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Association of the age at smoking initiation and cessation on all-cause and cause-specific mortality: The Japan Collaborative Cohort Study

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ABSTRACT

We estimated the association between the age at smoking initiation and cessation and all-cause and cause-specific mortality among Japanese men (n = 41,711; age 40–79 years) by analyzing data from the Japan Collaborative Cohort Study for the Evaluation of Cancer Risks. From 1988 and 1990 to 2009, 13,429 all-cause deaths (cancers, n = 4999; cardiovascular diseases, n = 3682) occurred in this cohort. Fitted Cox proportional hazard models, with never smokers as the reference group, were created. Former smokers demonstrated a lower risk for all-cause and cause-specific mortality than current smokers, with a dose-dependent reduction in the risk based on smoking-initiation age. Among former smokers who quit smoking aged 50 years or more, the highest hazard ratios were detected for those who started smoking at <20 years of age (all-cause, cancer, and cardiovascular disease mortality, hazard ratio [95% confidence interval] 1.51 [1.29–1.77], 1.68 [1.27–2.23], and 1.48 [1.12–1.96], respectively). Former smokers who quit smoking at <50 years of age had negligible all-cause or cardiovascular disease mortality regardless of the smoking-initiation age, whereas the cancer mortality risk remained significantly high among those who quit smoking at 40–49 years of age. Thus, smoking cessation significantly reduces the all-cause mortality risk; however, early initiation and later cessation do not provide a huge benefit, which earlier cessation does. Therefore, all smokers should be encouraged to quit smoking earlier in life regardless of their age at smoking initiation.

Keywords: initiation, cessation, CVDs, cancer, mortality

Abbreviations:
CVD: cardiovascular disease
CI: confidence interval
HR: hazard ratio

INTRODUCTION

Tobacco use is a significant public health concern worldwide and is one of the major causes of death and disability in both developed and developing countries. According to the World

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Health Organization (WHO) 2019 report, tobacco use is currently responsible for more than 8 million and 1.2 million deaths yearly, due to active and passive smoking, respectively,[1] and these numbers are likely to increase over the coming decades because of the increased use of tobacco in the developing world.[2,3] Reducing the global mortality burden of tobacco smoking requires comprehensive measures to prevent smoking initiation and to increase cessation rates among current smokers. Thus, smoking initiation should be prevented or delayed, or cessation should be promoted much earlier.[4,5]

Japan is the fourth largest tobacco-consuming country in the world.[6] The prevention of smoking-related diseases is an important public health concern because tobacco smoking remains a leading cause of deaths, especially among men in Japan.[7] Tobacco control in Japan has been evaluated as insufficient in view of the WHO Framework Convention on Tobacco Control.[8] Although the proportion of regular male smokers has markedly decreased to 29.9% in 2018 from roughly one-third the proportion in 1966, when it peaked at 83.7%,[9,10] smoking prevalence in Japan remains higher than that in other high-income countries, including the United States and several European countries.[11]

Increasingly, there is evidence that quitting smoking contributes to the reduction of risk of total mortality, and the age at which an individual starts or stops smoking is a determinant factor for whether individuals are prone to premature death. Previous studies have shown that early smoking initiation, in addition to immediate effects such as increased cough, fatigue, shortness of breath, and wheezing,[12-14] confers a greater risk for the development of vascular diseases (such as cardiovascular diseases [CVDs], coronary artery diseases, cerebrovascular diseases),[15] peripheral artery diseases,[16] respiratory diseases, and cancers, particularly lung cancer.[16-20] Moreover, early initiation of smoking is related to increased all-cause and cause-specific mortality.[15,21,22] The importance of quitting smoking at an early age has been highlighted in studies. A study conducted among US adults suggests that quitting smoking before the age of 40 years reduces the risk of smoking-related cancer mortality by approximately 90%.[23] Similar findings have been reported in a cohort study among Chinese men who quit smoking at a higher age, which was associated with higher all-cause deaths compared to those who quit at a lower age.[24] However, these studies focused on the association of age at cessation alone or years since cessation with all-cause mortality, and studies on all-cause and cause-specific mortality with regard to age at both initiation and cessation are limited. Information on smoking initiation and cessation age in the same cohort provides an ideal setting for examining the risks associated with lifetime smoking. Thus, we aimed to study and evaluate the association between smoking initiation and cessation age with the risk of all-cause, cancer, and CVD mortality among Japanese men in a large cohort study.

MATERIALS AND METHODS

Study population

We analyzed data from the dataset of the Japan Collaboration Cohort Study for Evaluation of Cancer Risk (JACC Study) which was sponsored by the Ministry of Education, Science, Sports, and Culture and has been described elsewhere.[25] Briefly, the cohort was established from 1988 to 1990 and followed until the end of 2009. As shown in Fig. 1, a total of 110,585 participants (46,395 men and 64,190 women) aged between 40 and 79 years completed a questionnaire on lifestyle and medical history at baseline. Participants were enrolled from 45 study areas across Japan, mostly during municipal health checkups. The present analysis was restricted to male participants because of the limited number of female ex-smokers (only 963).

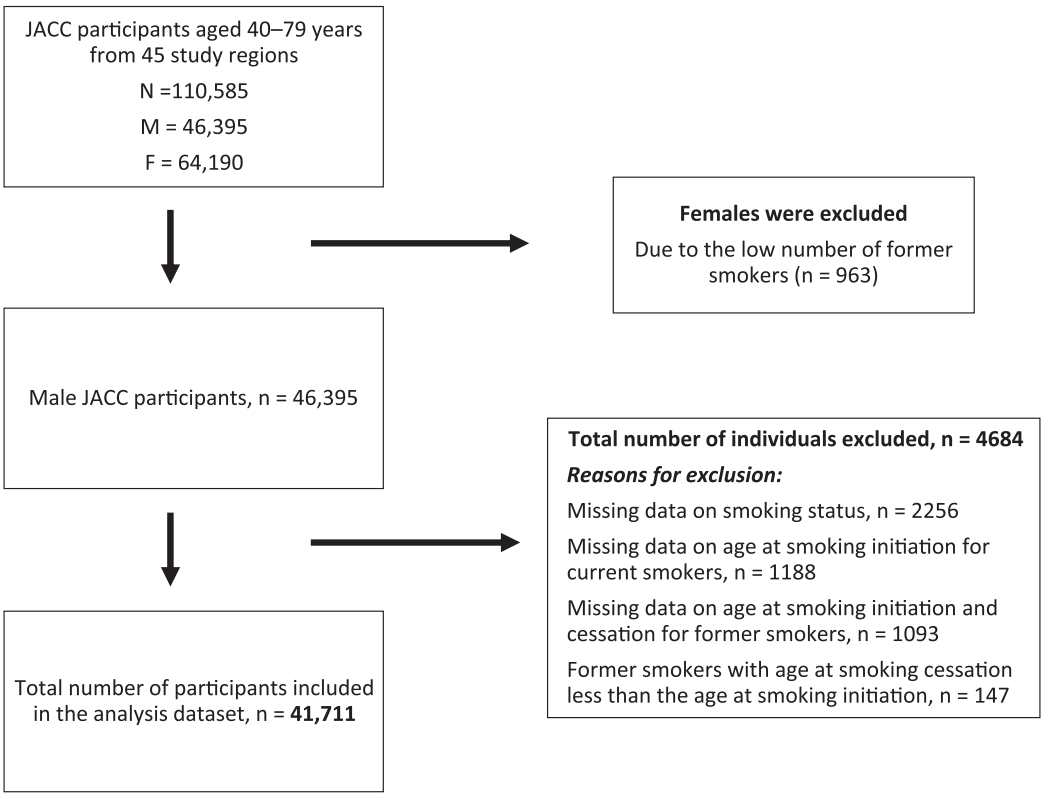

Fig. 1 Flowchart depicting the enrollment of participants in the study
JACC: Japan Collaborative Cohort Study

Of the 46,395 initial male participants at baseline, we excluded individuals who did not provide data on smoking-related variables, such as smoking status (n = 2,256), smoking-initiation age for current smokers (n = 1,188), and smoking-initiation age or smoking-cessation age for former smokers (n = 1,093). Former smokers who reported a smoking-cessation age less than the starting age (n = 147) were excluded. After these exclusions, data from 41,711 men were included in the analysis.

Variables measured at baseline

Data on cigarette smoking were collected using a cohort-specific self-administered questionnaire in the baseline survey. Participants were then categorized into "current smokers" if the participants smoked currently, "former smokers (or ex-smokers)" if they had smoked in the past but reported having already quit at the time of the baseline study entry, and "never smokers" if they had never smoked. Moreover, for current smokers, data on age at smoking initiation and, for former smokers, age at both smoking initiation and cessation were obtained. For some participants (n = 126) who did not state their age at smoking cessation but stated the years since quitting, the age at smoking cessation was estimated using the time interval from baseline to the year of smoking cessation. Based on this information, current and former smokers were categorized into four groups according to their age at smoking initiation: <20, 20–24, 25–29, and ≥30 years. Former smokers were further grouped into three categories based on their age at smoking ces-

sation: <40, 40–49, and ≥50 years. In addition, age, marital status (married, widowed, divorced, or single), children (yes vs no), education level (≤18 years vs >18 years), occupation (employed vs unemployed), exercise (≥1 h or almost never per week), walking (≥30 min or almost never per day), alcohol drinking (current, former, or never), number of cigarettes smoked per day (<20 vs ≥20), passive smoking (yes vs no), body mass index (BMI: <25 kg/m^2 vs ≥25 kg/m^2), and history of diabetes, CVD, hypertension, and/or cancer (yes vs no) were self-reported.

Outcome ascertainment

The vital status of the participants was determined using resident registration records in the municipalities, and the causes of death were ascertained from death certificates. Based on the 10th revision of the International Statistical Classification of Diseases (ICD–10), the mortality outcomes that we focused on in this study were deaths from all causes (A00–Y98), cancers (C00–C97), and CVDs (I00–I99). The follow-up time was defined as the period from the date of enrollment to the date of death, loss to follow-up, or end of follow-up, whichever occurred first.

Statistical analyses

Categorical and continuous variables for each subgroup of participants are presented as numbers (percentages) and means (standard deviations), respectively. Cox proportional hazard models were used to derive hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for deaths of current and former smokers, with never smokers as the reference. Missing values for each variable were considered as a single category. Three models were constructed: Model 1 was adjusted for age at baseline and stratified by study area; Model 2 was further adjusted for current and past illnesses (diabetes, CVDs, hypertension, and/or cancer); and Model 3 was further adjusted for marital status, children, education, occupation, exercise, walking, BMI, passive smoking, drinking habit, and number of cigarettes smoked per day. As participants aged 40–49 years at baseline were excluded from the category of former smokers who quit in their 50s or when older by definition, we ran the same analyses by limiting the participants to those aged ≥50 years at baseline to eliminate an age-distribution gap between the subgroups. In addition, as the effect of smoking cessation on the reduction of mortality risk may be underestimated due to the health problems that participants might have had before the study, a sensitivity analysis was performed after excluding participants who died in the first 3 years of the follow-up. An additional sensitivity analysis was conducted by excluding participants who were diagnosed with CVDs or cancer before the baseline. All analyses were conducted using Statistical Package for Social Science (SPSS) version 26, and $p<0.05$ was considered statistically significant.

RESULTS

This study included 41,711 male participants aged 40–79 years (mean age, 57.3 years). During a total of 658,470.4 person-years of follow-up, a total of 13,429 all-cause deaths occurred (including 3682 from CVDs and 4999 from cancers). Table 1 presents the baseline characteristics of the participants according to the age at smoking initiation and cessation for current and former smokers, respectively. The percentages of current, former, and never smokers were 53.4%, 25.0%, and 21.6%, respectively. The mean ages at baseline for the current smokers who initiated smoking at <20, 20–24, 25–29, and ≥30 years were 53.7, 56.2, 58.2, and 60.9 years, respectively, whereas those of former smokers who quit smoking at <40, 40–49, and ≥50 years were 51.9, 55.9, and 65.8 years, respectively. In general, current smokers were less educated than former smokers, and those who started smoking at an age <20 years were the least educated, with individuals with

education over 18 years representing 9.7%. The employment rate was 60–90% and tended to increase in individuals who started smoking when younger, among current smokers, and in those who quit smoking at a lower age among former smokers. Furthermore, 25–40% of participants reported exercising for 1 h or more per week, with the lowest proportion (24.2%) detected in current smokers who started smoking at age <20 years; the majority (70–80%) reported walking for 30 min or more per day regardless of the smoking status. In addition, 70–80% of participants were current drinkers, regardless of their smoking status, and 60% or more reported smoking ≥20 cigarettes per day among both current and former smokers, and there was a clear tendency of being greater in individuals who started smoking earlier among current smokers. Passive smoking was reported in 40% or more former or never smokers and in less than 15% of current smokers. Moreover, 70–80% of participants had normal BMI and were almost equally distributed regardless of smoking status or categories of current and former smokers by the age at smoking initiation and cessation. With regard to past illness, 3–5%, 0.5–1%, 15–20%, and 5–7% of participants reported a history of CVDs, cancers, hypertension, and diabetes, respectively, before the baseline survey, with a consistent tendency wherein former smokers who quit smoking at ≥50 years of age reported the highest rates among all smoker subcategories.

Table 1 Baseline characteristics of the male participants according to the smoking status and the age at smoking initiation and cessation

No. of participants (%)	Current smokers by the age of initiation			
	<20	20–24	25–29	≥30
	4404 (10.6)	13942 (33.4)	2426 (5.8)	1484 (3.6)
Mean age (SD)	53.7 (9.3)	56.2 (9.9)	58.2 (9.7)	60.9 (9.9)
Marital status (%)				
Married	3553 (92.8)	11263 (93.3)	1944 (92.7)	1139 (90.7)
Widowed	103 (2.7)	401 (3.3)	84 (4.0)	71 (5.7)
Divorced	85 (2.2)	214 (1.8)	28 (1.3)	18 (1.4)
Single	89 (2.3)	198 (1.6)	41 (2.0)	28 (2.2)
Children (%)				
Have children	3554 (96.1)	12039 (97.1)	2078 (96.2)	1290 (96.7)
No child	145 (3.9)	365 (2.9)	82 (3.8)	44 (3.3)
Education (%)				
≤18 years	2755 (90.3)	8587 (82.4)	1496 (80.9)	928 (84.2)
>18 years	296 (9.7)	1836 (17.6)	354 (19.1)	174 (15.8)
Occupation (%)				
Employed	3127 (83.0)	9585 (79.8)	1552 (75.7)	878 (73.0)
Unemployed	640 (17.0)	2427 (20.2)	498 (24.3)	324 (27.0)
Exercise/week (%)				
≥1 hour	820 (24.2)	3517 (30.2)	657 (31.6)	438 (35.4)
Hardly ever	2563 (75.8)	8136 (69.8)	1420 (68.4)	801 (64.6)
Walk/day (%)				
≥30 min	2682 (83.9)	9699 (87.7)	1764 (90.1)	1035 (91.1)
Hardly ever	516 (16.1)	1354 (12.3)	194 (9.9)	101 (8.9)
Drinking habit (%)				
Current	3204 (74.8)	10587 (78.1)	1888 (80.6)	1146 (79.7)
Former	241 (5.6)	670 (4.9)	109 (4.7)	63 (4.4)
Never	836 (19.5)	2291 (16.9)	345 (14.7)	229 (15.9)

No. of cigarettes/day (%)				
<20	1091 (25.0)	4390 (31.7)	986 (40.8)	726 (49.3)
≥20	3278 (75.0)	9462 (68.3)	1430 (59.2)	746 (50.7)
Passive smoking (%)				
Yes	566 (27.3)	1983 (27.1)	373 (27.4)	215 (26.7)
No	1507 (72.7)	5332 (72.9)	987 (72.6)	591 (73.3)
BMI (kg/m^2) (%)				
<25	3422 (80.9)	11132 (83.2)	1950 (84.2)	1141 (81.1)
25–29.9	693 (16.4)	1996 (14.9)	315 (13.6)	226 (16.1)
≥30	116 (2.7)	259 (1.9)	51 (2.2)	40 (2.8)
CVDs (%)				
Yes	136 (3.5)	445 (3.6)	78 (3.7)	41 (3.1)
No	3721 (96.5)	11817 (96.4)	2041 (96.3)	1266 (96.9)
Cancer (%)				
Yes	32 (0.9)	80 (0.7)	12 (0.6)	5 (0.4)
No	3529 (99.1)	11173 (99.3)	1954 (99.4)	1174 (99.6)
Hypertension (%)				
Yes	680 (17.3)	2417 (19.3)	405 (18.8)	279 (20.8)
No	3244 (82.7)	10094 (80.7)	1751(81.2)	1065 (79.2)
Diabetes (%)				
Yes	287 (7.4)	817 (6.7)	115 (5.4)	88 (6.7)
No	3578 (92.6)	11444 (93.3)	2010 (94.6)	1220 (93.3)

	Former smokers by the age of cessation			Never-smokers
No. of participants (%)	<40	40–49	≥50	
	2422 (5.8)	2737 (6.6)	5269 (12.6)	9027 (21.6)
Mean age (SD)	51.9 (10.1)	5.9 (8.4)	65.8 (6.6)	57.3 (10.2)
Marital status (%)				
Married	2096 (95.0)	2385 (96.4)	4248 (94.0)	7482 (93.8)
Widowed	37 (1.7)	44 (1.8)	221 (4.9)	232 (2.9)
Divorced	30 (1.4)	27 (1.1)	40 (0.9)	88 (1.1)
Single	43 (1.9)	19 (0.8)	11 (0.2)	172 (2.2)
Children (%)				
Have children	2105 (96.9)	2390 (97.2)	4558 (97.0)	7518 (96.7)
No child	67 (3.1)	70 (2.8)	143 (3.0)	255 (21.8)
Education (%)				
≤18 years	1368 (75.6)	1621 (79.6)	3132 (80.1)	5372 (81.7)
>18 years	442 (24.4)	415 (20.4)	780 (19.9)	1205 (18.3)
Occupation (%)				
Employed	1876 (85.3)	1963 (80.4)	2457 (55.7)	5920 (77.9)
Unemployed	323 (14.7)	480 (19.6)	1952 (44.3)	1684 (22.1)
Exercise/week (%)				
≥1 hour	708 (34.7)	755 (33.1)	1539 (36.1)	2345 (31.7)
Hardly ever	1331 (65.3)	1529 (66.9)	2728 (63.9)	5048 (68.3)
Walk/day (%)				
≥30 min	1696 (86.4)	1922 (87.8)	3657 (89.4)	6040 (87.0)
Hardly ever	268 (13.6)	266 (12.2)	433 (10.6)	904 (13.0)

Drinking habit (%)					
	Current	1950 (82.5)	2101 (78.7)	3423 (67.2)	6086 (69.6)
	Former	132 (5.6)	175 (6.6)	681 (13.4)	422 (4.8)
	Never	282 (11.9)	393 (14.7)	993 (19.5)	2237 (25.6)
No. cigarettes/day (%)					
	<20	807 (36.2)	711 (27.3)	1466 (29.4)	
	≥20	1423 (63.8)	1894 (72.7)	3517 (70.6)	
Passive smoking (%)					
	Yes	872 (58.2)	841 (49.8)	1417 (44.7)	3098 (57.8)
	No	626 (41.8)	847 (50.2)	1750 (55.3)	2264 (42.2)
BMI (kg/m^2) (%)					
	<25	1798 (76.3)	1946 (73.1)	4100 (81.3)	6542 (76.6)
	25–29.9	497 (21.1)	637 (23.9)	821 (16.3)	1747 (20.5)
	≥30	62 (2.6)	79 (3.0)	120 (2.4)	251 (2.9)
CVDs (%)					
	Yes	73 (3.4)	124 (5.1)	607 (13.5)	336 (4.1)
	No	2090 (96.6)	2289 (94.9)	3873 (86.5)	7840 (95.9)
Cancer (%)					
	Yes	21 (1.0)	24 (1.1)	144 (3.6)	45 (0.6)
	No	2008 (99.0)	2206 (98.9)	3870 (96.4)	7305 (99)
Hypertension (%)					
	Yes	458 (20.8)	643 (25.9)	1544 (33.7)	1673 (20.1)
	No	1745 (79.2)	1839 (74.1)	3039 (66.3)	6640 (79.9)
Diabetes (%)					
	Yes	150 (6.9)	208 (8.6)	454 (10.3)	487 (6.0)
	No	2010 (93.1)	2197 (91.4)	3934 (89.7)	7662 (94.0)

Due to missing data, the sum of the participants for each item category is different from the total no. of participants.
SD: standard deviation
CVDs: cardiovascular diseases
BMI: body mass index

Table 2 Association of mortality risk and the age at smoking initiation and cessation among male participants

		P-years	Deaths (n)	HR (95% CI) [a]	HR (95% CI) [b]	HR (95% CI) [c]
Current-smokers		All-cause mortality				
Age at smoking initiation	<20	70414.1	1353	1.88 (1.76–2.02)	1.88 (1.76–2.02)	1.84 (1.72–1.98)
	20–24	220596.4	4689	1.60 (1.52–1.68)	1.61 (1.53–1.69)	1.61 (0.83–1.76)
	25–29	37777.2	891	1.44 (1.34–1.56)	1.47 (1.36–1.59)	1.47 (1.36–1.59)
	≥30	22290.1	634	1.39 (1.27–1.52)	1.43 (1.31–1.56)	1.45 (1.33–1.59)
Never-smokers		148425.9	2330	Ref		
		Cancer-mortality				
Age at smoking initiation	<20	70414.1	563	2.29 (2.04–2.56)	2.27 (2.02–2.53)	2.19 (1.95–2.45)
	20–24	220596.4	1904	2.05 (1.87–2.23)	2.04 (1.86–2.22)	1.98 (1.81–2.16)
	25–29	37777.2	356	1.92 (1.68–2.17)	1.91 (1.68–2.17)	1.86 (1.63–2.11)
	≥30	22290.1	212	1.62 (1.39–1.89)	1.63 (1.40–1.91)	1.61 (1.37–1.87)
Never-smokers		148425.9	707	Ref		

				CVD-mortality		
Age at smoking initiation	<20	70414.1	331	1.68 (1.46–1.92)	1.74 (1.52–1.99)	1.70 (1.48–1.95)
	20–24	220596.4	1239	1.45 (1.32–1.58)	1.48 (1.36–1.64)	1.52 (1.38–1.67)
	25–29	37777.2	237	1.26 (1.08–1.45)	1.31 (1.12–1.51)	1.35 (1.16–1.57)
	≥30	22290.1	199	1.36 (1.16–1.59)	1.45 (1.24–1.72)	1.51 (1.27–1.77)
Never-smokers		148425.9	705	Ref		
Former smoker's age at smoking cessation (≥50 years)				All-cause mortality		
Age at smoking initiation	<20	14367.9	514	1.50 (1.36–1.65)	1.42 (1.29–1.56)	1.51 (1.29–1.77)
	20–24	44775.4	1562	1.28 (1.21–1.37)	1.24 (1.15–1.32)	1.34 (1.16–1.54)
	25–29	7298	255	1.17 (1.03–1.34)	1.14 (1.00–1.30)	1.26 (1.05–1.51)
	≥30	5121.6	211	1.11 (0.95–1.27)	1.05 (0.91–1.21)	1.12 (0.93–1.35)
Never-smokers		148425.9	2330	Ref		
				Cancer-mortality		
Age at smoking initiation	<20	14367.9	187	1.82 (1.55–2.14)	1.79 (1.52–2.11)	1.68 (1.27–2.23)
	20–24	44775.4	545	1.57 (1.39–1.75)	1.54 (1.38–1.73)	1.48 (1.15–1.91)
	25–29	7298	68	1.12 (0.87–1.44)	1.12 (0.87–1.43)	1.10 (0.78–1.53)
	≥30	5121.6	60	1.18 (0.91–1.54)	1.17 (0.90–1.53)	1.14 (0.81–1.61)
Never-smokers		148425.9	707	Ref		
				CVD-mortality		
Age at smoking initiation	<20	14367.9	140	1.35 (1.13–1.62)	1.22 (1.01–1.45)	1.48 (1.12–1.96)
	20–24	44775.4	437	1.16 (1.03–1.30)	1.07 (0.95–1.21)	1.38 (1.08–1.76)
	25–29	7298	87	1.24 (0.99–1.55)	1.23 (0.99–1.51)	1.65 (1.23–2.21)
	≥30	5121.6	69	1.09 (0.85–1.40)	1.21 (0.97–1.51)	1.53 (1.14–2.06)
Never-smokers		148425.9	705	Ref		
Former smoker's age at smoking cessation (40–49 years)				All-cause mortality		
Age at smoking initiation	<20	12094.0	139	1.05 (0.89–1.25)	1.03 (0.87–1.22)	1.13 (0.91–1.40)
	20–24	28319.8	373	1.01 (0.90–1.12)	0.99 (0.89–1.11)	1.09 (0.93–1.29)
	25–29	3466.0	56	1.07 (0.83–1.40)	1.05 (0.81–1.37)	1.16 (0.86–1.56)
	≥30	1943.9	23	0.67 (0.44–1.01)	0.68 (0.45–1.03)	0.77 (0.50–1.19)
Never-smokers		148425.9	2330	Ref		
				Cancer-mortality		
Age at smoking initiation	<20	12094.0	68	1.51 (1.17–1.93)	1.49 (1.16–1.91)	1.44 (1.03–2.01)
	20–24	28319.8	145	1.21 (1.01–1.44)	1.19 (0.99–1.42)	1.17 (0.87–1.55)
	25–29	3466.0	23	1.44 (0.95–2.17)	1.42 (0.93–2.15)	1.41 (0.87–2.25)
	≥30	1943.9	7	0.70 (0.33–1.48)	0.70 (0.33–1.48)	0.71 (0.32–1.54)
Never-smokers		148425.9	707	Ref		
				CVD-mortality		
Age at smoking initiation	<20	12094.0	28	0.79 (0.54–1.16)	0.76 (0.53–1.12)	0.97 (0.63–1.51)
	20–24	28319.8	96	0.91 (0.74–1.13)	0.93 (0.75–1.15)	1.22 (0.91–1.64)
	25–29	3466.0	15	0.95 (0.57–1.58)	0.92 (0.54–1.55)	1.16 (0.66–2.03)
	≥30	1943.9	5	0.47 (0.19–1.13)	0.48 (0.19–1.22)	0.66 (0.26–1.67)
Never-smokers		148425.9	705	Ref		

Former smoker's age at smoking cessation (<40 years)						
				All-cause mortality		
Age at smoking initiation	<20	13261.2	118	1.11 (0.92–1.33)	1.08 (0.90–1.31)	1.18 (0.94–1.47)
	20–24	25813.8	246	0.88 (0.77–1.01)	0.87 (0.76–0.99)	0.96 (0.81–1.15)
	25–29	2040.2	31	1.04 (0.73–1.48)	1.04 (0.73–1.48)	1.21 (0.86–1.76)
	≥30	464.9	4	0.39 (0.15–1.06)	0.37 (0.14–1.01)	0.43 (0.16–1.18)
Never-smokers		148425.9	2330	Ref		
				Cancer-mortality		
Age at smoking initiation	<20	13261.2	45	1.18 (0.87–1.60)	1.16 (0.86–1.57)	1.13 (0.78–1.64)
	20–24	25813.8	97	1.07 (0.86–1.32)	1.06 (0.85–1.31)	1.06 (0.78–1.43)
	25–29	2040.2	10	1.13 (0.61–2.12)	1.12 (0.60–2.10)	1.18 (0.61–2.29)
	≥30	464.9	2	0.71 (0.18–2.85)	0.69 (0.17–2.77)	0.73 (0.18–3.01)
Never-smokers		148425.9	707	Ref		
				CVD-mortality		
Age at smoking initiation	<20	13261.2	22	0.77 (0.5–1.17)	0.77 (0.51–1.18)	0.98 (0.62–1.56)
	20–24	25813.8	62	0.77 (0.59–0.99)	0.75 (0.57–0.97)	0.96 (0.69–1.33)
	25–29	2040.2	10	1.08 (0.57–2.02)	1.11 (0.58–2.13)	1.44 (0.73–2.86)
	≥30	464.9	0	0.00 (0)	0.08 (0.00–4.11)	0.09 (0.00–6.76)
Never-smokers		148425.9	705	Ref		

HR: hazard ratio
CI: confidence interval
CVD: cardiovascular disease
P-years: person-years
Ref: reference
a: Model 1: Adjusted for age at baseline and study areas
b: Model 2: Model 1+ (cancer, cardiovascular diseases, diabetes, and hypertension)
c: Model 3: Model 2+ (marital status, children, education, occupation, exercise, walking, body mass index, passive smoking, drinking habit, and number of cigarettes smoked)

Table 2 indicates the risk of mortality from all causes, cancers, and CVDs after adjustment for age at baseline and stratification by study area in Model 1, followed by further adjustment for past/present illness (diabetes, CVDs, hypertension, and/or cancer) in Model 2, and additional adjustment for marital status, children, education, occupation, exercise, walking, BMI, passive smoking, drinking habit, and number of cigarettes smoked per day in Model 3. The results were similar in terms of the extent of association and dose–response patterns between Models 1, 2, and 3 (except for slightly diminished HR for CVD mortality among former smokers who started smoking at lower ages and quit smoking in their 50s or older in Model 2). A dose–response relationship was detected between mortality and the age at smoking initiation among current smokers: specifically, compared with never smokers in Model 3, participants who started smoking at <20 years of age had the highest HR for all-cause (HR, 1.84, 95% CI, 1.72–1.98), cancer (HR, 2.19, 95% CI, 1.95–2.45), and CVD mortality (HR, 1.70, 95% CI, 1.48–1.95). The HR for cancer mortality was consistently higher than that for CVD mortality. Figure 2 indicates the dose-response relationship between age at smoking cessation and mortality where; former smokers who even quit at an older age (≥50 years) demonstrated a lower risk of all-cause and cause-specific mortality than current smokers: all-cause (HR, 1.34, 95% CI, 1.17–1.54), cancer (HR, 1.43, 95% CI, 1.12–1.84), and CVD mortality (HR, 1.32, 95% CI, 1.03–1.70). However,

among former smokers who quit smoking in their 50s or more, the risk of mortality remained high and showed dose dependency with regard to the age at smoking initiation, where the highest HR was detected in those who started smoking at <20 years of age: all-cause (HR, 1.51, 95% CI, 1.29–1.77), cancer (HR, 1.68, 95% CI, 1.27–2.23), and CVD (HR, 1.48, 95% CI, 1.12–1.96), mortality. Among former smokers who quit smoking when younger than 50 years, although the risk for all-cause or CVD mortality was absent or negligible, regardless of the age at smoking initiation, the risk for cancer mortality remained significantly high among those who quit smoking at 40–49 years of age (HR, 1.44, 95% CI, 1.03–2.01). The results remained almost the same (Table 3) when the participants were limited to those aged 50 years and above. Tables 4 and 5 demonstrate the results of sensitivity analyses after excluding participants who died during the first 3 years of follow-up and after excluding participants with CVDs and/or cancers at baseline, respectively. The results of these sensitivity analyses were similar to those described in Table

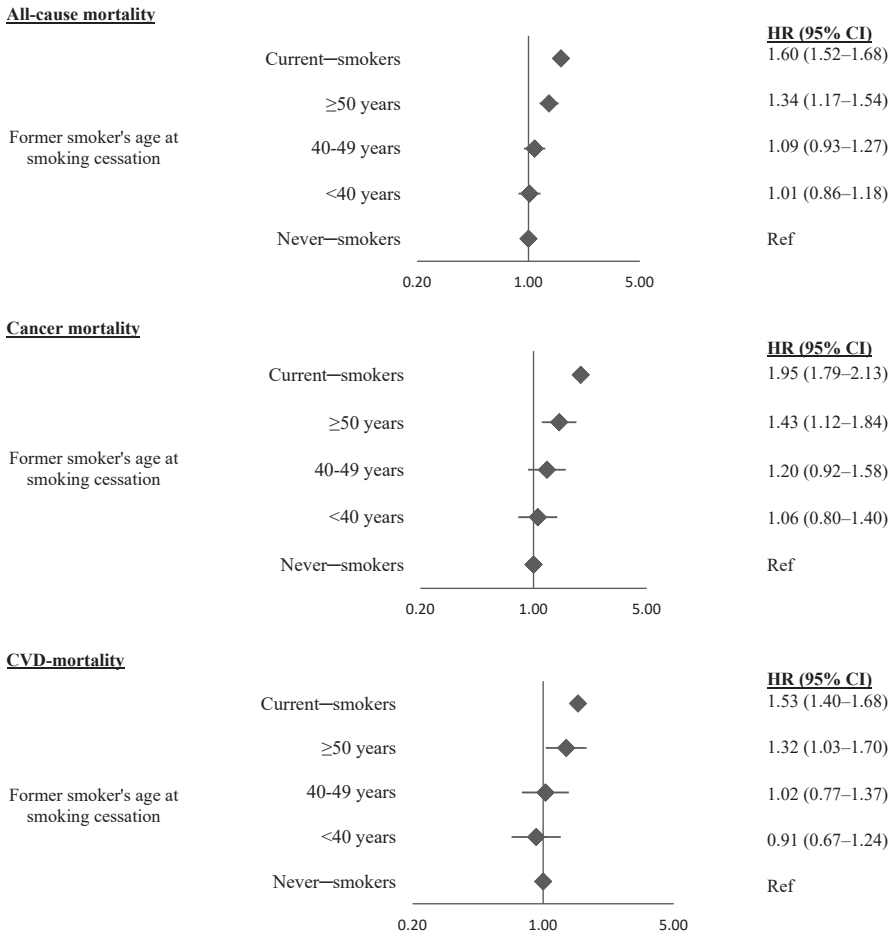

Fig. 2 Dose-response relationship between age at smoking cessation and mortality among male participants
Adjusted with age, study area, cancer, cardiovascular disease, diabetes, hypertension, marital-status, children, education, occupation, exercise, walking, body mass index, passive-smoking, drinking habit and number of cigarettes smoked.
HR: hazard ratio; CI: confidence interval; CVD: cardiovascular disease; Ref: reference.

2 with regard to the extent of association and the dose–response pattern, albeit with a general tendency of the highest HRs being slightly diminished in these analyses except for CVDs in current smokers and former smokers who quit smoking at 40–49 years of age.

Table 3 Association of mortality risk and the age at smoking initiation and cessation among male participants aged 50 years and above

		P-years	Deaths (n)	HR (95% CI)
Current-smokers			All-cause mortality	
Age at smoking initiation	<20	40600.6	1158	1.83 (1.70–1.97)
	20–24	144897.6	4258	1.59 (1.51–1.67)
	25–29	28385.3	854	1.48 (1.37–1.61)
	≥30	18362.6	607	1.43 (1.31–1.57)
Never-smokers		103876.7	2187	Ref
			Cancer-mortality	
Age at smoking initiation	<20	40600.6	484	2.23 (1.98–2.52)
	20–24	144897.6	1715	1.99 (1.81–2.19)
	25–29	28385.3	340	1.91 (1.67–2.18)
	≥30	18362.6	201	1.60 (1.36–1.88)
Never-smokers		103876.7	644	Ref
			CVD-mortality	
Age at smoking initiation	<20	40600.6	290	1.68 (1.46–1.94)
	20–24	144897.6	1133	1.47 (1.33–1.62)
	25–29	28385.3	229	1.34 (1.15–1.56)
	≥30	18362.6	193	1.50 (1.27–1.76)
Never-smokers		103876.7	681	Ref
Former smokers' age at smoking cessation (≥50 years)			All-cause mortality	
Age at smoking initiation	<20	14367.9	514	1.49 (1.26–1.75)
	20–24	44775.4	1562	1.32 (1.14–1.53)
	25–29	7298.0	255	1.25 (1.04–1.50)
	≥30	5121.6	211	1.10 (0.91–1.33)
Never-smokers		103876.7	2187	Ref
			Cancer-mortality	
Age at smoking initiation	<20	14367.9	187	1.67 (1.25–2.22)
	20–24	44775.4	545	1.48 (1.14–1.92)
	25–29	7298.0	68	1.11 (0.79–1.55)
	≥30	5121.6	60	1.17 (0.82–1.66)
Never-smokers		103876.7	644	Ref
			CVD-mortality	
Age at smoking initiation	<20	14367.9	140	1.41 (1.05–1.90)
	20–24	44775.4	437	1.28 (0.99–1.66)
	25–29	7298.0	87	1.43 (1.04–1.96)
	≥30	5121.6	69	1.11 (0.79–1.54)
Never-smokers		103876.7	681	Ref

Former smokers' age at smoking cessation (40–49 years)		All-cause mortality		
Age at smoking initiation	<20	8340.0	122	1.11 (0.89–1.39)
	20–24	20665.2	341	1.08 (0.91–1.29)
	25–29	2829.4	51	1.09 (0.80–1.49)
	≥30	1483.7	21	0.74 (0.47–1.16)
Never-smokers		103876.7	2187	Ref
		Cancer-mortality		
Age at smoking initiation	<20	8340.0	60	1.41 (0.99–2.00)
	20–24	20665.2	131	1.14 (0.84–1.53)
	25–29	2829.4	21	1.32 (0.80–2.16)
	≥30	1483.7	6	0.65 (0.28–1.49)
Never-smokers		103876.7	644	Ref
		CVD-mortality		
Age at smoking initiation	<20	8340.0	26	0.95 (0.60–1.50)
	20–24	20665.2	91	1.11 (0.81–1.53)
	25–29	2829.4	14	1.03 (0.57–1.83)
	≥30	1483.7	5	0.63 (0.25–1.58)
Never-smokers		103876.7	681	Ref
Former smokers' age at smoking cessation (<40 years)		All-cause mortality		
Age at smoking initiation	<20	5227.7	85	1.09 (0.85–1.40)
	20–24	11891.3	208	0.95 (0.79–1.15)
	25–29	1048.4	24	1.05 (0.68–1.60)
	≥30	319.9	4	0.46 (0.17–1.25)
Never-smokers		103876.7	2187	Ref
		Cancer-mortality		
Age at smoking initiation	<20	5227.7	29	1.00 (0.65–1.54)
	20–24	11891.3	80	1.09 (0.79–1.50)
	25–29	1048.4	6	0.85 (0.37–1.98)
	≥30	319.9	2	0.81 (0.19–3.30)
Never-smokers		103876.7	644	Ref
		CVD-mortality		
Age at smoking initiation	<20	5227.7	18	0.91 (0.54–1.53)
	20–24	11891.3	55	0.93 (0.66–1.32)
	25–29	1048.4	8	1.23 (0.59–2.57)
	≥30	319.9	0	0.00 (0)
Never-smokers		103876.7	681	Ref

Adjusted for age, study areas, cardiovascular diseases, cancers, diabetes, hypertension, marital status, children, education, occupation, exercise, walking, body mass index, passive smoking, drinking habit, and number of cigarettes smoked.

HR: hazard ratio

CI: confidence interval

CVD: cardiovascular disease

P-years: person-years

Ref: reference

Table 4 Association of mortality risk and the age at smoking initiation and cessation analyzed after excluding the male participants who died/moved-out in the first 3 years of follow-up

		P-years	Deaths (n)	HR (95% CI)
Current-smokers			All-cause mortality	
Age at smoking initiation	<20	70145.2	1252	1.88 (1.75–2.02)
	20–24	219728.6	4305	1.62 (1.54–1.71)
	25–29	37646.1	837	1.52 (1.41–1.65)
	≥30	22198.3	588	1.49 (1.36–1.63)
Never-smokers		147981.6	2126	Ref
			Cancer-mortality	
Age at smoking initiation	<20	70145.2	522	2.23 (1.98–2.51)
	20–24	219728.6	1758	2.02 (1.84–2.22)
	25–29	37646.1	332	1.92 (1.68–2.20)
	≥30	22198.3	192	1.61 (1.37–1.90)
Never-smokers		147981.6	644	Ref
			CVD-mortality	
Age at smoking initiation	<20	70145.2	303	1.78 (1.54–2.05)
	20–24	219728.6	1115	1.53 (1.39–1.70)
	25–29	37646.1	223	1.43 (1.22–1.67)
	≥30	22198.3	187	1.62 (1.37–1.91)
Never-smokers		147981.6	632	Ref
Former smokers' age at smoking cessation (≥50 years)			All-cause mortality	
Age at smoking initiation	<20	14252.5	451	1.41 (1.18–1.67)
	20–24	44438.3	1388	1.26 (1.08–1.47)
	25–29	7238.6	223	1.16 (0.96–1.41)
	≥30	5081.7	190	1.06 (0.87–1.30)
Never-smokers		147981.6	2126	Ref
			Cancer-mortality	
Age at smoking initiation	<20	14252.5	165	1.57 (1.16–2.14)
	20–24	44438.3	468	1.35 (1.02–1.79)
	25–29	7238.6	58	0.99 (0.68–1.42)
	≥30	5081.7	51	1.03 (0.71–1.51)
Never-smokers		147981.6	644	Ref
			CVD-mortality	
Age at smoking initiation	<20	14252.5	123	1.42 (1.04–1.95)
	20–24	44438.3	386	1.27 (0.96–1.67)
	25–29	7238.6	75	1.38 (0.98–1.94)
	≥30	5081.7	62	1.12 (0.79–1.61)
Never-smokers		147981.6	632	Ref

Former smokers' age at smoking cessation (40–49 years)			All-cause mortality	
Age at smoking initiation	<20	12063.0	127	1.06 (0.85–1.33)
	20–24	28265.8	353	1.07 (0.90–1.28)
	25–29	3461.7	54	1.15 (0.85–1.56)
	≥30	1940.6	23	0.70 (0.52–1.23)
Never-smokers		147981.6	2126	Ref
			Cancer-mortality	
Age at smoking initiation	<20	12063.0	64	1.36 (0.95–1.95)
	20–24	28265.8	136	1.11 (0.82–1.52)
	25–29	3461.7	23	1.42 (0.87–2.31)
	≥30	1940.6	7	0.72 (0.32–1.58)
Never-smokers		147981.6	644	Ref
			CVD-mortality	
Age at smoking initiation	<20	12063.0	26	0.94 (0.59–1.49)
	20–24	28265.8	92	1.14 (0.83–1.59)
	25–29	3461.7	13	1.03 (0.56–1.88)
	≥30	1940.6	5	0.65 (0.26–1.64)
Never-smokers		147981.6	632	Ref
Former smokers' age at smoking cessation (<40 years)			All-cause mortality	
Age at smoking initiation	<20	13242.3	112	1.16 (0.92–1.46)
	20–24	25741.4	224	0.91 (0.75–1.09)
	25–29	2036.1	29	1.19 (0.81–1.76)
	≥30	464.9	4	0.45 (0.16–1.21)
Never-smokers		147981.6	2126	Ref
			Cancer-mortality	
Age at smoking initiation	<20	13242.3	40	1.02 (0.68–1.52)
	20–24	25741.4	87	0.96 (0.69–1.34)
	25–29	2035.1	9	1.10 (0.54–2.22)
	≥30	464.9	2	0.74 (0.18–3.03)
Never-smokers		147981.6	644	Ref
			CVD-mortality	
Age at smoking initiation	<20	13242.3	22	1.01 (0.62–1.63)
	20–24	25741.4	58	0.94 (0.66–1.34)
	25–29	2035.1	10	1.57 (0.81–3.08)
	≥30	464.9	0	0.00
Never-smokers		147981.6	632	Ref

Adjusted for age, study areas, cardiovascular diseases, cancers, diabetes, hypertension, marital status, children, education, occupation, exercise, walking, body mass index, passive smoking, drinking habit, and number of cigarettes smoked.

HR: hazard ratio

CI: confidence interval

CVD: cardiovascular disease

P-years: person-years

Ref: reference

Table 5 Association of mortality risk and the age at smoking initiation and cessation analyzed after excluding the male participants who had cardiovascular diseases and cancer at baseline

		P-years	Deaths (n)	HR (95% CI)
Current-smokers			All-cause mortality	
Age at smoking initiation	<20	57011.2	975	1.78 (1.64–1.93)
	20–24	177511.1	3404	1.59 (1.49–1.68)
	25–29	30432.3	656	1.49 (1.36–1.63)
	≥30	17560.9	470	1.48 (1.33–1.64)
Never-smokers		120134.1	1739	Ref
			Cancer-mortality	
Age at smoking initiation	<20	57011.2	413	2.12 (1.86–2.42)
	20–24	177511.1	1421	1.99 (1.79–2.21)
	25–29	30432.3	277	1.97 (1.71–2.29)
	≥30	17560.9	167	1.72 (1.44–2.05)
Never-smokers		120134.1	536	Ref
			CVD-mortality	
Age at smoking initiation	<20	57011.2	247	1.71 (1.46–2.01)
	20–24	177511.1	891	1.48 (1.33–1.66)
	25–29	30432.3	178	1.39 (1.17–1.66)
	≥30	17560.9	145	1.54 (1.27–1.85)
Never-smokers		120134.1	524	Ref
Former smokers' age at smoking cessation (≥50 years)			All-cause mortality	
Age at smoking initiation	<20	10454.2	322	1.37 (1.12–1.68)
	20–24	33413.2	1057	1.26 (1.06–1.51)
	25–29	5714.9	177	1.15 (0.92–1.43)
	≥30	3766.8	154	1.14 (0.91–1.43)
Never-smokers		120134.1	1739	Ref
			Cancer-mortality	
Age at smoking initiation	<20	10454.2	116	1.54 (1.07–2.18)
	20–24	33413.2	371	1.44 (1.04–1.97)
	25–29	5714.9	41	0.87 (0.57–1.34)
	≥30	3766.8	41	1.08 (0.71–1.64)
Never-smokers		120134.1	536	Ref
			CVD-mortality	
Age at smoking initiation	<20	10454.2	81	1.11 (0.76–1.62)
	20–24	33413.2	296	1.13 (0.81–1.57)
	25–29	5714.9	64	1.31 (0.89–1.94)
	≥30	3766.8	57	1.27 (0.89–1.87)
Never-smokers		120134.1	524	Ref

Former smokers' age at smoking cessation (40–49 years)		All-cause mortality		
Age at smoking initiation	<20	9852.0	94	0.99 (0.76–1.28)
	20–24	22747.1	272	1.07 (0.87–1.31)
	25–29	2722.9	41	1.07 (0.75–1.51)
	≥30	1664.5	17	0.68 (0.41–1.13)
Never-smokers		120134.1	1739	Ref
		Cancer-mortality		
Age at smoking initiation	<20	9852.0	51	1.42 (0.94–2.13)
	20–24	22747.1	108	1.18 (0.83–1.68)
	25–29	2722.9	15	1.21 (0.67–2.16)
	≥30	1664.5	4	0.51 (0.18–1.41)
Never-smokers		120134.1	536	Ref
		CVD-mortality		
Age at smoking initiation	<20	9852.0	14	0.55 (0.29–1.01)
	20–24	22747.1	70	0.97 (0.66–1.43)
	25–29	2722.9	13	1.03 (0.55–1.92)
	≥30	1664.5	4	0.52 (0.18–1.45)
Never-smokers		120134.1	524	Ref
Former smokers' age at smoking cessation (<40 years)		All-cause mortality		
Age at smoking initiation	<20	10903.2	87	1.21 (0.93–1.57)
	20–24	21648.0	184	0.95 (0.76–1.18)
	25–29	1596.6	21	1.09 (0.69–1.72)
	≥30	362.5	3	0.42 (0.13–1.32)
Never-smokers		120134.1	1739	Ref
		Cancer-mortality		
Age at smoking initiation	<20	10903.2	33	1.14 (0.73–1.79)
	20–24	21648.0	77	1.11 (0.76–1.59)
	25–29	1596.6	7	1.11 (0.50–2.46)
	≥30	362.5	1	0.53 (0.07–3.88)
Never-smokers		120134.1	536	Ref
		CVD-mortality		
Age at smoking initiation	<20	10903.2	18	0.95 (0.55–1.63)
	20–24	21648.0	43	0.77 (0.51–1.18)
	25–29	1596.6	8	1.37 (0.64–2.92)
	≥30	362.5	0	0.00
Never-smokers		120134.1	524	Ref

Adjusted for age, study areas, diabetes, hypertension, marital status, children, education, occupation, exercise, walking, body mass index, passive smoking, drinking habit, and number of cigarettes smoked.

HR: hazard ratio

CI: confidence interval

CVD: cardiovascular disease

P-years: person-years

Ref: reference

DISCUSSION

In this population-based prospective study in Japan, our main findings are as follows. First, smoking cessation is beneficial, regardless of the age at smoking initiation, as former smokers demonstrated a lower risk for all-cause and cause-specific mortality compared to current smokers, with a clear tendency of the reduction being greater when cessation occurred at lower ages. Second, among former smokers who quit smoking in their 50s or more, the mortality risk remained elevated and showed dose dependency with the age at smoking initiation, where the highest HRs were detected in those who started smoking at lower ages.

These results have important public health implications. The first finding suggests that former smokers who initiate smoking when younger but quit smoking earlier in life can gain the largest benefit from cessation. However, even participants who quit smoking during their 50s or when older had, despite higher risks than never smokers, a substantially decreased mortality risk compared to the participants who continued to smoke. This result suggests that smokers will benefit from cessation even later in life, which provides evidence that all smokers should be encouraged to quit smoking, regardless of their age at smoking initiation. This finding is in agreement with studies that have examined age at or time since quitting in former Australian smokers in the Sax Institute's "45 and Up" Study, which showed that cessation is beneficial even when attempted in the 50s.[12] Similarly, the Zutphen Study found that, in 1373 men who quit cigarette smoking at age 40, life expectancy increased by 4.6 years and the number of disease-free life years by 3.0 years.[26] Another study among a US population reported that smokers who stopped smoking at 25–34, 35–44, or 45–54 years of age gained approximately 10, 9, and 6 years of life, respectively, as compared to persistent smokers.[27] With regard to the second finding, a possible explanation is that smoking initiation at a lower age induces nicotine addiction and dependency, which leads to lifelong daily smoking and increases the smoking duration,[18,20,24,28] which results in long-term exposure to smoking in the lifetime. Even when cessation occurred at 50 years or above, the beneficial effects persisted, which suggests that earlier initiation and later cessation do not provide a huge benefit when compared with earlier cessation. In other words, when smoking is initiated at younger age and quit at an older age, the duration in which an individual is exposed to tobacco would also increase which suggest that the longer the duration of smoking the lesser the beneficial effects. Moreover, adolescence is a crucial period for organ development, and early smoking initiation is likely to change immature organs (probably through genetic alteration, to some extent), which may exacerbate the development of cancers and other smoking-related diseases and, in turn, increases the risk of smoking-related premature deaths.[21,29]

Furthermore, our study suggests that the decline in mortality risk due to smoking cessation is different for cancer and CVD mortality. Although the CVD mortality risk was seemingly totally eliminated by smoking cessation at <40 years of age, the cancer-related mortality risk remained higher than in never smokers even among former smokers who quit smoking at <50 years of age. This suggests that, to prevent cancer, smoking cessation should occur as early as possible and preferably at lower ages. This is in line with the British doctor study that followed up participants for 50 years and highlighted that, even among former smokers who stopped smoking at ages 35–44, excess risk of lung cancer mortality persisted even at 75–84 years of age,[30] which indicated a prolonged effect of smoking on cancer that extended beyond several decades. With regard to the association of smoking cessation with CVD mortality, similar findings were observed in several Japanese studies, where the mortality risk of former smokers who abstained from smoking for 10–15 years was almost equivalent to that of never smokers.[31-33] These results suggest different biological effects of smoking on CVD and cancer mortality. With regard to the relationship between smoking habits and the increased risk of CVD, various processes, such as the

incitement of oxidative stress to vascular injury[34] and the enhancement of platelet aggregation,[35] as well as changes in the fibrinolytic system,[36] are involved. Several clinical and epidemiological studies have indicated that these smoking-related biological changes disappear immediately after smoking cessation.[37,38] In contrast, numerous carcinogenic substances in cigarettes act as initiators or promoters of malignancies. These harmful carcinogens induce mutations that disrupt cell-cycle regulation[39] or influence immune or endocrine systems.[40] As carcinogenicity is a long-term multistage process, prolonged exposure to and subsequent accumulation of carcinogenic substances would increase the chance of developing and expanding malignancies.[39] Therefore, it is likely that it takes a long time to diminish the influence of these substances after smoking cessation.

In our study, we found that the age at first smoking is an important determinant of mortality risk, as the risk of all-cause and cause-specific mortality compared to never smokers was 1.5–2.0 times higher among current smokers, especially among those who initiated smoking when younger. These results confirm the results of previous studies in the general population and have important public health implications,[15,18,21,30,33,41] which indicates the particular importance of non-smoking campaigns among young people.

Taken together, the results of this study reinforce the findings from other studies among different populations that, although smoking greatly increases the risks of all-cause and cause-specific mortality, the sooner smokers quit, the lower is their risk of premature death; moreover, those who quit successfully before the age of 40 years (and preferably well before that) could garner great benefits and avoid most of the excess risk of premature death that would otherwise be caused by smoking.

The strength of this study lies in the inclusion of population-based prospective cohorts enrolled from throughout Japan. Comprehensive data on lifetime smoking history (initiation age for current smokers and both initiation and cessation ages for former smokers) along with extended follow-up and a large sample size allowed us to quantify the time course and magnitude of the mortality risk of continued smoking as well as the reduction of the risk after smoking cessation.

Nonetheless, our study has some limitations. First, due to only one measurement of smoking status at baseline, we assumed that the same smoking behavior persisted throughout the follow-up period. It is, however, possible that some quitters relapsed into smoking, and some current smokers quit smoking during the course of the follow-up. Furthermore, as the age at smoking initiation and cessation was recorded based on the participants' memory at the time of the baseline study, the possibility of recall bias should not be ignored. In addition, as the causes of smoking cessation are unknown, it was impossible to determine whether smoking cessation occurred as a voluntary choice of participants or due to health-related issues. However, the latter case, if it occurred, is unlikely to have affected our results because the sensitivity analysis after excluding participants who had CVDs or cancer at baseline yielded similar results. Finally, our findings are limited to cigarette smoking without considering other types of smoking. However, in Japan, 60–70% of male smokers were cigarette smokers between 1988 and 1990.[42] Therefore, studies should be conducted to investigate the association of other types of tobacco smoking with all-cause mortality.

CONCLUSION

The present study demonstrated a dose–response relationship between the age at smoking cessation as well as initiation and the risks of all-cause, cancer, and CVD mortality among Japanese men. Former smokers demonstrated a lower risk for all-cause and cause-specific mortality than current smokers, with the risk reduction being greater among smokers who quit smoking at a

lower age. Furthermore, our results showed that smoking cessation at <40 years of age leads to a reduction in CVD mortality; however, the cancer-related mortality risk persisted even when cessation occurred before the age of 50 years. These findings imply that all smokers should be encouraged to quit smoking earlier in life regardless of their age at smoking initiation.

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Author contributions

Akiko Tamakoshi was involved in the study design. Sulaiman Haares Zuhal and Takashi Kimura contributed to the data analysis and manuscript preparation. Sulaiman Haares Zuhal and Akiko Tamakoshi revised the manuscript. All authors approved the final manuscript.

Ethical considerations

Informed written consent was provided from the participants themselves or the community leaders. The JACC study protocol was approved by the ethics committees of Hokkaido University, Nagoya University, and Osaka University.

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