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Smoking and Risk of Premature Death among Middle-aged Japanese: Ten-year Follow-up of the Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases (JPHC Study) Cohort I

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To update the evidence on the association between smoking and mortality, we analyzed data from a population-based prospective study in Japan. In total, 19 950 men and 21 534 women aged 40–59 who reported their smoking history and had no serious disease at baseline survey were followed. During 1990–1999, 1014 men and 500 women died. Smokers were associated with an unhealthy lifestyle. Relative risks (RRs) for selected cause of death due to smoking were slightly attenuated by adjusting for possible confounding factors. Age- and area-adjusted RRs of male current smokers compared with never smokers were 1.66 (95% confidence intervals (CI): 1.40, 1.95) for all causes, 1.69 (1.31, 2.18) for all cancers, 1.67 (1.20, 2.34) for all circulatory system disease, and 1.63 (1.24, 2.15) for other causes, while those of females were 2.03 (1.52, 2.73), 2.06 (1.35, 3.15), 2.99 (1.75, 5.11), 1.31 (0.69, 2.51), respectively. After adjusting for multivariate variables, the corresponding RRs of male smokers were 1.55 (1.29, 1.86), 1.61 (1.20, 2.15), 1.41 (0.97, 2.03), and 1.61 (1.17, 2.19), against 1.89 (1.36, 2.62), 1.83 (1.14, 2.95), 2.72 (1.45, 5.07), and 1.39 (0.71, 2.73) for females. Twenty-two percent of death from all causes, 25% of all cancer, and 17% of all circulatory system disease deaths, could be attributed to cigarette smoking in males, and 5%, 4%, and 11% in females, respectively. Cumulative dose as indicated by pack-years was clearly associated with cancer death. These findings provided information as to the quantitative risk for premature death due to smoking among middle-aged Japanese men and women, and showed that the elevated risk was not explained by the unhealthy lifestyle of smokers.

Key words: Smoking — Mortality — Prospective study

Cigarette smoking is an important and well-established risk factor of mortality and incidence of many cancers and cardiovascular disease.[1–13] Prevalence of current cigarette smoking in Japan is higher than in the US and European countries, while relative risks (RRs) due to smoking and population attributable fraction (PAF) are lower in Japan. In the Cancer Prevention Study (CPS) II (1982–86), RRs due to smoking for all causes of death were reported 2.3 and 1.9 for men and women, respectively, and PAF% could be calculated 33% and 14% for men and women, respectively.[14] In Japan, RRs were reported to be 1.3 for either sex, while the PAF% was reported 18% and 4% for men and women, respectively, in a six-prefecture cohort study (1965–82).[8]

Because smokers are considered to have an unhealthy lifestyle,[15–17] smoking-related mortality has been considered to be affected by factors other than smoking itself, such as diet, alcohol, physical activity, and educational level.[13, 18–22] In the US, RRs of smoking for death were slightly altered by adjustment for other exposures in a recent study.[21] In Japan, Hirayama *et al.* conducted a six-prefecture cohort study (1965–82), and established the risk of smoking,[8] although they calculated RRs while adjusting only for age. Since then, there have been no recent updates and no reports which analyzed RRs for death associated with tobacco smoking adjusted for other lifestyle-related factors from such a large cohort.

Premature death represents a serious cost to society, and death at younger ages is one of the most important targets for future prevention of diseases. It is therefore of interest to study the etiological fraction of smoking in such premature death in the current Japanese population. In this study, we update the potential health hazards of cigarette smoking adjusted for other lifestyle-related factors in a large, prospective study of Japanese.

MATERIALS AND METHODS

Study cohort The Japan Public Health Center-based prospective study on cancer and cardiovascular diseases (JPHC Study) Cohort I, which was partly reported else-

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where,[23] covered 5 Public Health Center areas (Ninohe PHC in Iwate Prefecture, Yokote PHC in Akita Prefecture, Saku PHC in Nagano Prefecture, Ishikawa PHC in Okinawa Prefecture and Katsushika PHC in Tokyo Metropolitan area). Since the Katsushika PHC covers urban areas, different definitions of study population were applied, and complete death information from that area could not be obtained; it was not included in this analysis. For the remaining 4 PHC areas, the study population was defined to be all inhabitants in the study areas (14 cities, towns or villages in 4 PHC), aged 40–59 years old at baseline (January 1, 1990). Study populations were identified from population registries, which are maintained by each local municipal office. A population-based cohort of 54 498 subjects (27 063 men and 27 435 women) was established.

Baseline survey Self-administered questionnaires, which included socio-demographic characteristics, personal medical history, smoking and drinking history, diet, and other lifestyle-related factors were distributed to all registered residents in 1990. After excluding 102 subjects (65 men, 37 women) from 54 498 subjects (27 063 men, 27 435 women) for various reasons (non-Japanese, and had already moved away at the baseline), which we confirmed during the follow-up period, a total of 26 998 men and 27 398 women were asked to complete the baseline questionnaire survey. Of these, 20 658 men (76.5%) and 22 482 women (82.1%) returned the completed questionnaire. Of these persons, 42 men and 51 women did not answer as to smoking status, and 666 men and 897 women reported a past history of cancer, cardiovascular disease, or cerebrovascular disease, implying they might have changed their lifestyle. The final study population considered of 41 484 (19 950 men, 21 534 women): 9092 subjects (4219 men, 4873 women) from Ninohe City and Karumai Town in the Ninohe PHC area of Iwate Prefecture, 11 539 subjects (5390 men, 6149 women) from Yokote PHC area of Yokote City and Omonogawa Town in the Yokote PHC area of Akita Prefecture, 10 608 subjects (5278 men, 5330 women) from eight districts of Minami-Saku County in the Saku PHC area of Nagano Prefecture, and 10 245 subjects (5063 men, 5182 women) from Gushikawa City and Onna Village in the Ishikawa PHC area of Okinawa Prefecture in January 1, 1990. All subjects were born between 1930 and 1949 (40–59 years of age at baseline survey).

Smoking status was initially classified as current, past, or never smoker, based on responses to the two questions: “Have you ever smoked cigarettes regularly?” and “Do you smoke cigarettes regularly now?” Current smokers were defined as the subjects who answered “Yes” to both questions, past smokers as those who answered “Yes” to the first question, “No” to the second question, and never smokers were defined as the subjects who answered “No” to the first question. Ever smokers were then asked questions about the age at which they started smoking, and the average number of cigarettes smoked per day. Former smokers were also asked the age they quit smoking. Pack-years were defined as the number of years of smoking times the number of packs of cigarettes per day. Usual alcohol intake was first reported as frequency of consumption in six categories: <1 day/month, 1–3 days/month, 1–2 days/week, 3–4 days/week, 5–6 days/week, and every day. We calculated the weekly ethanol consumption from the usual amount and type of alcohol.[23] The weekly intake frequency of 27 food items was reported in four categories: rarely, 1–2 days/week, 3–4 days/week, and almost every day. For rice, miso soup, and nine kinds of beverage, the daily amount consumed was also asked. Body mass index (BMI) (kg/m^2) was computed from self-reported height and weight at baseline, and were divided into quintiles.

Follow-up In Japan, all death certificates are submitted to a local government office, and forwarded to the PHC in the area of residence. Mortality data are then sent to the Ministry of Health, Labour and Welfare, and coded for the National Vital Statistics. Registration of death is required by the Family Registration Law, and is believed to be complete in Japan. Therefore, all deaths were certified by a Public Health Center. Changes in residence status were identified through the residential registry in each area every year. We actively followed vital status (living or dead) of subjects who had moved by confirming with the local government at their last address in 1998. If a subject was confirmed to have died, the cause of death was extracted from the death certificates kept by the then Ministry of Health and Welfare (currently the Ministry of Health, Labour and Welfare). We could not confirm the vital status of 120 men and 107 women before 1998 in this analysis, mainly because they had moved again and their new address could not be obtained. These cases were treated as a censored cases at the last date when the survival status had been confirmed. We classified the causes of death according to the International Classification of Diseases, 10th Revision (ICD10) as follows; deaths from all cancers (ICD10: C00–C97), all circulatory system disease (ICD10: I00–I99). The profiles of this cohort have been reported elsewhere.[23]

Statistical analysis Person-years of follow-up were counted from baseline (January 1, 1990) until the date of death of the deceased, the last date when the survival status had been confirmed for censored cases, and the end of the study period (December 31, 1999) for the survivors. We calculated the crude mortality rate per 100 000 person-years for selected causes. Cox’s proportional hazard model[24] was used to compare the mortality according to smoking status. We adjusted for age (four 5-year age groups) and area (4 PHC area), then further adjusted for educational background (junior high school, high school,

college or more), medication (none, any), past history of hypertension (no, yes), sports in leisure time (<1 day/month, 1–3 days/month, ≥1 day/week), four categories (1 day/week, 1–2 days/week, 3–4 days/week, ≥5 days/week) of selected dietary habits (green vegetables, yellow vegetables, white vegetables, fruit, fish, pickled vegetables, soy products, red meat), alcohol habit (nondrinker, occasional drinker, ≤150 g/week, ≤300 g/week, 300+ g/week) and quintiled BMI. Using PROC PHREG of the SAS program,[25] the whole observation period was analyzed. PAF was calculated as $pd \times ((RR-1)/RR)$ where pd=proportion of cases exposed to the risk factor. This formula is known to be more valid than the popular form $(RR-1) \times Pe/(1+(RR-1) \times Pe)$, where Pe=proportion of source population exposed to the risk factor when confounding variables exist.[26] Ninety-five percent confidence intervals (95%CIs) of adjusted PAFs were calculated by using the formula of Greenland.[27]

RESULTS

Table I shows baseline characteristics according to smoking status in 19 950 men and 21 534 women. Current smokers were a younger, smaller proportion of highly educated persons, less physically active, had lower BMI, showed a larger proportion of alcohol drinkers, and a lower proportion of daily fruit and vegetable intake than never smokers of either sex. Subjects who stopped smoking more often had a past history of hypertension and drug use for medication than current smoker and never smokers, and they were the most educated among any smoking status.

During the follow-up of 10 years, 1514 subjects (1014 men and 500 women) died. Among all causes of death, 424 (42%) of men and 246 (49%) of women died from cancer. Numbers of deaths, death rates per 100 000 person-years, and RRs of cigarette smoking for selected causes of death are presented in Table II. With regard to past smokers, RR for death from all circulatory system disease was high, but without statistical significance in females. Concerning current smokers, age- and area-adjusted RRs for all causes, cancer at all sites, and all circulatory system diseases were high with statistical significance in both sexes. RRs for all causes in women were higher than those in men. When further adjusted for education level, medication, past history of hypertension, sports in leisure time, BMI, alcohol consumption, vegetable intake, and fruit intake, the RRs of male current smokers varied slightly. The decrease in RRs ranged from 1% (noncancer-noncirculatory system disease) to 16% (all

Table I. Baseline Characteristics According to Smoking Status among 19 950 Men and 21 534 Women in Japan during 1990–1999

	Men (n=19 950)			Women (n=21 534)		
	Never	Past	Current	Never	Past	Current
No.	4 819	4 400	10 731	19 936	354	1 244
Age (SD)	49.6 (5.6)	50.2 (6.0)	49.0 (6.0)	49.6 (5.8)	49.0 (6.3)	48.6 (5.9)
Alcohol drinking, at least once per week (%)	59.1	69.9	71.7	20.8	41.3	44.6
Education, College or more (%)	15.2	17.1	13.4	11.9	19.5	11.7
Past history of Hypertension	15.1	18.6	13.1	13.4	19.3	12.2
Any drug for medication	20.9	27.2	19.8	24.2	33.8	24.7
Physical activity, 1+/week (%)	19.3	21.3	15.2	14.5	18.2	13.1
Body mass index (SD)	23.9 (2.9)	23.9 (2.9)	23.2 (2.9)	23.6 (3.2)	24.0 (3.4)	23.2 (2.9)
Diet (daily, %)						
Fruit	30.0	27.3	20.8	45.7	37.1	30.1
Green vegetables	31.0	30.3	26.4	36.7	30.3	31.6
Yellow vegetables	16.6	16.7	12.3	24.3	19.3	18.4
White vegetables	34.0	35.5	32.6	45.4	35.9	35.5
Pickled vegetables	39.2	41.7	46.9	53.1	46.6	46.3
Soy products	37.1	36.3	34.5	46.3	35.6	36.8
Fresh fish	15.5	14.7	15.0	19.8	15.4	14.9
Red meat	26.2	27.7	28.9	26.3	31.6	30.7

Figures are means (SD) unless otherwise specified.

Table II. Number of Deaths, Death Rates per 100 000 Person-years, Risk Ratios According to Status of Cigarette Smoking for Selected Causes of Death

	Never		Past				Current			
	No. of deaths	Death rate[a)]	No. of deaths	Death rate[a)]	RR1[b)] (95%CI)	RR2[c)] (95%CI)	No. of deaths	Death rate[a)]	RR1[b)] (95%CI)	RR2[c)] (95%CI)
Men										
Person-years	46 986		42 798				103 537			
All causes	184	391.6	184	429.9	1.05 (0.85–1.29)	1.02 (0.82–1.28)	646	623.9	1.66 (1.40–1.95)	1.55 (1.29–1.86)
All Cancer	75	159.6	82	191.6	1.10 (0.80–1.50)	1.09 (0.77–1.54)	267	257.9	1.69 (1.31–2.18)	1.61 (1.20–2.15)
All circulatory system disease	44	93.6	45	105.1	1.11 (0.73–1.69)	0.99 (0.67–1.43)	154	148.7	1.67 (1.20–2.34)	1.41 (0.97–2.03)
Noncancer-noncirculatory system disease	65	138.3	57	133.2	0.96 (0.67–1.37)	0.97 (0.67–1.43)	225	217.3	1.63 (1.24–2.15)	1.61 (1.17–2.19)
Women										
Person-years	196 137		3 432				11 985			
All causes	439	223.8	11	320.5	1.50 (0.82–2.73)	1.27 (0.65–2.48)	50	417.2	2.03 (1.52–2.73)	1.89 (1.36–2.62)
All Cancer	219	111.7	3	87.4	0.87 (0.28–2.72)	0.89 (0.28–2.81)	24	200.3	2.06 (1.35–3.15)	1.83 (1.14–2.95)
All circulatory system disease	91	46.4	4	116.6	2.48 (0.91–6.78)	2.51 (0.90–6.99)	16	133.5	2.99 (1.75–5.11)	2.72 (1.45–5.07)
Noncancer-noncirculatory system disease	129	65.8	4	116.6	1.75 (0.64–4.74)	0.90 (0.22–3.68)	10	83.4	1.31 (0.69–2.51)	1.39 (0.71–2.73)

a) Crude death rate per 100 000 person-years.
b) Rate ratios compared with nonsmokers, adjusted for age in 1990 (40–44, 45–49, 50–54, 55–59), and area (Iwate, Akita, Nagano, Okinawa).
c) Further adjusted for educational background (junior high school, high school, college or more), medication (none, any), past history of hypertension (no, yes), sports in leisure time (<1 day/month, 1–3 days/month, ≥1 day/week), four categories (1 day/week, 1–2 days/week, 3–4 days/week, ≥5 days/week) of selected dietary habits (green vegetables, yellow vegetables, white vegetables, fruit, fish, pickled vegetables, soy products, red meat), alcohol habit (nondrinker, occasional drinker, ≤150 g/week, ≤300 g/week, 300+ g/week) and quintiled BMI.

circulatory system disease) in men. For women, changes of RRs ranged from a 6% increase in noncancer-noncirculatory system disease to an 11% decrease in all cancers. As for the population attributable risk fraction of smoking in this cohort (i.e., PAF of current and past smokers): 22.2% (95%CI: 10.1, 32.6) of all causes, 24.7% (95%CI: 5.3, 40.1) of all cancer, and 17.2% (95%CI: −10.5, 37.9) of all circulatory system disease deaths could be attributed to cigarette smoking in males, and 5.2% (95%CI: 1.9, 8.4), 4.2% (95%CI: −0.4, 8.5), and 11.3% (95%CI: 2.9, 18.9) in females, respectively. These results did not change after excluding deaths within 2 years. Table III gives RRs and 95%CI for selected causes of deaths by cumulative dose as indicated by pack-years for cigarette smoking. A statistically significant cumulative dose-response trend of RRs was seen in all causes of death, all cancer deaths in men, and all cancer deaths in women. High cumulative dose (above 30 pack-years) smokers had statistically significantly more elevated RRs for cancer death than never smokers in both sexes. The heaviest cumulative dose smokers presented a 1.8 times greater risk than never smokers in men, and a 4.5 times higher risk in women.

Table IV presents RRs for selected causes of death by the number of daily cigarettes smoked, and the age of starting smoking, further adjusted by age at the start of smoking and the number of cigarettes, respectively. There were no statistically significant dose-response relationships between the number of cigarettes smoked and any causes of death, except female cancer. The earlier the start of smoking, the higher the RRs among any selected cause of deaths in men, though there was no statistical significance.

DISCUSSION

This population-based prospective study provides an important evaluation of the impact of cigarette smoking on mortality adjusted for age, alcohol habit, dietary habit, physical activity, and BMI in middle-aged Japanese. A multivariate adjusted risk of smoking has never been reported in such a large population-based cohort study in Japan, and it has been some time since Hirayama *et al.* conducted their six-prefecture cohort study to analyze lifestyle and mortality.[8] In addition, the results could show the influence of smoking on premature death, because subjects were aged 40 to 59 years at the start of the study.

Our principal finding is that after adjusting for age, and then making further adjustment for other health-related behavior, RRs for selected causes of death altered only minimally. Reduction of RR by multivariate adjustment was greater for women than men, and it was also greater in circulatory system disease than other causes in men. Thun *et al.* reported that RR of smoking for death was slightly altered by adjusting for socioeconomic and behavioral factors such as race, education, marital status, employment, total weekly consumption of vegetables, citrus fruit, alcohol consumption, BMI, physical activity in work or play, and weekly consumption of fatty food. Some of the explanations they considered are: that smokers and lifelong never smokers are similar with respect to socioeconomic and educational status, and that not all of the behaviors were detrimentally associated with survival.[21] In this study, more current smokers had unhealthy habits than never smokers at baseline, and these habits might attenuate the risk of smoking. However, even after multivariate analysis, RRs for all death due to smoking remained statistically significant in both sexes.

The RRs observed in our study were lower than those observed in Western countries, even after having been adjusted for considerable other risk factors. Concerning CPS II, age-adjusted RRs for all-causes deaths due to smoking among subjects who were 40 to 59 years old could be calculated as 2.9 for men and about 2.0 for women,[14] which were higher than those of our study. Therefore it is difficult to consider that the RRs in our study were lower than those in CPS II due to a younger age-distribution. One reason might be the lower exposure dose in cigarette smoking in Japan compared to Western countries. The increase in cigarette consumption in Japan took place after 1950.[28] Most of the study subjects were born during World War II, and some of the subjects might have had less chance to start smoking than Western people in their adolescence. The smoking rate among men was above 50% in our cohort; about 20% of ever smokers started smoking before 20 years, and about 60% of them

Table III. Effect from Cumulative Dose as Indicated by Pack-years among Current Smokers Compared with Never Smokers

Baseline category	Person-years	All causes			All cancer			All circulatory system disease			Noncancer-noncirculatory system disease		
		No.	RR[a]	(95%CI)	No.	RR[a]	(95%CI)	No.	RR[a]	(95%CI)	No.	RR[a]	(95%CI)
Men													
Never smoker	46 986	184	1.00		75	1.00		44	1.00		65	1.00	
Pack-year													
−19	25 145	145	1.44	(1.12−1.84)	46	1.33	(0.88−2.00)	32	1.02	(0.60−1.73)	67	1.89	(1.28−2.79)
20−29	29 999	150	1.56	(1.23−1.99)	53	1.41	(0.94−2.10)	37	1.44	(0.90−2.31)	60	1.82	(1.23−2.68)
30+	48 393	351	1.57	(1.28−1.93)	168	1.83	(1.34−2.51)	85	1.41	(0.95−2.12)	98	1.37	(0.96−1.95)
		P for trend: *P*<0.01			*P* for trend: *P*<0.01			*P* for trend: *P*=0.05			*P* for trend: *P*=0.17		
Women													
Never smoker	196 137	439	1.00		219	1.00		91	1.00		129	1.00	
Pack-year													
−9	5 752	19	1.64	(0.98−2.72)	7	1.03	(0.42−2.52)	8	3.37	(1.52−7.47)	4	1.30	(0.47−3.57)
10−19	3 445	12	1.52	(0.80−2.88)	2	0.64	(0.16−2.61)	4	2.12	(0.65−6.95)	6	2.58	(1.10−6.02)
20+	2 788	19	2.61	(1.52−4.47)	15	4.51	(2.45−8.30)	4	1.51	(0.35−6.57)	0		
		P for trend: *P*=0.07			*P* for trend: *P*<0.01			*P* for trend: *P*=0.06			*P* for trend: *P*=0.36		

a) Rate ratio adjusted for age in 1990 (40−44, 45−49, 50−54, 55−59), area (Iwate, Akita, Nagano, Okinawa), educational background (junior high school, high school, college or more), medication (none, any), past history of hypertension (no, yes), sports in leisure time (<1 day/month, 1−3 days/month, ≥1 day/week), four categories (1 day/week, 1−2 days/week, 3−4 days/week, ≥5 days/week) of selected dietary habits (green vegetables, yellow vegetables, white vegetables, fruit, fish, pickled vegetables, soy products, red meat), alcohol habit (nondrinker, occasional drinker, ≤150 g/week, ≤300 g/week, 300+ g/week) and quintiled BMI.

Table IV. Effect from Dose for Number of Cigarettes and Age at Start of Smoking in Current Smokers

Baseline category	Person-years	All causes			All cancer			All circulatory system disease			Noncancer-noncirculatory system disease		
		No.	RR[a)]	(95%CI)	No.	RR[a)]	(95%CI)	No.	RR[a)]	(95%CI)	No.	RR[a)]	(95%CI)
Men													
Number of cigarettes													
1–19	29 739	213	1.00		78	1.00		49	1.00		86	1.00	
20–29	46 466	287	0.95	(0.78–1.16)	135	1.21	(0.89–1.64)	61	0.93	(0.61–1.41)	91	0.73	(0.53–1.02)
30+	27 331	146	0.96	(0.76–1.21)	54	1.00	(0.68–1.47)	44	1.20	(0.76–1.88)	48	0.78	(0.53–1.14)
		P for trend: *P*=0.88			*P* for trend: *P*=0.80			*P* for trend: *P*=0.34			*P* for trend: *P*=0.20		
Age at start of smoking													
–19	24 798	171	1.00		65	1.00		44	1.00		62	1.00	
20–24	63 611	389	0.81	(0.67–0.98)	164	0.86	(0.63–1.17)	92	0.80	(0.54–1.16)	133	0.74	(0.54–1.03)
25+	15 128	86	0.69	(0.52–0.92)	38	0.77	(0.49–1.19)	18	0.51	(0.27–0.97)	30	0.71	(0.44–1.14)
		P for trend: *P*=0.01			*P* for trend: *P*=0.21			*P* for trend: *P*=0.03			*P* for trend: *P*=0.20		
Women													
Number of cigarettes													
1–19	8 340	29	1.00		11	1.00		12	1.00		6	1.00	
20–29	2 832	16	1.27	(0.63–2.57)	9	1.77	(0.60–5.17)	3	0.15	(0.01–1.56)	4	1.28	(0.23–7.12)
30+	813	5	2.20	(0.75–6.44)	4	6.03	(1.36–26.64)	1	1.25	(0.11–13.76)	0		
		P for trend: *P*=0.14			*P* for trend: *P*=0.01			*P* for trend: *P*=0.44			*P* for trend: *P*=0.79		
Age at start of smoking													
–24	3 999	15	1.00		8	1.00		5	1.00		2	1.00	
25+	7 987	35	1.00	(0.50–2.02)	16	0.63	(0.20–1.92)	11	1.00	(0.21–4.66)	8	1.62	(0.23–11.61)
		P for trend: *P*=0.93			*P* for trend: *P*=0.22			*P* for trend: *P*=0.66			*P* for trend: *P*=0.56		

a) Adjusted for age in 1990 (40–44, 45–49, 50–54, 55–59), area (Iwate, Akita, Nagano, Okinawa), educational background (junior high school, high school, college or more), medication (none, any), past history of hypertension (no, yes), sports in leisure time (<1 day/month, 1–3 days/month, ≥1 day/week), four categories (1 day/week, 1–2 days/week, 3–4 days/week, ≥5 days/week) of selected dietary habits (green vegetables, yellow vegetables, white vegetables, fruit, fish, pickled vegetables, soy products, red meat), alcohol habit (nondrinker, occasional drinker, ≤150 g/week, ≤300 g/week, 300+ g/week), quintiled BMI and each factor listed.

started between 20 and 25 years of age. In this study, the mean age for beginning to smoke was 20.5 and 21.4 for men aged 40–49, and aged 50–59 at baseline, respectively, while in CPS II, the corresponding ages were 17.2, and 17.6, respectively, 3 years younger than in the present study. The average number of cigarettes smoked per day in this study was 23.1 and 22.0 for men aged 40–49 and aged 50–59 at baseline, respectively, while in CPS II, the corresponding values were 26.6, and 26.8, respectively,[29)] higher than in the present study. Differences in the starting age and average number of cigarettes might explain the difference in RRs between Japanese and Western people. Another reason might be the misclassification of never smokers. If former smokers were included among never smokers, the risk for death in never smokers tends to be higher, possibly leading to a lower RR for smokers. One of the other explanations for lower RRs in the Japanese cohort might be a difference of race, since RRs of Japanese-American and Chinese were similar to those of Japanese,[5, 9, 30)] although it is difficult to compare the RRs among other cohorts due to differences in age distribution and follow-up period.

The strength of this study is the prospective design and new information it makes available, so as to allow control for potentially important confounding variables such as diet, alcohol use, body weight, body composition, physical activity, and socioeconomic status. Although the information was only obtained from self-reported questionnaires, the reliability should be relatively high. It has been reported that qualitative aspects of active and passive smoking can be assessed through a questionnaire, although quantitative aspects are assessed with less precision.[31, 32)] Our results are limited in that the smoking status was determined only once at baseline, and the influence of

changing smoking status might be considered relatively small. We conducted the second survey in 1995, and found that more subjects had stopped smoking than started smoking during the first 5 years of follow-up in both sexes (unpublished data). Therefore, if there were an influence from quitting smoking, it might result in underestimation of the true risk among continuing smokers.

In general, RRs increased when smoking duration increased, and when the amount of smoking increased. The present study detected a strong association and statistically significant dose-response relationship among cumulative dose as indicated by pack-years and death from all causes, and from all cancers. Because most smokers begin their habit over a relatively narrow age range at around 20 years, age and duration of smoking were correlated. There were no dose-response relationships for the number of cigarettes smoked per day in any cause, although early initiation affected the risk in men. Many epidemiological studies have shown the relationship between cancer and number of cigarettes per day.[1, 5, 6, 10, 11, 13, 33] However, there are some studies that did not show a dose-response relationship.[34, 35] One of the reasons why there were no dose-response relationships might an unstable number of cigarettes smoked per day during follow-up. We suspected that the number of daily cigarettes smoked was relatively stable in former cohort studies, because there were less social pressures against smoking. Moreover, we suspected that the number of daily cigarettes smoked in recent studies might be unstable, because some smokers might have tried to quit smoking, or others who reduced their number of cigarettes might have returned to their former number of cigarettes. We calculated mean number of cigarettes in the baseline survey and the second survey, which was conducted 5 years later, according to baseline categories (1–19, 20–29, and 30+) for men. The means of number of cigarettes in each category were 11.2, 20.6, and 36.6 for the baseline survey, while those at the 5-year survey were 14.7, 20.9, and 31.1. The daily number of cigarettes for the heaviest smokers decreased, while that for the lightest smokers increased. This might affect the dose-response relationships between baseline category and mortality. On the other hand, there were dose-response relationships between smoking duration and mortality (data not shown). Although pack-year was calculated by using smoking duration and the number of cigarettes per day, it might be influenced by smoking duration more strongly than by number of cigarettes. We considered that daily cigarette number might be an insufficient indicator to predict premature death, and cumulative dose, such as pack-years, might be a more useful indicator to predict premature death from cancer in this cohort. It might be considered that the influence of cumulative dose affects a large part of cancer deaths, while the influence of the smoking habit itself affects death for all circulatory system disease. However, even when low-dose subjects smoked, the risks for death were higher than among never smokers. Past smokers showed almost the same RRs after 10-year follow-up.

In conclusion, the present study evaluates the recent risk of death among Japanese with a smoking habit. Smoking habit contributes significantly to a high risk for mortality, and the cumulative dose (pack-year) had a dose-response relationship with cancer mortality. Although the risk of smoking might be attenuated by other lifestyle factors, such as sports in leisure time, BMI, alcohol consumption, vegetable intake, fruit intake, which are associated with both smokers' health habits and mortality, smoking is still a strong risk factor for death. Moreover, the risk of smoking exerted an influence both at the individual and population levels. These findings provide an assessment of the quantitative risk of smoking on premature death among middle-aged Japanese men both at the individual and population levels, and the elevated risk was not explained by the unhealthy lifestyle of smokers.

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REFERENCES

1) Akiba, S. and Hirayama, T. Cigarette smoking and cancer mortality risk in Japanese men and women—results from reanalysis of the six-prefecture cohort study data. *Environ. Health Perspect.*, **87**, 19–26 (1990).
2) Doll, R., Peto, R., Wheatley, K., Gray, R. and Sutherland, I. Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ*, **309**, 901–911 (1994).
3) Rogot, E. and Murray, J. Cancer mortality among nonsmokers in an insured group of U.S. veterans. *J. Natl. Cancer Inst.*, **65**, 1163–1168 (1980).
4) Rogot, E. and Murray, J. L. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public Health Rep.*, **95**, 213–222 (1980).
5) Yuan, J. M., Ross, R. K., Wang, X. L., Gao, Y. T., Henderson, B. E. and Yu, M. C. Morbidity and mortality in relation to cigarette smoking in Shanghai, China. A prospective male cohort study. *JAMA*, **275**, 1646–1650 (1996).
6) Akiba, S. Analysis of cancer risk related to longitudinal information on smoking habits. *Environ. Health Perspect.*, **102** (Suppl. 8), 15–19 (1994).
7) Floderus, B., Cederlof, R. and Friberg, L. Smoking and mortality: a 21-year follow-up based on the Swedish Twin Registry. *Int. J. Epidemiol.*, **17**, 332–340 (1988).
8) Hirayama, T. Smoking and mortality. *In* "Life-style and Mortality; a Large-scale Census-based Cohort Study in Japan," ed. J. Wahrendorf, pp. 1–59 (1990). Karger, Japan.
9) Chyou, P. H., Nomura, A. M. and Stemmermann, G. N. A prospective study of the attributable risk of cancer due to cigarette smoking. *Am. J. Public Health*, **82**, 37–40 (1992).
10) McLaughlin, J. K., Hrubec, Z., Blot, W. J. and Fraumeni, J. F., Jr. Smoking and cancer mortality among U.S. veterans: a 26-year follow-up. *Int. J. Cancer*, **60**, 190–193 (1995).
11) Nordlund, L. A., Carstensen, J. M. and Pershagen, G. Cancer incidence in female smokers: a 26-year follow-up. *Int. J. Cancer*, **73**, 625–628 (1997).
12) Scheidt, S. Changing mortality from coronary heart disease among smokers and nonsmokers over a 20-year interval. *Prev. Med.*, **26**, 441–446 (1997).
13) Chyou, P. H., Burchfiel, C. M., Yano, K., Sharp, D. S., Rodriguez, B. L., Curb, J. D. and Nomura, A. M. Obesity, alcohol consumption, smoking, and mortality. *Ann. Epidemiol.*, **7**, 311–317 (1997).
14) Thun, M. J., Day-Lally, C., Myers, D. G., Calle, E. E., Flanders, W. D., Zhu, B. P., Namboodiri, M. M. and Health, C. W. J. Trends in tobacco smoking and mortality from cigarette use in cancer prevention studies I (1959 through 1965) and II (1982 through 1988). *In* "National Cancer Institute, Smoking and Tobacco Control, Monograph 8: Changes in Cigarette-related Disease Risks and Their Implication for Prevention and Control," NIH Publication No. 97-4213, pp. 305–382 (1997). NIH, Washington, DC.
15) Subar, A. F., Harlan, L. C. and Mattson, M. E. Food and nutrient intake differences between smokers and non-smokers in the US. *Am. J. Public Health*, **80**, 1323–1329 (1990).
16) Phillips, E. L., Arnett, D. K., Himes, J. H., McGovern, P. G., Blackburn, H. and Luepker, R. V. Differences and trends in antioxidant dietary intake in smokers and nonsmokers, 1980–1992: the Minnesota Heart Survey. *Ann. Epidemiol.*, **10**, 417–423 (2000).
17) Tsubono, Y., Tsugane, S. and Gey, K. F. Differential effects of cigarette smoking and alcohol consumption on the plasma levels of carotenoids in middle-aged Japanese men. *Jpn. J. Cancer Res.*, **87**, 563–569 (1996).
18) Zhu, B. P., Giovino, G. A., Mowery, P. D. and Eriksen, M. P. The relationship between cigarette smoking and education revisited: implications for categorizing persons' educational status. *Am. J. Public Health*, **86**, 1582–1589 (1996).
19) Pierce, J. P., Fiore, M. C., Novotny, T. E., Hatziandreu, E. J. and Davis, R. M. Trends in cigarette smoking in the United States. Projections to the year 2000. *JAMA*, **261**, 61–65 (1989).
20) Ferrucci, L., Izmirlian, G., Leveille, S., Phillips, C. L., Corti, M. C., Brock, D. B. and Guralnik, J. M. Smoking, physical activity, and active life expectancy. *Am. J. Epidemiol.*, **149**, 645–653 (1999).
21) Thun, M. J., Apicella, L. F. and Henley, S. J. Smoking vs other risk factors as the cause of smoking-attributable deaths: confounding in the courtroom. *JAMA*, **284**, 706–712 (2000).
22) Malarcher, A. M., Schulman, J., Epstein, L. A., Thun, M. J., Mowery, P., Pierce, B., Escobedo, L. and Giovino, G. A. Methodological issues in estimating smoking-attributable mortality in the United States. *Am. J. Epidemiol.*, **152**, 573–584 (2000).
23) Tsugane, S., Fahey, M., Sasaki, S. and Baba, S. Alcohol consumption and all-cause and cancer mortality among middle-aged Japanese men: seven-year follow-up of the JPHC study Cohort I. Japan Public Health Center. *Am. J. Epidemiol.*, **150**, 1201–1207 (1999).
24) Cox, D. Regression models and life tables (with discussion). *J. R. Stat. Soc. Ser. B. Methodol.*, **34**, 187–220 (1972).
25) SAS Institute, Inc. SAS/STAT software: changes and enhancements through release 6.11. SAS Institute, Inc., Cary, NC (1996).
26) Rockhill, B., Newman, B. and Weinberg, C. Use and misuse of population attributable fractions. *Am. J. Public Health*, **88**, 15–19 (1998).
27) Greenland, S. Re: "Confidence limits made easy: interval estimation using a substitution method." *Am. J. Epidemiol.*, **149**, 884; discussion 885–886 (1999).
28) Ministry Health and Welfare (MHW). "Smoking and Health," 2nd Ed., pp. 3–75 (1993). Health Promotion and Fitness Foundation, Tokyo (in Japanese).
29) Thun, M. J., Myers, D. G., Day-Lally, C., Namboodiri, M.

M., Calle, E. E., Flanders, W. D., Adams, S. L. and Health, C. W. J. Age and exposure-response relationships between cigarette smokinig and premature death in cancer prevention study II. *In* "National Cancer Institute, Smoking and Tobacco Control, Monograph 8: Changes in Cigarette-related Disease Risks and Their Implication for Prevention and Control," NIH Publication No. 97-4213, pp. 383–412 (1997). NIH, Washington, DC.

30) Niu, S. R., Yang, G. H., Chen, Z. M., Wang, J. L., Wang, G. H., He, X. Z., Schoepff, H., Boreham, J., Pan, H. C. and Peto, R. Emerging tobacco hazards in China: 2. Early mortality results from a prospective study [see comments]. *BMJ*, **317**, 1423–1424 (1998).
31) Coultas, D. B., Peake, G. T. and Samet, J. M. Questionnaire assessment of lifetime and recent exposure to environmental tobacco smoke. *Am. J. Epidemiol.*, **130**, 338–347 (1989).
32) Klesges, R. C., Debon, M. and Ray, J. W. Are self-reports of smoking rate biased? Evidence from the Second National Health and Nutrition Examination Survey. *J. Clin. Epidemiol.*, **48**, 1225–1233 (1995).
33) Kono, S., Ikeda, M., Tokudome, S., Nishizumi, M. and Kuratsune, M. Cigarette smoking, alcohol and cancer mortality: a cohort study of male Japanese physicians. *Jpn. J. Cancer Res.* (Gann), **78**, 1323–1328 (1987).
34) LaCroix, A. Z., Lang, J., Scherr, P., Wallace, R. B., Cornoni-Huntley, J., Berkman, L., Curb, J. D., Evans, D. and Hennekens, C. H. Smoking and mortality among older men and women in three communities. *N. Engl. J. Med.*, **324**, 1619–1625 (1991).
35) Burns, D. M., Shanks, T. G., Choi, W., Thun, M. J., Health, C. W. J. and Garfinkel, L. The American Cancer Society cancer prevention study I: 12-year follow-up of 1 million men and women. *In* "National Cancer Institute, Smoking and Tobacco Control, Monograph 8: Changes in Cigarette-related Disease Risks and Their Implication for Prevention and Control," NIH Publication No. 97-4213, pp. 113–114 (1997). NIH, Washington, DC.