International Journal of Epidemiology, 2021, 1–12
doi: 10.1093/ije/dyab087
Original Article

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Reduction in total and major cause-specific mortality from tobacco smoking cessation: a pooled analysis of 16 population-based cohort studies in Asia

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editorial decision 25 March 2021; Accepted 26 October 2020

Abstract

Background: Little is known about the time course of mortality reduction following smoking cessation in Asians who have smoking behaviours distinct from their Western counterparts. We evaluated the level of reduction in all-cause, cardiovascular disease (CVD) and lung cancer mortality by years since quitting smoking, in Asia.

Methods: Using Cox regression, we analysed individual participant data ($n = 709\,151$) from 16 prospective cohorts conducted in China, Japan, Korea/Singapore, and India/Bangladesh, separately by cohorts. Cohort-specific hazard ratios (HRs) were combined using a random-effects meta-analysis.

Results: During a mean follow-up of 12.0 years, 108 287 deaths were ascertained—35 658 from CVD and 7546 from lung cancer. Among Asian men, a dose-response relationship of risk reduction in deaths from all causes, CVD and lung cancer was observed with an increase in years after smoking cessation. Compared with never smokers, however, all-cause and CVD mortality among former smokers remained elevated 10–14 years after quitting [multivariable-adjusted HR (95% confidence interval (CI) = 1.25 (1.13–1.37) and 1.20 (1.02–1.41), respectively]. Lung cancer mortality stayed almost 2-fold higher than among never smokers 15–19 years after smoking cessation [1.97 (1.41–2.73)], particularly among former heavy smokers [2.62 (1.71–4.00)]. Women who quitted for ≥5 years retained a significantly elevated mortality from all causes, CVD and lung cancer. Overall patterns of the cessation-mortality associations were similar across countries.

Conclusions: Our findings suggest that adverse effects of tobacco smoking persist for an extended time period, even for more than two decades, which is beyond the time windows defined in current clinical guidelines for risk assessment of lung cancer and CVD.

Key Messages

- Harmful effects of tobacco smoking persist for an extended time period, even for more than two decades, which is beyond the time windows defined in current clinical guidelines for lung cancer screening and cardiovascular disease risk assessment.
- Our findings suggest that adverse effects of tobacco smoking among former smokers may be underestimated by current guidelines for disease risk assessment.
- Given the increasing numbers of former smokers over the years, it is imperative to provide strong support for implementing effective preventive measures in former smokers to reduce their potential disease burdens and excess mortality.

Key words: Smoking cessation, mortality, lung cancer, cardiovascular disease, cohort, Asia

Introduction

Tobacco smoking is one of the biggest public health challenges, causing more than eight million deaths per year globally.[1] While high-income Western countries have made significant progress in tobacco control over the past several decades, Asia has now become the epicentre of tobacco smoking.[2–5] Many Asian countries such as China and India are facing a growing health burden due to smoking, with a significant increase in smoking-attributable mortality.[5] Of note, Asian smokers show unique patterns in smoking behaviours that are distinct from their Western counterparts.[5] Despite some variations by economic status across countries, in general, smoking patterns in middle-aged and elderly Asians are characterized by relatively late initiation, less cigarette consumption per day and a lower likelihood of smoking cessation.[5,6]

Benefits of smoking cessation have been well documented.[3,7–10] Several large cohort studies in the USA and UK have consistently reported that former smokers have a substantially reduced total and major cause-specific mortality such as cardiovascular disease (CVD) and lung cancer mortalities, as compared with current smokers.[7–11] Similar findings have been also reported in Asian populations,[12–16] including our own study based on the Asia Cohort Consortium (ACC).[4] However, it remains unclear how long residual effects of smoking could persist after cessation and when the underlying risk of former smokers would be comparable to that of never smokers, particularly among Asian smokers who have distinct smoking behaviours from those of Westerners.

Clinical guidelines have now provided personalized interventions based on the individual's smoking history, i.e. years since quitting and cumulative smoking pack-years, for cost-efficient prevention programmes. For example, the US Preventive Services Task Force (USPSTF) recommends an annual lung cancer screening with low-dose computed tomography for smokers with a history of ≥20 pack-years smoking who are either current smokers or quit smoking within <15 years.[17,18] In CVD risk assessment, the underlying risk of former smokers is generally regarded to be equivalent to never smokers after 5 years of smoking abstinence.[19] However epidemiological evidence to date, although mostly limited to Western countries, indicates that elevated risks/mortality of lung cancer and CVD for former smokers do not reach those of lifelong never smokers until up to 10 to ≥25 years after cessation,[20–24] suggesting the possibility of underestimating residual effects of tobacco smoking in current guidelines.

Quantifying the time course of risk reduction following cessation is important in identifying high- vs. low-risk smokers for disease prevention. In this study including multiple Asian populations, we sought to evaluate the impact of smoking cessation on subsequent total and cause-specific mortality among Asian former smokers and to further quantify the level of mortality reduction by years of quitting smoking, with stratification of lifetime smoking intensity and sex.

Methods

Study population

This pooling project includes 16 population-based cohort studies that are conducted in China, Japan, Korea, Singapore, Bangladesh and India, participating in the ACC (Table 1). The study protocols of all cohorts and the current project were approved by their individual institutional review boards and ethics committees. Each cohort obtained the consent of participants to collect their baseline and outcome data, according to the study protocol. De-identified, individual-participant data from each cohort were harmonized by the ACC coordinating centre. Detailed descriptions of the ACC and all participating cohorts have been provided previously.[4,5,25]

Exposure assessment

At the baseline survey, data on lifetime smoking history were collected using cohort-specific questionnaires. Smokers were typically defined as participants who smoked at least one cigarette per day for at least 6 months or who smoked more than 20 packs in their lifetime. Given the weight of tobacco flakes per bidi and per cigarette,[4] one bidi was regarded as a quarter of a cigarette. Smoking status was categorized into current, former and never. For current and former smokers, data on age at smoking initiation, usual daily cigarette consumption and smoking duration were obtained. Lifetime smoking intensity was measured as cumulative pack-years, calculated by multiplying the number of packs of cigarettes smoked per day by the number of years of smoking. For former smokers, age at smoking cessation was also obtained; years since quitting smoking were estimated using the time interval from age at quitting to age at interview.

Outcome ascertainment

Through data linkage to cancer registries and death certificates, a repeated active follow-up survey and medical record reviews, we ascertained vital status at the latest follow-up and the primary cause of death for the deceased. Based on the ninth or tenth revision of the International Statistical Classification of Diseases (ICD-9 or 10), the mortality outcomes that we focused on were deaths from all causes (001-E999 or A00-Y98), CVD (390–459 or I00–I99) and lung cancer (162 or C34). Follow-up time was defined by years from the date of enrolment to the date of death, loss-to-follow-up, or end of follow-up, whichever came first.

Statistical analysis

Of the 879 449 initial participants from 16 cohorts, we excluded individuals having invalid data on smoking-related variables [smoking status ($n = 15\,528$), smoking pack-years ($n = 13\,217$) and age at quitting among former smokers ($n = 2422$)] or follow-up ($n = 2740$)]. To minimize the possibility of reverse causation, we also excluded individuals who had a history of cancer or CVD at baseline

Table 1 Characteristics of the participating cohorts in the Asia Cohort Consortium

Participating cohorts	No. participants[a]	Baseline survey	Follow-up years	Age at baseline[b]	Men (%)	Current smoking		Former smoking		No. deaths		
						Men (%)	Women (%)	Men (%)	Women (%)	All causes	CVD	Lungcancer
China												
CHEFS	135 007	1990–1992	7.8	55.5	48.2	59.0	12.6	3.6	0.6	14 744	6495	860
SCS	18 010	1986–1989	16.4	55.2	100.0	50.6	–	6.7	–	4902	1660	621
SMHS	56 165	2002–2006	9.6	54.4	100.0	61.0	–	9.4	–	3886	1031	573
SWHS	67 268	1997–2000	15.0	51.8	0.0	–	2.3	–	0.4	5637	1629	515
Japan												
3Pref Aichi	29 318	1985–1985	11.9	56.1	49.2	55.5	12.7	28.5	4.2	5198	1810	346
JPHC1	40 788	1990–1992	21.1	49.5	47.6	53.6	5.6	21.7	1.5	6753	1625	518
JPHC2	52 827	1992–1995	17.9	54.0	46.7	51.5	5.9	23.5	1.2	11 213	2760	850
3Pref Miyagi	26 810	1984–1984	11.9	56.4	43.8	60.5	9.3	17.5	1.9	4865	1872	244
Miyagi	36 240	1990–1990	16.5	51.4	52.5	62.7	8.1	16.6	1.5	4129	1063	347
Ohsaki	42 034	1994–1994	11.4	59.9	45.3	53.9	5.7	22.4	1.5	7293	2115	480
LSS	44 089	1963–1993	13.9	60.4	40.7	84.2	14.2	1.1	0.2	22 328	8183	1037
Korea												
KMCC	10 300	1993–2004	13.6	55.7	32.4	51.3	4.3	19.3	1.0	1797	435	133
Seoul Male	11 630	1992–1993	15.6	48.9	100.0	53.2	–	22.9	–	682	105	76
Singapore												
SCHS	57 714	1993–1999	11.7	56.1	43.9	36.8	6.2	20.3	2.2	8234	2725	874
India												
Mumbai	76 719	1991–1997	5.3	50.8	67.3	41.6	0.9	5.7	0.1	6194	1963	47
Bangladesh												
HEALS	4232	2000–2002	12.3	43.7	67.9	78.1	14.7	4.6	0.8	432	187	25
Total	709 151	1963–2006	12.0	54.4	50.8	55.0	7.4	12.3	1.1	108 287	35 658	7546

CVD, cardiovascular disease; CHEFS, China Hypertension Survey Epidemiology Follow-up Study; SCS, Shanghai Cohort Study; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study; 3Pref Aichi, 3 Prefecture Aichi Study; JPHC, Japan Public Health Centre-based prospective Study; 3Pref Miyagi, 3 Prefecture Miyagi; Miyagi, Miyagi Cohort; Ohsaki, Ohsaki National Health Insurance Cohort Study; LSS, Life Span Study Cohort; KMCC, Korean Multi-centre Cancer Cohort Study; Seoul Male, Seoul Male Cancer Cohort; SCHS, Singapore Chinese Health Study; Mumbai, Mumbai Cohort Study; HEALS, Health Effects for Arsenic Longitudinal Study.

[a]Including only participants eligible for the current analysis.

[b]Mean age at the enrolment of the baseline (smoking) survey.

($n = 35\,872$) and who were censored (i.e. died or lost-to-follow-up) within the first year after enrolment ($n = 25\,101$). All analyses were limited to participants aged >35, given the rarity of smoking-attributable deaths in early adulthood, thus excluding another 6956. Additionally, current users of smokeless tobacco products were excluded ($n = 68\,462$) due to the significant association of smokeless smoking with excess mortality.[26] After those exclusions, a total of 709 151 participants, 360 415 men and 348 736 women, remained for the analysis.

Based on a two-stage individual-participant data meta-analysis,[27] we first performed Cox regression analysis to estimate hazard ratios (HRs) for mortality outcomes in each cohort. Then cohort-specific HRs were combined using the DerSimonian and Laird random-effects meta-analysis.[28] Cox models were stratified by 5-year groups of birth year and enrolment year. Time scale was defined by age at enrolment and age at censoring. Analyses were conducted separately by sex, given the substantial difference in smoking prevalence and patterns across sexes.[5] All models were adjusted for baseline age (continuous), education (none, primary, secondary, vocational school, university and postgraduate studies), marital status (single/separated/divorced/widowed and married), residence area (urban and rural), and body mass index (BMI; <18.5, 18.5–24.9, 25.0–29.9, and ≥30.0 kg/m^2), all of which previously showed significant associations with mortality in the ACC populations. For missing covariates, we assigned the cohort-specific median (for continuous) or mode values (for categorical) of the non-missing covariates.

The time course and magnitude of reduction in mortality were estimated in former smokers relative to current smokers, according to years since quitting smoking as a categorical variable (<5, 5–9, 10–14, 15–19, 20–24 and ≥ 25 years) in Cox models. We also evaluated the shape of dose-response relation with years since quitting as a continuous variable using restricted cubic splines with four knots. Current smokers were coded as a value of 0, and former smokers who quit smoking more than 25 years ago were coded as a value of 26. The spline models were built in a pooled dataset incorporating all study participants, with stratification of cohort. Similarly, we also investigated the time course and risk reduction in former smokers relative to never smokers. In the analysis of a continuous variable using spline models, never smokers were assigned a value of 50, considering that for former smokers, years since quitting were all below 50 years. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 709 151 Asians were followed for a mean of 12.0 years, and their mean age at baseline was 54.4 years. The overall rates of current and former smoking were 55.0% and 12.3% among men, respectively, whereas the rates dropped dramatically among women at 7.4% and 1.1%, respectively. During the follow-up, 108 287 deaths were confirmed, which included 35 658 deaths from CVD and 7546 deaths from lung cancer (Table 1).

Compared with never smokers (Table 2), former smokers had a 22% to 26% increased risk of death from all causes or CVD {multivariable-adjusted HR [95% confidence interval (CI) = 1.26 (1.18–1.34) and 1.22 (1.11–1.34), respectively] and showed a 2.09-fold increased risk of dying of lung cancer [2.09 (1.82–2.40)]}. The corresponding HRs (95% CIs) for current smokers elevated to 1.55 (1.44–1.68), 1.49 (1.36–1.64) and 4.34 (3.59–5.25), respectively. The smoking-mortality associations were more pronounced in heavy smokers: former and current smokers who smoked more than 20 cumulative pack-years had a 3.06- and 5.72-fold increased risk of lung cancer mortality, respectively. The overall pattern of the associations was similar between men and women.

Among Asian men (Table 3), smoking cessation was associated with a substantial decrease in all-cause, CVD and lung cancer mortalities in a dose-response manner with years since quitting. Compared with current smokers, former smokers who quit smoking less than 5 years ago had an 11%–34% lower risk of death from all causes [HR (95% CI) = 0.89 (0.80–0.99)] and lung cancer [0.66 (0.53–0.80)]. Compared with never smokers, however, the risk of death from all causes and CVD among former smokers remained higher 10–14 years after cessation [1.25 (1.13–1.37) and 1.20 (1.02–1.41), respectively]. Furthermore, the risk of death due to lung cancer associated with tobacco smoking remained almost 2-fold elevated 15–19 years after quitting [1.97 (1.41–2.73)]. In particular, former smokers who smoked more than 20 pack-years had a 2.20-fold increased risk of death due to lung cancer even after 25 years since smoking cessation [2.20 (1.00–4.83)].

Dose-response relationships between risks of death and years since smoking cessation are shown in Figure 1 and Supplementary Figure S1 (available as Supplementary data at *IJE* online). An increased risk of death from lung cancer among Asian men persisted beyond 26 years after smoking cessation, and the risk of dying from CVD among former smokers approached the level of never smokers after 14 years of smoking abstinence (i.e. including the null value of 1).

Among Asian women (Table 4), the number of former smokers was very limited and thus was classified into <5

Table 2 Hazard ratios (95% CIs) of death from all causes, cardiovascular disease and lung cancer associated with tobacco smoking among Asian populations

		All causes		Cardiovascular disease		Lung cancer	
Smoking status	No. participants	No. deaths	HR (95% CI)[a]	No. deaths	HR (95% CI)[a]	No. deaths	HR (95% CI)[a]
Total							
Never	437 355	53 948	1 (ref.)	19 047	1 (ref.)	2062	1 (ref.)
Former	47 876	9872	1.26 (1.18–1.34)	2904	1.22 (1.11–1.34)	664	2.09 (1.82–2.40)
≤20 pack-years	24 745	3844	1.15 (1.06–1.25)	1236	1.20 (1.07–1.35)	156	1.38 (1.12–1.70)
>20 pack-years	23 131	5983	1.36 (1.28–1.45)	1668	1.22 (1.12–1.33)	508	3.06 (2.58–3.64)
Current	223 920	44 512	1.55 (1.44–1.68)	13 707	1.49 (1.36–1.64)	4820	4.34 (3.59–5.25)
≤20 pack-years	97 675	14 490	1.43 (1.33–1.53)	4800	1.40 (1.28–1.54)	888	2.72 (2.27–3.26)
>20 pack-years	126 245	30 022	1.63 (1.49–1.79)	8907	1.56 (1.41–1.72)	3932	5.72 (4.73–6.92)
Men							
Never	117 953	15 525	1 (ref.)	5530	1 (ref.)	532	1 (ref.)
Former	44 178	9084	1.24 (1.15–1.33)	2611	1.16 (1.04–1.28)	614	2.31 (1.99–2.69)
≤20 pack-years	21 790	3307	1.09 (0.98–1.21)	1011	1.09 (0.94–1.26)	130	1.39 (1.07–1.80)
>20 pack-years	22 388	5777	1.34 (1.26–1.44)	1600	1.19 (1.08–1.31)	484	3.12 (2.57–3.78)
Current	198 284	39 028	1.53 (1.40–1.66)	11 575	1.41 (1.27–1.56)	4361	5.08 (4.01–6.43)
≤20 pack-years	79 850	11 135	1.39 (1.29–1.49)	3478	1.31 (1.19–1.45)	674	2.89 (2.27–3.68)
>20 pack-years	118 434	27 893	1.57 (1.43–1.73)	8097	1.45 (1.30–1.61)	3687	5.94 (4.74–7.45)
Women							
Never	319 402	38 423	1 (ref.)	13 517	1 (ref.)	1530	1 (ref.)
Former	3698	743	1.31 (1.18–1.46)	293	1.46 (1.24–1.71)	50	2.47 (1.84–3.30)
≤20 pack-years	2955	537	1.29 (1.16–1.44)	225	1.53 (1.29–1.82)	26	1.88 (1.27–2.78)
>20 pack-years	743	206	1.44 (1.20–1.72)	68	1.32 (1.04–1.68)	24	5.17 (3.41–7.85)
Current	25 636	5484	1.54 (1.40–1.69)	2132	1.60 (1.44–1.77)	459	3.49 (2.86–4.26)
≤20 pack-years	17 825	3355	1.44 (1.34–1.55)	1322	1.49 (1.35–1.65)	214	2.59 (2.18–3.09)
>20 pack-years	7811	2129	1.73 (1.51–1.98)	810	1.75 (1.51–2.03)	245	5.72 (4.47–7.32)

[a]All models were stratified by cohort, 5-year groups of birth year, and enrolment year and adjusted for age, sex (for total), education, marital status, rural/urban residence and body mass index.

vs. ≥5 years since quitting. Compared with current smokers, former smokers who quit smoking 5 or more years ago had a 17% and 36% lower risk of death from all causes [HR (95% CI) = 0.83 (0.69–1.00)] and lung cancer [0.64 (0.44–0.94)], respectively. As compared with never smokers, the risks of death from all causes, CVD and lung cancer among former smokers remained elevated after 5 or more years of cessation: the corresponding HRs (95% CIs) were 1.29 (1.12–1.48), 1.41 (1.16–1.72) and 2.64 (1.82–3.83), respectively. Dose-response relationships between risks of death and years since smoking cessation are given in Supplementary Figures S2 and S3 (available as Supplementary data at *IJE* online), despite unstable findings due to small numbers.

Results from the country-specific analyses indicate that overall patterns of the cessation-mortality associations are similar across Asian countries, highlighting that our findings were not driven by any single country (Supplementary Tables S1 and S2, available as Supplementary data at *IJE* online). Further restricted analyses of elderly Asians who were followed up until at least age 70 or older also support the robustness of the study findings (Supplementary Tables S3 and S4, available as Supplementary data at *IJE* online).

Discussion

In this prospective investigation of 709 151 Asians, we found a dose-response relationship of risk reduction in deaths due to all causes, CVD and lung cancer with years after smoking cessation. Compared with never smokers, however, elevated mortality of those diseases stayed among former smokers for at least 10 to 20 years after smoking cessation. Alarmingly, among former smokers with a history of ≥20 pack-year smoking, a more than 2-fold elevated risk of lung cancer mortality was found even more than 25 years after smoking cessation. Our study provides strong evidence that adverse effects associated with tobacco smoking persist for an extended time period, beyond the time windows defined in current clinical guidelines for risk assessment of lung cancer and CVD.

Although previous studies have consistently reported a significant risk reduction in mortality with time since quitting smoking, a limited number of studies estimated the

Table 3 Hazard ratios (95% CIs)[a] of death from all causes, cardiovascular disease and lung cancer associated with years since quitting tobacco smoking among Asian men

Years since quitting	No. participants	Person-years	All causes: No. deaths	All causes: Former vs. current	All causes: Former vs. never	Cardiovascular disease: No. deaths	Cardiovascular disease: Former vs. current	Cardiovascular disease: Former vs. never	Lung cancer: No. deaths	Lung cancer: Former vs. current	Lung cancer: Former vs. Never
All former smokers											
Current smokers	198 284	2 239 574	39 028	1 (ref.)		11 575	1 (ref.)		4361	1 (ref.)	
<5	14 125	176 611	2850	0.89 (0.80–0.99)	1.38 (1.28–1.49)	810	0.89 (0.76–1.06)	1.27 (1.12–1.44)	266	0.66 (0.53–0.80)	3.51 (2.75–4.48)
5 to 9	10 123	131 937	2047	0.84 (0.75–0.94)	1.32 (1.22–1.43)	560	0.81 (0.69–0.94)	1.18 (1.07–1.30)	142	0.47 (0.37–0.59)	2.57 (2.11–3.14)
10 to 14	7750	102 533	1617	0.80 (0.70–0.91)	1.25 (1.13–1.37)	478	0.84 (0.68–1.03)	1.20 (1.02–1.41)	95	0.37 (0.30–0.46)	2.01 (1.59–2.53)
15 to 19	5260	72 127	900	0.67 (0.58–0.78)	1.06 (0.94–1.20)	253	0.70 (0.56–0.87)	1.02 (0.86–1.22)	50	0.33 (0.23–0.46)	1.97 (1.41–2.73)
20 to 24	3162	40 807	665	0.67 (0.60–0.76)	1.05 (0.97–1.14)	186	0.67 (0.55–0.80)	0.97 (0.84–1.13)	26	0.29 (0.18–0.46)	1.46 (0.96–2.21)
≥25	3758	45 472	1005	0.67 (0.59–0.75)	1.04 (0.96–1.13)	324	0.76 (0.62–0.93)	1.06 (0.93–1.21)	35	0.25 (0.15–0.42)	1.21 (0.84–1.75)
Never smokers	117 953	1 230 990	15 525		1 (ref.)	5530		1 (ref.)	532		1 (ref.)
Former smokers with >20 cumulative pack-years											
Current smokers	198 284	2 239 574	39 028	1 (ref.)		11 575	1 (ref.)		4361	1 (ref.)	
<5	9349	120 026	2211	0.91 (0.82–1.01)	1.42 (1.31–1.54)	601	0.88 (0.75–1.02)	1.26 (1.12–1.42)	234	0.74 (0.59–0.94)	4.17 (3.20–5.44)
5 to 9	5999	79 714	1529	0.88 (0.79–0.98)	1.39 (1.28–1.51)	403	0.82 (0.69–0.96)	1.19 (1.07–1.33)	121	0.52 (0.43–0.62)	2.97 (2.40–3.67)
10 to 14	3924	51 275	1089	0.83 (0.73–0.94)	1.29 (1.18–1.41)	313	0.83 (0.70–0.99)	1.19 (1.05–1.36)	75	0.44 (0.33–0.57)	2.37 (1.83–3.06)
15 to 19	1734	22 171	501	0.74 (0.63–0.86)	1.18 (1.03–1.35)	133	0.72 (0.53–0.97)	1.06 (0.80–1.39)	33	0.43 (0.31–0.62)	2.62 (1.71–4.00)
20 to 24	876	10 569	264	0.66 (0.57–0.75)	1.05 (0.93–1.19)	85	0.74 (0.59–0.91)	1.12 (0.90–1.39)	14	0.34 (0.20–0.57)	1.79 (1.02–3.14)
≥25	506	5581	183	0.65 (0.56–0.76)	1.05 (0.90–1.22)	65	0.75 (0.59–0.96)	1.14 (0.89–1.47)	7	0.44 (0.21–0.94)	2.20 (1.00–4.83)
Never smokers	117 953	1 230 990	15 525		1 (ref.)	5530		1 (ref.)	532		1 (ref.)
Former smokers with ≤20 cumulative pack-years											
Current smokers	198 284	2 239 574	39 028	1 (ref.)		11 575	1 (ref.)		4361	1 (ref.)	
<5	4776	56 585	639	0.80 (0.67–0.95)	1.25 (1.10–1.42)	209	0.93 (0.74–1.18)	1.32 (1.20–1.59)	32	0.55 (0.32–0.95)	2.68 (1.59–4.51)
5 to 9	4124	52 222	518	0.74 (0.62–0.88)	1.16 (1.02–1.32)	157	0.81 (0.65–1.01)	1.18 (0.98–1.42)	21	0.41 (0.24–0.71)	2.01 (1.22–3.31)
10 to 14	3826	51 258	528	0.73 (0.61–0.88)	1.15 (0.99–1.34)	165	0.80 (0.57–1.11)	1.15 (0.85–1.55)	20	0.30 (0.19–0.46)	1.65 (1.04–2.62)
15 to 19	3526	49 956	399	0.62 (0.51–0.74)	0.98 (0.84–1.14)	120	0.69 (0.55–0.85)	1.03 (0.85–1.23)	17	0.32 (0.16–0.63)	2.00 (1.10–3.63)
20 to 24	2286	30 238	401	0.67 (0.59–0.77)	1.07 (0.97–1.19)	101	0.63 (0.50–0.80)	0.91 (0.75–1.11)	12	0.42 (0.18–1.01)	1.75 (0.98–3.16)
≥25	3252	39 892	822	0.68 (0.59–0.78)	1.06 (0.95–1.18)	259	0.77 (0.61–0.98)	1.08 (0.92–1.28)	28	0.24 (0.14–0.42)	1.24 (0.80–1.91)
Never smokers	117 953	1 230 990	15 525		1 (ref.)	5530		1 (ref.)	532		1 (ref.)

[a]All models were stratified by cohort, 5-year groups of birth year, and enrollment year and adjusted for age, education, marital status, rural/urban residence and body mass index.

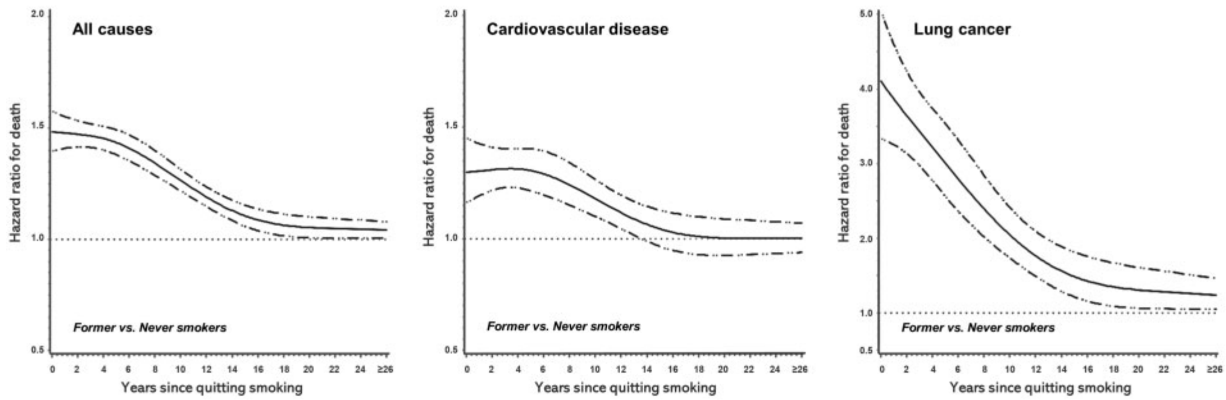

Figure 1 Hazard ratios (95% CIs) of death from all causes, cardiovascular disease and lung cancer associated with tobacco smoking among Asian men: former vs. never smokers. Hazard ratios (solid line) and 95% CIs (dashed line) were estimated with stratification by cohort, birth year and enrolment year and adjustment for age, education, marital status, rural/urban residence and body mass index. Splines have four knots at 1, 5, 15 and 22 years since quitting

time course of risk reduction following cessation. The Nurses' Health Study, analysing 104 519 women, reported a 13–31% reduction in all-cause, CVD and lung-cancer mortality within 5 years of quitting as compared with current smokers.[20] The excess risk of death from all causes was attenuated to the level of a never smoker 20 years after quitting, and risks of death from lung cancer, respiratory disease and smoking-related cancers remained statistically significant even after 20 years of cessation.[20] Similar findings were noted in the Physicians' Health Study ($n = 22\,071$)[21]: although total mortality became equivalent to never smokers 20 years after quitting, the risks of death from coronary heart disease, pulmonary disease and lung cancer among former smokers declined to the level of never smokers after 20–30 years since quitting. A pooled analysis of 503 905 participants from Europe and the USA found that CVD mortality among former smokers aged ≥60 decreased in a time-dependent manner with cessation duration, but ≥20 years of abstinence was still associated with a 15% increased risk compared with never smokers.[22] In the same vein, the British Doctors' Study that followed up for 50 years highlighted that former smokers who stopped smoking at ages 35–44 had some excess risk of lung cancer mortality at their older ages of 75–84,[10] indicating a prolonged smoking effect beyond several decades. Two prospective studies in China showed that the relative risk of all-cause mortality among former male smokers who quit by choice (not due to illness) <5, 5–14 and ≥15 years ago were 1.21 (1.07–1.37), 1.00 (0.90–1.11) and 0.98 (0.87–1.11), respectively, compared with never smokers.[12] In several Japanese studies, the risk estimates for all-cause and CVD mortality gradually declined with time after quitting, and risk estimates of former smokers who were abstinent from smoking for about 10 to 15 years were almost equivalent to those of never smokers.[13–15] Taken all together, previous studies showed that the excess all-cause mortality due to tobacco smoking diminished sooner in Asian former smokers (10–15 years after quitting) than in Western counterparts (~20 years).

However, in the current study with a longer term of follow-up and larger sample size than previous Asian studies, we found the excess all-cause mortality due to tobacco smoking among former smokers, particularly those who had smoked ≥20 pack-years, more than 15 years after quitting, which was similar to the findings reported previously in studies conducted in the USA and European countries. We also observed that the excess lung-cancer mortality among former smokers lingered over two decades or more, which was an extended time period comparable to that observed among Westerners. Our findings suggest that a much longer time would be needed to diminish nearly all the excess risk of Asian former smokers than what was reported previously. Several analyses used results from published studies to estimate the years after quitting smoking when the excess risk became half that of current smokers and found that the risk was reduced by 50% about 4.40 years after quitting for ischaemic heart disease, 4.78 years for stroke, 9.94 years for lung cancer and 13.32 years for chronic obstructive pulmonary disease.[29–32] The results from these studies support our findings, highlighting that the excess risk of tobacco smoking could remain for an extended period of time after smoking cessation. Whereas the relative risks of disease morbidity and mortality associated with tobacco smoking remain substantially lower in Asia than in Europe and North America,[4,5,33] it has been suggested that the time required to halve the risk after smoking cessation may be similar between Asia and Western countries.[29–32]

Table 4 Hazard ratios (95% CIs)[a] of death from all causes, cardiovascular disease and lung cancer associated with years since quitting tobacco smoking among Asian women

Years since quitting	No. participants	Person-years	All causes			Cardiovascular disease			Lung cancer		
			No. deaths	Former vs. current	Former vs. never	No. deaths	Former vs. current	Former vs. never	No. deaths	Former vs. current	Former vs. Never
Current smokers	25 636	296 137	5484	1 (ref.)		2132	1 (ref.)		459	1 (ref.)	
<5	1488	19 164	294	0.91 (0.81–1.03)	1.42 (1.22–1.64)	116	0.99 (0.82–1.20)	1.58 (1.32–1.90)	20	0.90 (0.57–1.43)	3.40 (2.18–5.32)
≥5	2210	27 847	449	0.83 (0.69–1.00)	1.29 (1.12–1.48)	177	0.90 (0.72–1.13)	1.41 (1.16–1.72)	30	0.64 (0.44–0.94)	2.64 (1.82–3.83)
Never smokers	319 402	4 133 106	38 423		1 (ref.)	13 517		1 (ref.)	1530		1 (ref.)

[a]All models were stratified by cohort, 5-year groups of birth year, and enrolment year and adjusted for age, education, marital status, rural/urban residence and body mass index.

Understanding the time course of risk reduction after smoking cessation is the first step to developing evidence-based guidelines to identify high-risk individuals who will benefit from interventions. The USPSTF currently recommends an annual low-dose computed tomography screening for smokers aged 55–80 years with a history of ≥20 pack-year smoking, who smoke currently or quit within 15 years.[17,18] However, approximately half of lung cancer patients do not meet this screening criterion. We found a more than 2-fold elevated risk of dying from lung cancer among Asian former smokers who smoked ≥20 pack-years and quitted for more than 25 years. Similar findings were also reported in a recent Framingham Heart Study, which showed that former smokers had a more than 3-fold higher risk of lung cancer compared with never smokers even after 25 years since quitting.[23] The underestimation of the staying power of tobacco smoking is also observed in CVD prevention guidelines. In current clinical practice, CVD risk of never vs. former smokers is generally considered as comparable after 5 years since quitting.[19,34] However, we found that it would take 10 to 14 years of smoking abstinence to attenuate risk of deaths from CVD to the level of never smokers. Our findings are supported by a recent study from Western populations, in which the excess risk of CVD among former smokers may last for at least 5 to 10 years and possibly up to 25 years after cessation as compared with never smokers.[24] All the findings suggest that the current clinical guidelines for lung cancer screening and CVD risk assessment lead many smokers to underestimate their risk for major smoking-attributable diseases, which may hinder the implementation of effective public health interventions for disease prevention and control. It is important that smokers should be aware of the persistence of their potential risk due to tobacco exposure for an extended time window.

This collaborative project includes multiple population-based prospective cohorts throughout Asia. Comprehensive data on lifetime smoking history, along with an extended follow-up and large sample size, allow us to quantify the time course and magnitude of mortality risk reduction in Asian former smokers without pre-existing medical conditions. However, our study has some limitations.

First, due to the lack of information, we assumed smoking behaviours were persistent throughout the follow-up period. It is possible that some quitters relapsed into smoking and some current smokers quit smoking during follow-up. Also, we could not rule out the possibility of measurement errors in self-reported smoking. All the limitations were more likely to bias the overall association towards the null. Thus, the true associations between smoking cessation and mortality outcomes may be stronger than those we observed in the current study. Second, the effect of second-hand smoke and other potential contributors in Asian populations, i.e. occupational exposure, air pollution and indoor smoke from cooking, could not be appropriately controlled due to data limitation. Also, we cannot be free of other residual confounding or unmeasured confounders in interpreting the study findings. Third, we have tried to include other forms of tobacco products and converted the amount of tobacco smoking to cigarette smoking in the analysis. However, some cohorts did not collect information on other forms of tobacco products, which might have influenced our risk estimates. Fourth, the potential effect of heterogeneous smoking patterns both among and within countries should be noted, although overall patterns of the smoking cessation-mortality associations identified in this study were consistent across countries. Finally, despite our large sample size, some subgroup analyses, e.g. female smokers (especially former smokers), heavy smokers who quit smoking >20 years ago, and South Asia, were based on a small number and thus yielded unstable estimates—some results should be interpreted with caution. In addition, most participants came from East Asia: future investigations are needed to include a large number of participants from other Asian countries and regions.

In conclusion, this large pooled analysis provides additional support for the substantial benefit of smoking cessation in disease prevention. However, the excess risk due to tobacco smoking persists over decades, particularly among heavy smokers, providing evidence to modify current clinical guidelines for lung cancer screening and CVD risk assessment in Asians. Given a low cessation rate in many Asian countries,[5] public health efforts in Asia must focus on how to prevent tobacco use and encourage smokers to quit as early as possible. Full commitments to implementing smoking prevention and cessation strategies are imperative to reduce a growing health burden due to the tobacco epidemic emerging throughout Asia.

Data access can be through permission from the Asia Cohort Consortium only; please find more details on [https://www.asiacohort.org/about/workingwith/index.html] and send any enquiries to the Asia Cohort Consortium Coordinating Centre at [cc@asiacohort.org].

Supplementary Data

Supplementary data are available at *IJE* online.

Acknowledgements

The authors would like to thank all research team members and participants of each cohort study for their contribution to this research. We also thank Mr Marshal S. Younger, BA, Vanderbilt University Medical Centre, for his assistance in preparing the manuscript.

Funding

This work was supported by research funds from the Anne Potter Wilson Chair endowment and National Institutes of Health grants (UM1CA182910 to W.Z. and UM1CA173640 to X-O.S.) at Vanderbilt University Medical Centre. Participating cohort studies (funding sources) in the consortium are: China National Hypertension Survey Epidemiology Follow-up Study [CHEFS, funding sources: American Heart Association (9750612 N), NHLBI (U01-HL072507), Chinese Academy of Medical Sciences]; Shanghai Cohort Study [SCS, funding sources: NIH (R01CA0403092, R01CA144034, UM1CA182876)]; Shanghai Men's Health Study [SMHS, funding sources: NIH (R01-CA82729 and UM1CA173640)]; Shanghai Women's Health Study [SWHS, funding sources: NIH (R37-CA70867 and UM1CA182910)]; Korea Multi-center Cancer Cohort (KMCC, funding sources: Ministry of Education, Science and Technology, Korea, National Research Foundation of Korea grant 2009–0087452); Seoul Male Cancer Cohort [Seoul Male, funding sources: National R&D Program for Cancer Control, Ministry of Health & Welfare, Republic of Korea (0520160–1)]; Singapore Chinese Health Study [SCHS, funding sources: NIH (R01CA55069, R35CA53890, R01CA80205, R01CA144034, UM1CA182876)]; Mumbai Cohort Study (Mumbai, funding sources: International Agency for Research on Cancer, Clinical Trials Service Unit/Oxford University, World Health Organization); and Health Effects of Arsenic Longitudinal Study [HEALS, funding sources: NIH (grants P42ES010349, R01CA102484, R01CA107431)]. For the Life Span Study [LSS], the Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan, is a private, non-profit foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the U.S. Department of Energy (DOE), the latter in part through DOE Award (DE-HS0000031) to the National Academy of Sciences. This publication was supported by RERF Research Protocol RP-A03-10. Other Japanese cohorts—Three Prefecture Cohort Study Aichi (3-Prefecture Aichi), Japan Public Health Centre-based Prospective Study (JPHC1 and JPHC2), Three Prefecture Cohort Study Miyagi (3-Prefecture Miyagi), Miyagi Cohort Study (Miyagi) and Ohsaki National Health Insurance Cohort Study (Ohsaki)—are supported by the Grant-in-aid for Cancer Research, the Grant for the Third Term Comprehensive Control Research for Cancer, the Grant for Health Services, the Grant for Medical Services for Aged and Health Promotion, the Grant for Comprehensive Research on Cardiovascular and Life-style Related Diseases from the Ministry of Health, Labour and Welfare, Japan, and the Grant for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. Japan Public Health Centre-Based Prospective Study (JPHC1 and JPHC2) are also supported by the National Cancer Centre Research and Development Fund.

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W.Z. conceived of, designed and supervised the study. J.J.Y., D.Y., X.O.S., W.W. and W.Z. contributed to data analysis, data interpretation and writing the manuscript. X.O.S., S.R., S.A., E.S., R.I., P.C.G., J.H., S.T., Y.T.G., J.M.Y., W.P.K., A.S., Y.T., I.T., Y.S., K.M., Y.O.A., S.K.P., Y.C., M.S.P., D.G., N.S., H.C., R.W., E.G., S.Z., S.K., H.I., M.H.S., H.A., P.B., K.S.C., Y.L.Q., N..R, M.I., D.K. and W.Z. contributed to data collection and provided study materials and administrative/technical support. All authors contributed to critical revision of the manuscript for important intellectual content and approved the final version of the manuscript.

Conflict of Interest

None declared.

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