged 40–69 years who completed a questionnaire that included their green tea consumption habit at baseline and were followed until the end of 2004. During this time, 404 men were newly diagnosed with prostate cancer, of whom 114 had advanced cases, 271 were localized, and 19 were of an undetermined stage. Green tea was not associated with localized prostate cancer. However, consumption was associated with a dose-dependent decrease in the risk of advanced prostate cancer. The multivariate relative risk was 0.52 (95% confidence interval: 0.28, 0.96) for men drinking 5 or more cups/day compared with less than 1 cup/day ($p_{trend} = 0.01$). Green tea may be associated with a decreased risk of advanced prostate cancer.

Camellia sinensis; catechin; Japan; men; neoplasm staging; prospective studies; prostatic neoplasms; tea

Abbreviations: CI, confidence interval; EGCG, (−)-epigallocatechin-3-gallate; JPHC Study, Japan Public Health Center-based Prospective Study; PHC, Public Health Center; RR, relative risk.

Although the incidence of prostate cancer is much lower in Asian men than in Western men (1), the incidence of latent or clinically insignificant prostate cancer in autopsy studies among men from Asian countries and from the United States is similar (1–3). Moreover, migration data show that the incidence increases in men migrating from areas of low incidence to areas of higher incidence (4, 5). These results suggest that the etiology of prostate cancer may involve dietary, lifestyle, and environmental factors. A large number of experimental studies have shown that tea and its constituents have preventive effects against the development of prostate cancer, including antioxidant properties against free radicals, induction of apoptosis, inhibition of cell growth, and the arrest of cell cycle progression (6, 7). Teas are made from a leaf extract of the plant *Camellia sinensis* and classified into two main types, depending on the manufacturing process: green tea, which is nonfermented, and black tea, which is fermented (8). In general, green tea has a higher content of catechins, such as (−)-epigallocatechin-3-gallate (EGCG), which play an important role in cancer prevention, than does black tea (9). Given the high consumption of green tea in Asia, it has been suggested that the low incidence of prostate cancer in Asia may be partly due to the effects of green tea.

Although the preventive effects of green tea on prostate cancer have been reported in many laboratory studies (6), results from epidemiologic studies researching the association

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between teas in general (including both black and green teas) or green tea alone and prostate cancer have been inconsistent. In a case-control study in southeast China, the risk of prostate cancer decreased with increasing frequency of green tea consumption in a dose-dependent manner (10). Similarly, in a case-control study in Canadian men, general tea consumption was associated with a decreased risk of prostate cancer (11), and green tea consumption was further associated with a modest reduction in risk in a case-control study in Japan (12). To the contrary, however, other case-control studies in Italy, Utah, and Canada found no difference in risk for prostate cancer between general tea drinkers and nondrinkers (13–15). Among prospective studies, moreover, no association was reported between green tea consumption and prostate cancer in Japanese men (16, 17), while risk was conversely increased with green tea consumption in a cohort of men of Japanese ancestry in Hawaii (18).

This inconsistency might be explained as follows. First, subjects in some of these previous studies did not commonly drink green tea, but rather black tea. Second, almost all of these previous studies did not analyze by cancer stage, notwithstanding that the effects of green tea on prostate cancer may differ between localized and advanced cancer (10, 14).

Here, we investigated the relation between green tea consumption and risk of prostate cancer according to stage in a large prospective study among Japanese, who generally consume green tea.

MATERIALS AND METHODS

Study population

This cohort was part of the Japan Public Health Center-based Prospective Study (JPHC Study), which was established in 1990 for cohort I and in 1993 for cohort II. The study design has been described in detail previously (19). Cohort I consisted of five Public Health Center (PCH) areas (Iwate, Akita, Nagano, Okinawa, and Tokyo), and cohort II consisted of six PHC areas (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka) across Japan. The study population was defined as all residents aged 40–59 years in cohort I and 40–69 years in cohort II at the start of the respective baseline survey. In the present analysis, the Tokyo subjects were not included in data analyses because incidence data for them were not available. Initially, we defined a population-based cohort of 65,802 men. After initiation of the study, 143 subjects were found to be ineligible and were excluded because of non-Japanese nationality ($n = 31$), late report of emigration occurring before the start of the follow-up period ($n = 107$), duplicate enrollment ($n = 2$), incorrect birth data ($n = 1$), and self-reported prostate cancer at baseline ($n = 2$), leaving 65,659 men eligible for participation. This study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan.

Baseline survey

A self-administered questionnaire, which included green tea consumption and other lifestyle factors, was distributed to all eligible registered residents in 1990 for cohort I and in 1993–1994 for cohort II. Completed questionnaires were collected from 50,436 men (response rate, 77 percent). Information on the frequency and amount of green tea intake was obtained by use of the answer categories of almost none, 1–2 days/week, 3–4 days/week, 1–2 cups/day, 3–4 cups/day, and ≥5cups/day. Exposure was categorized by approximate quartile (<1 cup/day, 1–2 cups/day, 3–4 cups/day, ≥5 cups/day), with the category of <1 cup/day including those who consume almost none, 1–2 days/week, and 3–4 days/week. The validity of green tea consumption was assessed among subsamples using 28-day dietary records. Spearman's correlation coefficients between green tea consumption from the questionnaire and from dietary records were 0.57 for cohort I (20) and 0.37 for cohort II (21). In the validation study, the median value of green tea was 150 ml based on dietary records. Dietary factors in the questionnaire used in this study have been provided elsewhere (22).

Follow-up

Subjects were followed from the baseline survey until December 31, 2004. Changes in residence status including survival were identified annually through the residential registry in each area or, for those who had moved out of the study area, through the municipal office of the area to which they had moved. Among questionnaire respondents at baseline, 5,517 (10.9 percent) died, 3,017 (6.0 percent) moved out of a study area, and 91 (0.2 percent) were lost to follow-up during the study period. Generally, mortality data for the residents included in a residential registry are forwarded to the Ministry of Health, Labor, and Welfare and coded for inclusion in the national vital statistics. Residency and death registration are required by the Basic Residential Register Law and Family Registry Law, respectively, and the registries are believed to be complete. Here, information on the cause of death for those who had not moved out of the original area was based on death certificates from the respective PHC.

The occurrence of cancer was identified by active patient notification from major local hospitals in the study area and data linkage with population-based cancer registries, with permission from the local governments responsible for the registries. Cases were confirmed from medical records, 94 percent of which included pathologic diagnoses, and were coded by use of the *International Classification of Diseases for Oncology*, Third Edition (23). Death certificate information was used as a supplementary information source, with 1.5 percent of cases of prostate cancer first notified by death certificate. The proportion of case patients with prostate cancer ascertained by death certificate only was 1.2 percent. These ratios were considered satisfactory for the present study.

We excluded men with incomplete information on green tea consumption ($n = 516$). For the present analysis, the earliest date of diagnosis was used in subjects with multiple primary cancers at different times. A total of 404 newly diagnosed prostate cancer cases were identified by December 31, 2004. Finally, a total of 49,920 men, including 404 prostate cancer patients, were used in the analysis.

Definition of localized and advanced prostate cancer

Cancer registration in our study required the entry of local staging, with the Gleason score used as supplementary information only. Cases were therefore classified as advanced cases (extraprostatic or metastatic cancer involving lymph nodes or other organs, 25 percent of total), localized cases (cancer confined within prostate, 54 percent of total), and undetermined cases (21 percent of total). The distribution of local staging in our study was similar to that in Japan overall (24). Moreover, cases for which local staging information was not available (83 undetermined cases) were divided into localized and advanced cancer by use of information on Gleason score or degree of differentiation. We added 11 cases with a high Gleason score of 8–10 or poor differentiation to the advanced cancer cases group. These criteria were selected to allow the identification of cases with a high likelihood of poor prognosis. Further, we added 53 cases with a low Gleason score of ≤7 or well or moderate differentiation to the localized cancer group (25). Finally, we confirmed 271 localized, 114 advanced, and 19 undetermined (5 percent of total) cases.

Statistical analysis

Person-years of follow-up were calculated for each person from the date of the baseline survey until the date of prostate cancer diagnosis, date of emigration from the study area, or date of death, whichever came first; if none of these occurred, follow-up was through the end of the study period (December 31, 2004). Subjects who were lost to follow-up were censored on the last confirmed date of their presence in the study area. The relative risks and 95 percent confidence intervals of prostate cancer according to green tea consumption were calculated by the Cox proportional hazards model, adjusted for age, study area (10 PHC areas), smoking status, alcohol consumption, body mass index, men who live with their wife, and coffee, black tea, and miso soup consumption according to the SAS PHREG procedure in SAS software, version 9.1 (SAS Institute, Inc., Cary, North Carolina). The questionnaires used with the JPHC Study cohort I and cohort II differed slightly with respect to food items, method of expression, and frequency categories (excluding green tea, black tea, coffee, and miso soup consumption). Thus, for adjustments that included food items, the following statistical methods were used. For analysis of the further covariates of fruits, green or yellow vegetables, dairy food, soy food, and genistein, we calculated separate estimates for cohort I and cohort II and then analyzed the combined result using a fixed-effects model. In the test for heterogeneity using an inverse variance method, the two cohorts were not heterogeneous ($p = 0.95$). The covariates used in the model were age at enrollment, study area (10 PHC areas), smoking status (never, former, and current smokers), alcohol consumption (non-, former, or occasional drinkers, 1–149 g/week, ≥150 g/week), body mass index (continuous), men who live with their wife (yes/no), coffee consumption (almost none, ≥1 time/week, ≥1 cup/day), black tea consumption (almost none, ≥1 time/week, ≥1 cup/day), miso soup consumption (<4 times/week, one bowl/day, two bowls/day, ≥3 bowls/day), consumptions of fruits (g/day), green or yellow vegetables (g/day), dairy food (g/day), and soy food (g/day), and genistein (mg/day). Respective consumption of fruits, green or yellow vegetables, dairy food, and soy food was calculated by use of the frequency and portion size of each food from the questionnaire, while values for genistein were calculated by a specially developed food composition table for isoflavones in Japanese foods (26, 27).

P_{trend} values were assessed by assigning ordinal values for categorical variables. All p values are two sided, and statistical significance was determined at the $p < 0.05$ level.

RESULTS

Subjects' characteristics at baseline according to category of green tea consumption are shown in table 1. Participants with higher green tea consumption tended to be older, to smoke more, to have a higher likelihood of living with their wife, to consume more miso soup, fruits, vegetables, and soy food, and to consume less coffee.

Table 2 shows relative risks and 95 percent confidence intervals for prostate cancer by green tea consumption. Consumption was not associated with all cases of prostate cancer, and relative risks did not change substantially after adjustment for all potential confounding factors (for highest vs. lowest: relative risk (RR) = 0.89, 95 percent confidence interval (CI): 0.65, 1.21; $p_{trend} = 0.43$). We next classified the data according to prostate cancer stage. No statistically significant association was seen between green tea consumption and localized prostate cancer risk (for highest vs. lowest: RR in model 2 = 1.04, 95 percent CI: 0.72, 1.52; $p_{trend} = 0.54$). In contrast, however, green tea consumption was associated with a decreased risk of advanced prostate cancer in a dose-dependent manner (<1 cup/day: reference; 1–2 cups/day: age- and area-adjusted RR = 1.12, 95 percent CI: 0.65, 1.94; 3–4 cups/day: RR = 0.86, 95 percent CI: 0.50, 1.47; ≥5 cups/day: RR = 0.60, 95 percent CI: 0.34, 1.06; $p_{trend} = 0.03$). This association was strengthened to statistical significance when adjustment was made for all potential confounding factors (for highest vs. lowest: RR = 0.52, 95 percent CI: 0.28, 0.96). Tests for linear trends were also strengthened ($p_{trend} = 0.01$).

DISCUSSION

In this prospective cohort study among Japanese men, green tea consumption was associated with a decreased risk of advanced prostate cancer. In contrast, no association was observed between consumption and localized prostate cancer. To our knowledge, this is the first prospective study to investigate the association between green tea and prostate cancer according to stage and to identify the preventive effects of green tea on advanced prostate cancer. Although green tea and its constituents have shown protective effects on prostate cancer in many experimental studies (6, 7), previous epidemiologic studies researching the association between teas or green tea and prostate cancer have been inconsistent. One reason for this inconsistency is that most

TABLE 1. Baseline characteristics of study subjects according to green tea consumption, JPHC* Study, 1990–2004

	Green tea consumption (cups/day)				$P_{difference}$†
	<1	1–2	3–4	≥5	
No. of subjects	12,940	11,772	13,176	12,031	
Proportion (%)‡	25.9	23.6	26.4	24.1	
Mean age (years)	49.7 (7.4)§	50.8 (7.9)	52.3 (8.1)	53.9 (7.8)	<0.001
Body mass index, ≥25 (%)‡	23.8 (3.0)	23.5 (2.8)	23.3 (2.8)	23.3 (2.8)	<0.001
Current smoker (%)‡	51.3	52.8	51.6	54.0	<0.001
Regular drinker (%)‡	63.9	68.6	66.3	61.2	<0.001
Men who live with their wife, yes (%)‡	80.6	86.6	88.4	87.9	<0.001
Coffee, daily (%)‡	42.6	47.3	40.2	30.5	<0.001
Black tea, daily (%)‡	2.6	3.2	2.9	2.5	<0.001
Miso soup, daily (%)‡	61.7	68.3	72.6	78.4	<0.001
Fruits, daily (%)‡	17.7	22.8	26.3	30.7	<0.001
Green or yellow vegetables, daily (%)‡	37.8	36.5	40.2	47.1	<0.001
Dairy food, daily (%)‡	33.2	37.2	36.8	36.6	<0.001
Soy food, daily (%)‡	78.6	82.4	86.2	90.2	<0.001

* JPHC Study, Japan Public Health Center-based Prospective Study.

† $P_{difference}$ values of characteristics between categories of green tea consumption were calculated by analysis of variance and the chi-square test for homogeneity.

‡ All variables except for age were standardized to the age distribution (categorized by 5-year intervals) of the entire cohort.

§ Numbers in parentheses, standard deviation.

of the studies included populations that drink black tea predominantly. In a case-control study among Canadian men, tea consumption was associated with a statistically significant 30 percent decrease in prostate cancer risk (11). In contrast, no association with prostate cancer (RR = 0.9) was seen in men with a tea-drinking habit compared with non-tea drinkers in Italy (13), while drinking more than 5 cups of tea per week was not associated with a decreased risk of prostate cancer (RR = 0.90) in Utah (14). Moreover, a population-based case-control study in Canada found no difference in risk for prostate cancer between tea drinkers and non-tea drinkers (RR = 1.1 in men drinking ≥4 cups per day) (15).

However, this inconsistency in the effects of black tea on prostate cancer has also been seen in studies on green tea and prostate cancer among populations who mainly consume green tea. In a case-control study in southeast China, an increasing frequency of green tea consumption dose dependently decreased the risk of prostate cancer (10). Ten or more cups of green tea per day produced a modest reduction in the risk of prostate cancer (RR = 0.67) in a case-control study in Japan (12). In two prospective studies among Japanese men, no association was reported between green tea consumption and prostate cancer (16, 17). In contrast, Severson et al. (18) reported a nearly 50 percent increase in risk in relation to green tea intake in a prospective cohort study among men of Japanese ancestry in Hawaii. However, no studies have examined the association between green tea consumption and prostate cancer risk with regard to cancer stage. Given our finding that the effects of green tea differ according to cancer stage, this lack of classification by stage may be another reason for the inconsistency among studies. Our study showed that green tea was associated with a decrease in the risk of advanced prostate cancer only. This result is not inconsistent with a previous paper on the preventive effects of green tea on prostate cancer in China, where prostate cancer is typically diagnosed at an advanced stage (10).

This result is also supported by several mechanisms of cancer pathogenesis. Green tea and its constituents, such as EGCG, induce apoptosis, inhibit cell growth, and arrest progression of the cell cycle (6). In addition, EGCG has been found to inhibit tumor cell invasion and the expression of matrix metalloprotease, which is reported to be overexpressed in angiogenesis and essential in penetrating the basement membrane barriers (6, 7, 28). High levels of matrix metalloprotease 2 in plasma have been correlated with metastasis in prostate cancer patients (29), and increased expression of matrix metalloprotease 2 has been correlated with a high Gleason score and aggressive prostate cancer (30). In animal models, Gupta et al. (31) demonstrated that oral infusion of green tea polyphenols inhibits prostate carcinogenesis in transgenic adenocarcinoma of the mouse prostate (TRAMP), a model for prostate cancer that closely mimics progressive forms of human disease (32), and Caporali et al. (33) similarly reported that oral feeding of tea polyphenol to these mice prevented prostate cancer development. Moreover,

TABLE 2. Relative risk of prostate cancer according to green tea consumption, JPHC* Study, 1990–2004

	Green tea consumption (cups/day)										
	<1		1–2			3–4		≥5			P_{trend}
	No.	Relative risk	No.	Relative risk	95% confidence interval	No.	Relative risk	95% confidence interval	No.	Relative risk	95% confidence interval	
						All cases (n = *404*)						
Cases	76		83			114			131			
Age and area adjusted†		1.00		1.04	0.75, 1.42		1.00	0.74, 1.35		0.92	0.69, 1.24	0.49
Mutivariate (model 1)‡		1.00		0.98	0.70, 1.37		0.95	0.69, 1.30		0.90	0.66, 1.23	0.48
Mutivariate (model 2)§		1.00		0.96	0.68, 1.35		0.94	0.68, 1.30		0.89	0.65, 1.21	0.43
						Localized cases (n = *271*)¶						
Cases	49		48			74			100			
Age and area adjusted†		1.00		0.92	0.61, 1.38		1.00	0.69, 1.45		1.06	0.75, 1.51	0.57
Mutivariate (model 1)‡		1.00		0.83	0.54, 1.27		0.95	0.64, 1.40		1.07	0.73, 1.55	0.48
Mutivariate (model 2)§		1.00		0.81	0.52, 1.25		0.93	0.63, 1.37		1.04	0.72, 1.52	0.54
						Advanced cases (n = *114*)#						
Cases	26		29			32			27			
Age and area adjusted†		1.00		1.12	0.65, 1.94		0.86	0.50, 1.47		0.60	0.34, 1.06	0.03
Mutivariate (model 1)‡		1.00		1.10	0.62, 1.96		0.83	0.47, 1.47		0.56	0.31, 1.00	0.02
Mutivariate (model 2)§		1.00		1.10	0.61, 1.97		0.83	0.47, 1.48		0.52	0.28, 0.96	0.01

* JPHC Study, Japan Public Health Center-based Prospective Study.

† Calculated from a proportional hazards regression analysis of the two cohorts together and adjusted for age and area.

‡ Calculated from a proportional hazards regression analysis of the two cohorts together and adjusted for age, area, smoking status, alcohol consumption, body mass index, marital status, and coffee, black tea, and miso soup consumption.

§ Calculated from the weighted average of results from separate proportional hazards regressions fitted to the individual cohorts and further adjusted for fruits, green or yellow vegetables, dairy food, soy food, and genistein consumption.

¶ Localized cases were defined as cancer confined within the prostate. If information on local staging was not available, localized cases were considered as cases with a Gleason score of ≤7 (or well or moderate differentiation).

Advanced cases were defined as extraprostatic or metastatic cancer involving lymph nodes or other organs. If information on local staging was not available, advanced cases were defined as cancer with a Gleason score of 8–10 (or poor differentiation).

oral EGCG decreased testosterone levels in an animal experiment (34), and EGCG repressed transcription of the androgen receptor gene, *AR*, and thereby inhibited the effect of androgen on prostate cancer (35). Given that androgen receptor genes are amplified in at least one third of advanced prostate cancers cases (36), advanced prostate cancer may be more sensitive to the effects of green tea on testosterone or androgen receptor than is localized prostate cancer. These reports indicate the biologic plausibility of our result that green tea decreased the risk of advanced prostate cancer only. Nevertheless, the number of advanced prostate cancers was relatively small, and the occurrence of this result by chance cannot be ruled out.

The major strength of the present study was its prospective design. Collection of green tea consumption data before the subsequent diagnosis of prostate cancer allowed us to avoid recall bias. Other strengths were its high response rate (approximately 80 percent) and negligible loss to follow-up (0.2 percent). Moreover, we were able to adjust possible confounding factors to remove associations with other substances. A high intake of green tea is associated with some substances that may have contributed to the risk of prostate cancer. In this study, the association between green tea and advanced prostate cancer was strengthened after adjustment for several confounding factors.

Several limitations of the study also warrant mention. First, we did not collect information on whether men had undergone screening for prostate cancer. It is possible that men who have health check-ups are more health conscious and may drink more green tea, which would attenuate the results for localized prostate cancer and obscure any preventive effects on localized prostate cancer. Second, misclassification of exposure due to changes in green tea consumption during the study period might have occurred, because the exposure assessment was done at a single point. Third, we have no information on the methods used to brew the tea, such as infusion time or strength. These inaccurate measurements of green tea consumption may lead to random misclassification. If present, however, such misclassification would tend to underestimate the true relative risk. Finally, misclassification may have occurred when local-stage cases with a high Gleason score of 8–10 were classified as localized but as advanced when stage information was missing. Unfortunately, we were unable to classify

cases by Gleason score only, because this was collected as supplementary information and available in only a relatively small number of cases (23 percent of total).

In conclusion, we observed that green tea dose dependently decreased the risk of advanced prostate cancer. Although this result is supported by many animal studies, further studies are required to confirm the preventive effects of green tea on prostate cancer, including well-designed clinical trials in humans.

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Passive smoking and lung cancer in Japanese non-smoking women: A prospective study

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Although smoking is a major cause of lung cancer, the proportion of lung cancer cases among Japanese women who never smoked is high. As the prevalence of smoking in Japan is relatively high in men but low in women, the development of lung cancer in non-smoking Japanese women may be significantly impacted by passive smoking. We conducted a population-based prospective study established in 1990 for Cohort I and in 1993 for Cohort II. The study population was defined as all residents aged 40–69 years at the baseline survey. 28,414 lifelong non-smoking women provided baseline information on exposure to tobacco smoke from their husband, at the workplace and during childhood. Over 13 years of follow-up, 109 women were newly diagnosed with lung cancer, of whom 82 developed adenocarcinoma. Compared with women married to never smokers, hazard ratio (HR) [95% confidence interval (CI)] for all lung cancer incidence in women who lived with a smoking husband was 1.34 (95% CI 0.81–2.21). An association was clearly identified for adenocarcinoma (HR 2.03, 95% CI 1.07–3.86), for which dose-response relationships were seen for both the intensity (p for trend = 0.02) and amount (p for trend = 0.03) of the husband's smoking. Passive smoking at the workplace also increased the risk of lung cancer (HR 1.32, 95% CI 0.85–2.04). Moreover, a higher risk of adenocarcinoma was seen for combined husband and workplace exposure (HR 1.93, 95% CI 0.88–4.23). These findings confirm that passive smoking is a risk factor for lung cancer, especially for adenocarcinoma among Japanese women.

Key words: lung cancer; passive smoking; histological type; prospective study; Japanese non-smoking women

In Japan, lung cancer has been the second leading cause of cancer death in women since the 1980s.[1] Although the majority of lung cancers can be attributed to cigarette smoking, 53% of all women with lung cancer world-wide are never smokers.[2,3] The proportion of Japanese female lung cancer patients who have never smoked is as high as 70%,[4] whereas the proportion of Japanese women aged 20 or more who smoke is only around 10%.[5] The major risk for lung cancer in Japanese women cannot therefore be attributed to smoking. Given that the urine of non-smokers exposed to passive smoking contains concentrations of carcinogenic N-nitroso compounds, which are specific to tobacco[6] and the smoking rate in Japanese men is high, at around 50%,[5] passive smoking might be an important risk factor for lung cancer in non-smoking Japanese women.

Since the publication of the first positive findings by Hirayama in Japan, many studies have investigated the relation between passive smoking and lung cancer in non-smoking women.[7] Recently, the International Agency for Research on Cancer (IARC) concluded that findings on the risk of lung cancer associated with environmental tobacco smoke were consistent.[8] Moreover, a meta-analysis of published studies estimated that the excess risk of lung cancer in non-smokers who lived with a smoker compared to those who lived with a non-smoker was 24%.[9] However, relatively few prospective studies have appeared,[7,10–16] and almost all of previous studies have been case–control studies, for which the limitation of recall bias is controversial.[17–37] Additionally, information on spousal smoking status in most of the prospective studies has been obtained from wives. The accuracy of this exposure evaluation is questionable, however, because while high concordance has been shown between information on spousal ever smoking from wives and data from husbands themselves, agreement on the duration and intensity of smoking is lower.[38,39] Further, few prospective studies have considered the importance of multiple sources of exposure to passive smoking.[15,16]

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Here, we identified married couples among subjects of a large prospective study in Japan, and examined the association between passive smoking from the husband and the risk of lung cancer in the non-smoking wife using smoking status information obtained from the husband himself. Further, we also analyzed the association between passive smoking from other sources (at the workplace or during childhood) in lifelong non-smoking women with lung cancer.

Material and methods

JPHC study

The Japan Public Health Center-based Prospective study (JPHC Study) was launched in 1990 for the first population-based cohort (Cohort I) and in 1993 for the second (Cohort II). Cohort I covered 5 public health center (PHC) areas (Iwate, Akita, Nagano, Okinawa and Tokyo) and Cohort II covered 6 (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa and Osaka). All study subjects were residents of Japanese nationality who lived in the study areas at the start of follow-up, and who were aged 40–59 in Cohort I and 40–69 in Cohort II. In the present analysis, we excluded all subjects from the Tokyo and Osaka areas because incidence data in Tokyo were not available and the study population in Osaka included health checkup examinees, and was thus not fully population-based. A population-based cohort of 57,591 men (Cohort I: 26,998; Cohort II: 30,593) and 59,103 women (Cohort I: 27,397; Cohort II: 31,706) was identified using population registries, which were maintained by the respective local governments. Details of the study cohorts have been described elsewhere.[40]

A self-administered questionnaire, which included smoking history, previous disease history, and other lifestyle factors, was distributed to all eligible registered residents in 1990 for Cohort I and in 1993–1994 for Cohort II. Completed questionnaires were collected from 45,452 men and 49,924 women, giving response rates of 79 and 84%, respectively. To assess the carcinogenic effect of passive smoking exposure from the spouse, we further identified 31,261 pairs as married couples by surname, address, sex and an age difference of less than 16 years. To clarify the effects of passive smoking, we restricted analysis to lifelong non-smoking women only. A further 711 women with a history of cancer at any site were excluded. Thus, 28,414 women were left for analysis. The accuracy of identification was tested in 644 pairs using residence registries; results showed 604 pairs (93.8%) were married couples and 6 (0.9%) were relatives other than a spouse, while the relationship of 34 pairs (5.3%) could not be established.

The questions on smoking habit consisted of current and former smoking status, age at the initiation of smoking, average number of cigarettes smoked per day, and age at the cessation of smoking for former smokers. We determined that a woman who had a husband with a history of smoking had been exposed to passive smoking from her husband. We classified the passive smoking status of a woman by smoking status information from her husband himself (never, former, current), the number of cigarettes smoked per day (<20, ≥ 20), and the amount of smoking in current smokers (pack years: <30, ≥ 30). Information on passive smoking at the workplace (or public facilities) was also collected. We considered women who inhaled other people's smoke for more than 1 hr per day and at least 1 day per week as exposed to passive smoking at the workplace. We further asked a subgroup of subjects about passive smoking during childhood, namely whether there had been family members at home with a smoking habit when they were in elementary or junior high school (6–15 years old).

We followed the subjects from the baseline survey until December 31, 2004. Migration and survival status were obtained annually from the residential registry. Among subjects, 1,507 persons (5.3%) moved out of a study area and 74 (0.3%) were lost to follow-up during the study period. The occurrence of cancer was identified by continuous surveillance of hospital records and population-based cancer registries, with permission. Death certificate information was used as a supplementary information source. Cases were coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3).[41] In our cancer registry system, the proportion of cases for which information was available from death certificates only during the study period was 3.6%. This level of information quality was considered satisfactory for the present study. The earliest date of diagnosis was used in cases with multiple primary cancers at different times. A total of 109 newly diagnosed lung cancer cases were identified among 28,414 lifelong non-smoking women.

Person-years of follow-up were calculated for each subject from the date of questionnaire completion to the date of lung cancer diagnosis, the date of emigration from the study area, or the date of death, whichever came first. If none of these occurred, follow-up was through to the end of the study period (December 31, 2004). Persons who were lost to follow-up were censored at the last confirmed date of presence in the study area. Hazard ratios (HRs) and 95% confidence intervals (CIs) for passive smoking were estimated by the Cox proportional hazards model, according to the SAS procedure (SAS Institute, Cary, NC). Possible confounding factors included as covariates in the model were age (5-year groups), study area (9 PHC areas), menopause (pre/post), alcohol consumption (non-, ex- or occasional drinkers, 1–149 g/week, $\geq$150 g/week) and family history of lung cancer (yes/no).

p-Values for trends were assessed by assigning ordinal values for categorical variables. All *p*-values are 2-sided, and statistical significance was determined at the $p < 0.05$ level.

Results

During the 377,813 person-years of follow-up (average 13.3 years) for 28,414 lifelong non-smoking women, a total of 109 cases of lung cancer were newly diagnosed and included in the analyses. Among all lung cancer cases in this analysis ($n = 109$), 98 (90%) were histologically confirmed as follows: adenocarcinoma (83.7%), large cell carcinoma (7.2%), squamous cell carcinoma (5.0%), small cell carcinoma (2.1%) and other histological types (1.0%).

Table I shows subject characteristics according to passive smoking from the husband. About half of the women (49.1%) were exposed to passive smoking from husbands who were current smokers. Women with currently smoking husbands were slightly younger and more likely to be regular drinkers than those with husbands who were never or former smokers. The proportion of women who were in menopause was low in women exposed to passive smoking from their husbands. A higher proportion of women exposed to passive smoking from husbands had a family history of lung cancer.

Table II shows the HRs and 95% CIs for lung cancer in non-smoking women according to passive smoking from the husband. Passive smoking from a husband who was a current smoker slightly increased the risk of all lung cancer (HR 1.34, 95% CI 0.81–2.21). Compared with women without passive smoking, multivariate HRs of all lung cancer for passive smoking from a husband who smoked 20 or more cigarettes per day or had 30 or more pack-years of smoking were 1.47 (95% CI 0.87–2.49) and 1.46 (95% CI 0.85–2.50), respectively. Tests for linear trends were not statistically significant. However, a positive association with passive smoking and lung cancer became clear when our analysis was restricted to adenocarcinoma. Passive smoking from husbands who were current smokers significantly increased the risk of lung adenocarcinoma (never versus current: 2.03, 95% CI 1.07–3.86). The husband's number of cigarettes per day and number of pack-years were both significantly associated with lung adenocarcinoma risk in non-smoking wives, showing a dose-response relationship. Compared with women whose husbands never smoked, multivariable HRs were 2.20 for passive smoking from husbands who

TABLE I – SUBJECT CHARACTERISTICS ACCORDING TO PASSIVE SMOKING STATUS FROM THE HUSBAND IN 28,414 LIFELONG NON-SMOKING WOMEN

	Passive smoking status from husband			Total
	Never	Former	Current	
Number	7,331	7,122	13,961	28,414
Percentage (%)	25.8	25.1	49.1	100
Age, years ± SD	50.5 ± 6.8	52.1 ± 7.4	50.2 ± 7.0	50.8 ± 7.1
Regular drinker, yes (%)	7.5	8.7	8.9	8.6
Menopause, yes (%)	52.0	59.4	50.5	54.7
Family history of lung cancer, yes (%)	19.1	21.2	21.1	20.6

SD, standard deviation.

TABLE II – ASSOCIATION BETWEEN LUNG CANCER INCIDENCE AND PASSIVE SMOKING FROM THE HUSBAND IN LIFELONG NON-SMOKING WOMEN (n = 28,414)

Type of exposure	All lung cancer			Adenocarcinoma		
	Case (N)	Person-years	Multivariate HR (95% CI)	Case (N)	Person-years	Multivariate HR (95% CI)
From husband						
Never	25	97,466	1	15	97,392	1
Former	28	94,427	1.12 (0.63–1.98)	21	94,358	1.50 (0.73–3.09)
Current	56	185,919	1.34 (0.81–2.21)	46	185,855	2.03 (1.07–3.86)
Number of cigarettes per day						
<20	14	52,441	1.02 (0.51–2.04)	13	52,438	1.73 (0.77–3.88)
≥20	41	131,107	1.47 (0.87–2.49)	33	131,055	2.20 (1.13–4.28)
p for trend			0.14			0.02
Pack years of exposure						
<30	17	76,125	1.05 (0.55–2.02)	16	76,122	1.86 (0.86–4.01)
≥30	36	104,330	1.46 (0.85–2.50)	28	104,279	2.06 (1.04–4.10)
p for trend			0.17			0.03

Adjusted for age, study area, alcohol consumption, family history of lung cancer and menopausal status.

TABLE III – ASSOCIATION BETWEEN LUNG CANCER INCIDENCE AND PASSIVE SMOKING AT THE WORKPLACE AND FROM TWO SOURCES IN LIFELONG NON-SMOKING WOMEN (n = 28,414)

Type of exposure	All lung cancer			Adenocarcinoma		
	Case (N)	Person-years	Multivariate HR (95%CI)	Case (N)	Person-years	Multivariate HR (95% CI)
At workplace						
<1 time/week	77	279,421	1	60	279,299	1
≥1 times/week	30	94,652	1.32 (0.85–2.04)	20	94,568	1.16 (0.69–1.97)
From two sources						
Source of exposure						
Almost never[1]	17	80,428	1	12	80,395	1
Workplace only[2]	8	16,236	2.74 (1.11–6.76)	3	16,195	1.21 (0.26–5.55)
Husband only[3]	60	198,994	1.49 (0.84–2.62)	48	198,904	1.79 (0.90–3.55)
Workplace + Husband	22	78,417	1.61 (0.83–3.11)	17	78,373	1.93 (0.88–4.23)

[1]Women exposed at the workplace less than one time per week.–[2]Women exposed at the workplace one or more times per week.–[3]Women exposed from husbands who are former or current smokers.
Adjusted for age, study area, alcohol consumption, family history of lung cancer and menopausal status.

smoked 20 or more cigarettes per day (95% CI 1.13–4.28, p for trend = 0.02), and 2.06 for those at 30 or more pack-years (95% CI 1.04–4.10, p for trend = 0.03).

The association between passive smoking from 2 sources (at the workplace and from the husband) and lung cancer is shown in Table III. Passive smoking at the workplace tended to increase the risk of lung cancer, with HRs for these women of 1.32 for all lung cancer and 1.16 for adenocarcinoma. Concerning passive smoking from 2 sources, no dose-dependent increase in the risk of all lung cancers was found, with HRs in non-smoking women exposed at the workplace only of 2.74 (95% CI 1.11–6.76) but 1.61 (95% CI 0.83–3.11) in those exposed to 2 sources. In contrast, a dose-response relationship was seen for exposure to 2 sources and adenocarcinoma. HR of women exposed to 2 sources was 1.93 (95% CI 0.88–4.23) in adenocarcinoma, but this was not statistically significant.

We also analyzed the association between self-reported passive smoking during childhood and lung cancer in non-smoking women who answered this item (n = 15,467). Passive smoking during childhood was not associated with lung cancer (HR 0.93, 95% CI 0.52–1.66) (data not shown).

Discussion

In the present study, we found that passive smoking from husbands was associated with a 30% excess risk of lung cancer in non-smoking women. This result is supported by the findings of the IARC[8] and many previous papers,[10,11,13,18,21–23,25,26,34] and accords with a summary risk of 1.24 obtained in a meta-analysis.[9]

Because adenocarcinoma is the predominant lung cancer type in non-smoking women,[17,42–44] and so the effects of passive smoking may be particularly relevant to it, we also carried out analyses by histological type. Results showed a clear association between adenocarcinoma and an increased risk from passive smoking from the husband. Previous papers have reported a hazard ratio of 1.0–1.6 in adenocarcinoma, ratios smaller than those for other cell types.[22,23,26,30–33,36] Only Fontham *et al.* similarly reported that passive smoking from the husband increases the risk of adenocarcinoma.[21]

Nevertheless, our findings might be supported by findings on the mechanism of passage of sidestream smoke components through the nasal passages, which showed that volatile sidestream smoke constituents would be more likely to reach the peripheral

portions of the lung than mainstream smoke.[45] For example, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a tobacco-specific lung carcinogen, and its metabolites are found in urine of non-smokers exposed to passive smoking.[6] Moreover, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone predominantly induces adenocarcinoma in animal experiments.[46,47] Particularly in Japan, where room sizes tend to be small and living conditions congested, sidestream smoke may be directly transmitted to non-smoking women before dilution by room air.[10,45]

As further support, our use of information from the husband himself likely enhanced the accuracy of exposure to passive smoking, owing to the low agreement between the husband's information on the duration or intensity of his smoking with that from the wife.[38,39] Further, our identification of a statistically significant dose-response relationship between the quantity and intensity of husbands' smoking and their wives' incidence of lung cancer suggest that our findings were not due to chance.

Passive smoking at the workplace tended to increase the risk of lung cancer in non-smoking women. Previous findings on this risk have been inconsistent, with some studies reporting positive results[15,16,21,23,27,29,31–33,35] while others have not.[19,24,25,28,30,34] This inconsistency may be due to a lack of accuracy assessment of exposure to passive smoking at the workplace. However, our study showed a higher risk of adenocarcinoma for combined husband and workplace exposure, suggesting a modest role of the 2 exposures combined in the incidence of adenocarcinoma.

Our study showed no association between passive smoking during childhood and lung cancer. Previous studies of this risk have also been inconsistent,[15,16,20–25,27–37] perhaps unsurprisingly given the difficulty of recall of exposures occurring far in the past.

Our study has several methodological strengths. First, it was a prospective design, which diminishes the probability of the recall bias inherent to case–control studies. Second, passive smoking from the husband could be evaluated with accuracy. We identified married couples and used information on smoking provided by the husbands themselves. Third, the response rate was sufficiently high (approximately 80%), and the proportion of subjects lost to follow-up was negligible (0.3%). Finally, a relatively large number of cases accrued among never-smokers.

Several limitations also warrant mention. First, information was collected only once at baseline. Second, misclassification may have occurred due to errors in identifying married couples. However, even if some men identified as husbands were in fact relatives, time spent with the husband would likely be longer than that with a relative. If present, therefore, such misclassification may have attenuated the true risk. Third, misclassification that women who had in fact smoked were included in category of non-smokers may also have occurred. However, such misclassification might not have substantially affected the increased the risk of adenocarcinoma with passive smoking because the relation between active smoking and adenocarcinoma is weak. Finally, we do not have information on the time spent together in the same room or on the time period when the husband and wife live together. Some misclassification may therefore have occurred.

In conclusion, our study found a positive association between passive smoking from husbands and lung adenocarcinoma in non-smoking women in Japan. The positive results for quantitative indicators (such as the number of cigarette smoked and pack-years) of passive smoking from husbands reinforce this conclusion. We also identified a higher risk of adenocarcinoma for combined husband and workplace exposure. Prohibition of smoking at home and in public places may yield considerable health benefits for non-smoking women.

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Dairy Product, Saturated Fatty Acid, and Calcium Intake and Prostate Cancer in a Prospective Cohort of Japanese Men

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Abstract

Many epidemiologic studies have reported a positive association between dairy products and prostate cancer. Calcium or saturated fatty acid in dairy products has been suspected as the causative agent. To investigate the association between dairy products, calcium, and saturated fatty acid and prostate cancer in Japan, where both the intake of these items and the incidence of prostate cancer are low, we conducted a population-based prospective study in 43,435 Japanese men ages 45 to 74 years. Participants responded to a validated questionnaire that included 138 food items. During 7.5 years of follow-up, 329 men were newly diagnosed with prostate cancer. Dairy products were associated with a dose-dependent increase in the risk of prostate cancer. The relative risks (95% confidence intervals) comparing the highest with the lowest quartiles of total dairy products, milk, and yogurt were 1.63 (1.14-2.32), 1.53 (1.07-2.19), and 1.52 (1.10-2.12), respectively. A statistically significant increase in risk was observed for both calcium and saturated fatty acid, but the associations for these were attenuated after controlling for potential confounding factors. Some specific saturated fatty acids increased the risk of prostate cancer in a dose-dependent manner. Relative risks (95% confidence intervals) on comparison of the highest with the lowest quartiles of myristic acid and palmitic acid were 1.62 (1.15-2.29) and 1.53 (1.07-2.20), respectively. In conclusion, our results suggest that the intake of dairy products may be associated with an increased risk of prostate cancer. (Cancer Epidemiol Biomarkers Prev 2008;17(4):930–7)

Introduction

Although the incidence of prostate cancer in Japan is much lower than in western populations (1), latent prostate cancer appears to be equally distributed across areas with high and low incidence of prostate cancer (2). Further, prostate cancer incidence increases in men migrating from areas of low incidence to areas of higher incidence (3, 4). These results support the view that the development of prostate cancer may be impacted by environmental factors, including diet.

In the years since World War II, the Japanese diet has changed to a more westernized diet. Ecologic studies have shown an association between westernized dietary habits and the mortality of cancers that are more common in western countries. In particular, milk intake shows a strong positive association with prostate cancer (5). Given that the incidence of prostate cancer in Japan has increased (6), as has the consumption of dairy foods (7), increased dairy consumption might increase the risk of prostate cancer in Japanese men. However, previous epidemiologic studies regarding dairy product intake and prostate cancer in Japanese are few, and the results are equivocal (8-10).

High dairy product intake in western populations has been associated with an increased risk of prostate cancer in case-control as well as cohort studies. A meta-analysis of prospective studies estimated that the excess risk of prostate cancer in men with higher intakes of dairy products compared with those with lower intakes was 11% (11). Moreover, a recent meta-analysis of case-control studies showed a combined odds ratio of 1.68 for the highest versus lowest category of milk consumption (12).

Dairy products contain both fat and calcium. A comprehensive review concluded that dietary fat may be related to prostate cancer risk but that the specific fat components responsible are not yet clear (13). On the contrary, a recent meta-analysis of prospective studies reported that men with the highest intake of calcium had a 39% higher risk of prostate cancer than those with the lowest intake (11). Average calcium intake in Japanese is lower than in western populations, however, at <600 mg/d in men (7), whereas positive associations with prostate cancer in previous studies were limited to those with high intakes over 1,000 mg/d (14-18). In Japan, dairy products are the main source of not only calcium but also saturated fatty acid (19). In a population based case-control study, moreover, Whittemore et al. reported (20) that saturated fat intake was associated with a higher risk of prostate cancer for Asian Americans than for Blacks and Whites.

These results suggest that the effects of dairy products and nutrients in dairy products, such as saturated fatty

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acid and calcium, on prostate cancer might differ between Japanese and western populations.

Here, we investigated the association between the intake of dairy products, saturated fatty acid, and calcium and the risk of prostate cancer in a prospective study in Japanese.

Materials and Methods

Study Population and Food Frequency Questionnaire. The Japan Public Health Center–Based Prospective Study was launched in 1990 for cohort I and in 1993 for cohort II, involving 11 prefectural public health center areas. Details of the study design have been described previously (21). The study was approved by the institutional review board of the National Cancer Center (Tokyo, Japan). In the present analysis, subjects registered at one public health center area were excluded because data on cancer incidence were not available. The study population was defined as all Japanese residents ages 40 to 69 years at each baseline survey, who had registered their addresses in 10 public health centers. The initial cohort consisted of 65,801 men.

At baseline, participants completed a self-administered questionnaire that assessed information on various lifestyle factors and medical history. Simultaneously, a food frequency questionnaire (FFQ) in the baseline survey had 44 food items for cohort I and 52 food items for cohort II, with 4 (cohort I) or 5 (cohort II) frequency categories but without standard portions/units. In contrast, the 5-year follow-up survey included a self-administered FFQ, which included lifestyle factors, medical history, and 138 food and beverage items with standard portions/units and 9 frequency categories. Owing to this greater detail, the present study therefore used the 5-year follow-up survey as baseline and followed the subjects from 1995 for cohort I and from 1998 for cohort II until 2004. At the 5-year follow-up survey, a population-based cohort of 58,541 men was established. After the 5-year follow-up survey, 128 subjects were found to be ineligible and were excluded because of non-Japanese nationality (n = 28), late report of emigration occurring before the start of the follow-up period (n = 97), incorrect birth data (n = 1), and duplicate registration (n = 2), leaving 58,413 men eligible for participation. Among eligible subjects, 46,036 men (79%) returned valid responses to the 5-year follow-up FFQ.

The FFQ asked about the usual consumption of 138 foods and beverages during the previous year. Dairy product consumption was assessed as the frequency of consumption and portion size of the following food items: "milk," "cheese," "yogurt," "lactic acid drink," "milk in black tea," and "milk in coffee." Milk is not fortified with vitamin D in Japan. The frequency of milk, cheese, and yogurt consumption was divided into nine categories (almost never, 1-3 times monthly, 1-2 times weekly, 3-4 times weekly, 5-6 times weekly, once daily, 2-3 times daily, 4-6 times daily, ≥7 times daily). Portion sizes were specified, and the amounts were provided in three categories (less than half, same, >1.5 times). Ten frequency categories were used for lactic acid drinks (almost never, 1-3 times monthly, 1-2 times weekly, 3-4 times weekly, 5-6 times weekly, 1 glass/d, 2-3 glasses/d, 4-6 glasses/d, 7-9 glasses/d, >9 glasses/d). Similarly, the frequency of black tea and coffee consumption was assessed using the 10 categories, and the amount of milk added to the black tea or coffee was provided in five categories (0, 0.5, 1, 2, ≥3 teaspoons). The total consumption of dairy products (g/d) or each food (g/d) was calculated by multiplying the frequency by the relative portion for each food item in the FFQ. The daily intake of calcium was calculated using the fifth revised edition of the *Standard Tables of Food Composition in Japan* (22), whereas that of saturated fatty acids and specific saturated fatty acids (myristic acid, palmitic acid, and stearic acid) was calculated using a fatty acid composition table of Japanese foods (23).

Validity among subsamples (102 men) was assessed using 14- or 28-day dietary records. Spearman's correlation coefficient between the energy-adjusted intake of dairy products from the questionnaire and from dietary records was 0.52 for cohort I and 0.69 for cohort II, respectively, whereas that for energy-adjusted intake of calcium and saturated fatty acid was 0.43 and 0.61 for cohort I and 0.65 and 0.62 for cohort II, respectively. With regard to the reproducibility of estimations between two questionnaires administered 1 year apart, respective correlation coefficients for the energy-adjusted intake of dairy products, calcium, and saturated fatty acid were 0.48, 0.49, and 0.53 for cohort I and 0.69, 0.70, and 0.61 for cohort II (24-28).

Among the 46,036 men who responded to the questionnaire, those with a history of prostate cancer (n = 65) and those who reported extreme total energy intake (<800 or >4,000 kcal; n = 2,536) were excluded, leaving 43,435 men for analysis.

Follow-up and Identification of Cancer Cases. We followed all registered cohort subjects from the 5-year follow-up survey until December 31, 2004. Changes in residence status, including survival, were identified annually through the residential registry in each area or, for those who had moved out of the study area, through the municipal office of the area to which they had moved. Among questionnaire respondents to the 5-year follow-up FFQ, 1,603 (3.5%) moved out of the study area and 129 (0.3%) were lost to follow-up during the study period. Incidence data for prostate cancer were identified by active patient notification from major local hospitals in the study area and data linkage with population-based cancer registries. Death certificate information was used as a supplementary information source. Cases were coded using the *International Classification of Diseases for Oncology, Third Edition* (29).

The proportion of cases of prostate cancer first notified by death certificate was 0.9%. The proportion of case patients with prostate cancer ascertained by death certificate only was 0.6%. These ratios were considered satisfactory for the present study. A total of 329 newly diagnosed prostate cancer cases were identified by December 31, 2004. Regarding detection, 38.3% were detected by screening, 32.2% by subjective symptoms, and 14.0% incidentally during attendance at hospital for another condition, whereas no information on detection available for 15.5%. Advanced cases were defined by a diagnosis of extraprostatic or metastatic cancer involving lymph nodes or other organs. If this information was not available, advanced cases were defined as those with a high Gleason score (8-10) or poor differentiation. These

criteria were selected to allow the identification of advanced cases with a high likelihood of poor prognosis. The remaining cases were organ localized. In this study, there were 90 advanced cases, 227 localized cases, and 12 (4% of total) cases of undetermined stage.

Statistical Analysis. Person-years of follow-up were calculated for each man from the date of completion of the 5-year follow-up questionnaire survey to the date of prostate cancer diagnosis, date of emigration from the study area, date of death, or end of the study period (December 31, 2004), whichever occurred first. For men who were lost to follow-up, the last confirmed date of presence in the study area was used as the date of censor.

The relative risks (RR) of prostate cancer were calculated by quartile for the categories of consumption of dairy products, milk, cheese, yogurt, calcium intake, and saturated fatty acid intake, with the lowest consumption category as the reference. RRs and 95% confidence intervals (95% CI) were calculated by the Cox proportional hazards model, adjusting for age at 5-year follow-up survey and study area (10 public health centers) according to the SAS PHREG procedure (version 9.1; SAS Institute). For further adjustment, additional possible confounders were incorporated into the model: smoking status (never, former, current), alcohol intake (almost never, <3-4, >5 days/wk), marital status (yes, no), and consumption of green tea (0, ≤6 times weekly, 1 cup/d, 2–3cups/d, ≥4 cups/d) and genistein (mg/d) in the analysis of the association between dairy products and prostate cancer. These variables are either known or suspected risk factors for cancer or have been found previously to be associated with the risk of prostate cancer (30, 31).

Trends were assessed by assignment of the median value in each category. All P values were two sided, and statistical significance was determined at the <0.05 level.

Results

During 323,648 person-years of follow-up (average follow-up, 7.5 years) for 43,435 men, a total of 329 cases of prostate cancer were newly diagnosed and included in the analyses.

Table 1 shows subject characteristics at baseline according to category of dairy product consumption. Participants with higher dairy product consumption tended to be older, smoke less, and drink less alcohol. The proportion of men who drank green tea daily and that of men who lived with their wives was low in the lowest category. The consumption of genistein increased with the consumption of dairy products from the first to third categories, although this consumption decreased in the highest categories. Naturally, consumption of milk, cheese, and yogurt increased as dairy product consumption increased. As expected, intake of saturated fatty acid calcium increased as dairy product consumption increased.

In Table 2, we observed a strong positive association between energy-adjusted intake of dairy products and total prostate cancer risk. The multivariate RRs of total prostate cancer across increasing quartiles of total dairy products were 1.00, 1.34, 1.29, and 1.63 (95% CI, 1.14-2.32; $P_{trend} < 0.01$). Similar findings were observed when we analyzed the association between milk and yogurt and total prostate cancer. Multivariable RRs for the highest versus lowest quartile of milk and yogurt consumption were 1.53 (95% CI, 1.07-2.19; $P_{trend} = 0.01$) and 1.52 (95% CI, 1.10-2.12; $P_{trend} < 0.01$), respectively. Intake of cheese was not clearly associated with total prostate cancer. Multivariable RR for the highest versus lowest quartile of cheese was 1.32 (95% CI, 0.93-1.89; $P_{trend} = 0.30$).

Table 3 shows the RRs for the intake of energy-adjusted calcium and whole and specific saturated fatty acid in relation to total prostate cancer risk. On adjustment for age and study area, intake of calcium and whole and specific saturated fatty acid increased the risk of total prostate cancer in a statistically significant manner. Age-area adjusted RRs for the highest versus lowest quartile of calcium and saturated fatty acid intake were 1.43 (95% CI, 1.03-1.97; $P_{trend} = 0.01$) and 1.53 (95% CI, 1.12-2.08; $P_{trend} = 0.01$), respectively. However, when we adjusted for further potential confounding factors, the associations were attenuated and became statistically nonsignificant, with multivariate RRs for the highest

Table 1. Characteristics of study subjects according to dairy products intake

	Dairy products intake			
	Lowest	Second	Third	Highest
Age (y) ± SD	56.5 ± 7.9	55.6 ± 7.7	56.8 ± 7.7	58.1 ± 7.9
Body mass index ± SD (kg/m^2)	23.5 ± 3.0	23.6 ± 2.9	23.6 ± 2.8	23.5 ± 2.8
Current smoker, %	51.1	47.9	41.4	34.3
Alcohol intake (>5 days/wk), %	57.0	49.8	49.5	35.9
Green tea intake (daily), %	50.5	55.0	59.4	55.7
Men who live with their wife, %	79.2	83.4	85.9	83.6
Milk ± SD (g/d)	4.5 ± 8.3	44.3 ± 43.0	143.2 ± 70.0	328.3 ± 309.8
Cheese ± SD (g/d)	1.0 ± 2.7	2.0 ± 4.7	2.5 ± 6.8	2.5 ± 7.1
Yogurt ± SD (g/d)	0.9 ± 3.1	7.4 ± 16.2	16.7 ± 31.4	34.5 ± 82.9
Meat ± SD (g/d)	66.2 ± 60.7	70.9 ± 57.0	69.9 ± 52.0	50.6 ± 38.3
Protein ± SD (g/d)	66.9 ± 28.8	72.8 ± 29.6	79.3 ± 27.2	72.1 ± 26.9
Genistein ± SD (mg/d)	23.2 ± 24.2	25.5 ± 23.6	28.2 ± 21.4	24.6 ± 19.9
Saturated fatty acid ± SD (g/d)	12.9 ± 8.2	15.4 ± 8.3	17.9 ± 7.9	19.3 ± 10.0
Calcium ± SD (mg/d)	325.3 ± 164.8	409.9 ± 193.2	555.0 ± 207.1	721.9 ± 410.6

NOTE: Values are reported as means with standard deviations.