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Original Contribution

Changes in Smoking Behavior and Subsequent Mortality Risk During a 35-Year Follow-up of a Cohort in Xi'an, China

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Prospective evidence of the associations of smoking cessation with chronic obstructive pulmonary disease (COPD) and other causes of death in Asia is scarce. Previous studies, which were mostly based on baseline smoking behavior only, were subject to sick-quitter bias and misclassification resulting from changes in smoking behavior during follow-up. We followed up a cohort for 18 years (1976–1994) to assess changes in smoking behavior and then for an additional 17 years (1994–2011) to examine the relationships of continuing to smoke and new quitting with mortality risk in 1,494 Chinese people (961 men, 533 women). Of the baseline current smokers, 38.7% quit between 1976 and 1994. From 1994 to 2011, a total of 488 persons (359 men, 129 women) died. Ever smokers had increased risks of lung cancer, coronary heart disease, thrombotic stroke, and COPD, with dose-response relationships. For all tobacco-related mortality, the relative risk for new quitters compared with continuing smokers was 0.68 (95% confidence interval: 0.46, 0.99) for those who had quit 2–7 years previously and 0.56 (95% confidence interval: 0.37, 0.85) for those who had quit 8 years or more previously. The corresponding relative risks were 0.69 and 0.45 for lung cancer, 0.78 and 0.51 for coronary heart disease, 0.76 and 0.84 for thrombotic stroke, and 0.89 and 0.61 for COPD, respectively. Smoking increased tobacco-related deaths, and particularly deaths from COPD, in China, whereas quitting at middle age (at approximately 50 years of age) substantially reduced the risks of death from these causes. The benefits of smoking cessation were underestimated in previous studies that did not use repeated measures.

Chinese; chronic obstructive pulmonary disease; cohort study; quitting; smoking; tobacco-related mortality

Abbreviations: CHD, coronary heart disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; RR, relative risk; SD, standard deviation; SHS, secondhand smoke.

Editor's note: *An invited commentary on this article appears on page 1071, and the authors' response appears on page 1074.*

In China, the risk of tobacco-related death has been demonstrated in several prospective studies (1–6) and 2 large case-control studies (7, 8). Whereas there is strong evidence of the benefits of smoking cessation in the West (9–11) and in developed countries in Asia, such as Japan (12, 13) and Singapore (14), evidence from prospective studies is scarce in China and other developing countries in which the tobacco epidemic is at an early stage and smoking cessation is uncommon. Our previous study of an elderly Chinese cohort, which was based on baseline smoking status only and in which 52% of participants were former smokers, showed that compared with current smokers, former smokers had lower risks of total mortality (excess risk reduction of 56%) and death from coronary heart disease (CHD) but had a greater risk of death from chronic obstructive pulmonary disease (COPD) (15). However, a lack of repeated measures of tobacco use is a common problem in studies of the associations of smoking

and quitting with subsequent mortality (1–6, 12, 13, 15). For COPD in particular, smoking-related lung disease may cause smokers to stop smoking 5 or 10 years before death; failure to exclude the initial years of follow-up after smoking cessation will substantially underestimate the benefits of smoking cessation. Two systematic reviews on COPD and smoking cessation showed that former smokers had a higher relative risk of death from respiratory diseases than did current smokers in Asia and suggested that further research is necessary, especially in China and in other populations in which the tobacco epidemic is at an early stage and the COPD prevalence is higher than that in developed countries (16, 17). It is a common misperception in less-developed countries that smoking in older people is not very harmful and that quitting after lifelong smoking could cause more harm than good (15). Most of the previous cohort studies had a major methodological limitation in that smoking status was only recorded at baseline, with no repeated measures to collect information on changes in smoking behaviors (quitting or relapse) during follow-up (16, 17). Hence, prospective evidence based on smoking status at baseline only is subject to survivor bias or sick-quitter bias, and changes in smoking status during follow-up could lead to misclassification bias. Furthermore, the rates at which people quit in middle and old age are usually higher than that at younger ages. Since 2006, there have been 6 cohort studies with repeated measures of tobacco use showing that quitting smoking during follow-up was associated with reduced subsequent mortality (14, 18–22). Our cohort of middle-aged men and women from Xi'an, China, in whom the percentage of former smokers changed from 4.0% at the 1976 baseline to 38.7% at the 1994 follow-up, has provided us a good opportunity to examine changes in smoking status between 1976 and 1994 and to relate these to mortality risks, particularly for COPD, in continuing smokers, new quitters, and never smokers during 1994–2011, with a total follow-up of 35 years.

METHODS

Study cohort and follow-up

Details of the methods were described previously in a 20-year follow-up study that showed that smoking was a major risk factor for total mortality (1). Briefly, from March to May 1976, a cross-sectional survey of risk factors for and prevalence of cardiovascular diseases was carried out in workers at a machinery factory in Xi'an, China. This cohort included 1,696 persons (1,124 men and 572 women) for whom we collected data on demographic factors, systolic and diastolic blood pressure, serum cholesterol and triglyceride levels, height, weight, alcohol consumption, and smoking.

From January to March 1994, we re-surveyed all 1,696 subjects in the 1976 cohort and collected information from 1,535 surviving participants (994 men and 541 women) about changes in health and smoking status (including secondhand smoke exposure) since 1976. Physical examinations were carried out by trained nurses and physicians, and face-to-face interviews were conducted by 4 trained interviewers. The 154 subjects who died during 1976–1994 and the 7 who were lost to follow-up (6 men and 1 woman) were excluded. Of the 1,535 subjects, 26 who were nonsmokers in 1976 became former (7 men and 4 women) or current (12 men and 3 women) smokers after 1976 through 1994, and of 15 former smokers (14 men and 1 woman) in 1976, there were 2 men who resumed smoking and became current smokers afterward. Because the small numbers would not allow for any meaningful analysis, these subjects were also excluded (Web Figure 1, available at http://aje.oxfordjournals.org/). The present analysis comprised 1,494 subjects (961 men, 533 women), including never smokers, continuing current smokers (through 1994), and new quitters (smokers who quit during 1976–1994), with a further follow-up of 17 years from 1994 to 2011 to study the benefits of smoking cessation after the 1976 baseline survey through 1994.

Vital status of all surviving subjects at the 1994 follow-up was triennially tracked and assessed by 2 senior doctors from the factory hospital. Because payment of employee pensions and post-death welfare benefits of all employees must be reported to the personnel department and confirmed by the factory hospital, the follow-up of deaths was simple and complete. If a subject did not have a confirmed death record, he or she was considered to be alive. Causes of death were obtained from death certificates from hospitals or local police departments. Hospital records were reviewed by 2 senior physicians (who were blinded to the smoking status of the subjects) from the 4th Military Medical University teaching hospital and then coded according to the *International Classification of Diseases, 9th Revision*. Ethics approvals were obtained from the ethics committees of Chinese People's Liberation Army General Hospital (EC0411-2001) and the Faculty of Medicine at the University of Hong Kong (EC1246-99).

Definitions of tobacco use and exposure

We defined an ever smoker as a person who had smoked at least 1 cigarette daily for 1 year or more. Current smokers were persons who were current smokers at either the 1976 baseline or the 1994 follow-up. Continuing current smokers were persons who smoked at the 1976 baseline and who were still smoking at 1994 follow-up. Former smokers were those who had quit for at least 2 years in 1976 or in 1994. New quitters were current smokers at the 1976 baseline who had stopped smoking during 1976 to 1994 and for whom the duration of quitting at 1994 was 2 years or more (21). Never smokers were never smokers both in 1976 and 1994, that is, persons who reported never having smoked regularly and who had not smoked up to 100 cigarettes in their lifetime. Ever smokers included new quitters and continuing current smokers in present study. Secondhand smoke (SHS) exposure was defined as exposure to another person's tobacco smoke at home or in the workplace for at least 15 minutes daily for more than 1 day per week (23).

Diagnoses of outcomes

CHD and stroke were defined using the World Health Organization/Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) criteria (24). Myocardial infarction was diagnosed using a representative set of electrocardiogram results, cardiac enzyme values,

and typical symptoms. Stroke and its subtypes were defined as events that required hospitalization, and 86 (85.1%) of 101 cases were confirmed by computed tomography and/or magnetic resonance imaging. According to Global Strategy for Diagnosis, Management, and Prevention of COPD diagnostic criteria (25), 62 (88.5%) of the 70 subjects who died of COPD were diagnosed before death as having COPD because they had a post-bronchodilator forced expiratory volume in 1 second/forced vital capacity ratio of less than 0.7, and normative values of forced expiratory volume in 1 second in the Chinese population were adjusted with conversion factors recommended by Zheng and Zhong in 2002 (26). Of the 150 cases of cancer that led to death, 87.3% (131 cases) had histopathological diagnoses, whereas the remaining 12.7% (19 cases) were diagnosed using clinical or radiological evidence. In our study, we defined smoking-related cancers using the 2004 US Surgeon General's report; these included cancer of the lip, mouth, pharynx, esophagus, larynx, pancreas, bladder and kidney, cervix, stomach, and trachea and lung, as well as acute myeloid leukemia (27). However, we observed only 7 cancer types with pathological diagnoses in the present data set; there were no cancers diagnosed in other minor sites and therefore no data were available.

Statistical analysis

The data were entered (double entry) using EpiData, version 3.1 (EpiData, Odense, Denmark) and analyzed using SPSS, version 19.0 (SPSS Inc., Chicago, Illinois) for Windows (Microsoft, Redmond, Washington). Multivariable Cox proportional hazard regression models were used to calculate relative risks and 95% confidence intervals. For consistency with our previous study (1, 15), the potential confounders for which we adjusted included age, marital status, occupation, educational level, diastolic blood pressure, triglyceride and total cholesterol levels, body mass index (weight (kg)/height $(m)^2$), and history of drinking for each sex separately. The interaction between smoking and sex was tested, and if it was not significant, men and women were analyzed together with an adjustment for sex. We analyzed and adjusted for data on history of chronic diseases (e.g., CHD, stroke, diabetes mellitus, COPD, and cancer) and SHS exposure collected in 1994. We conducted sensitivity analyses after excluding deaths that occurred during the first 2 years and 5 years of follow-up (after 1994). Kaplan-Meier survival analysis and log-rank tests were used to compare the cumulative survival rates for the major causes of death.

RESULTS

In 1976, of the 1,696 subjects (mean age, 44.7 (standard deviation, 5.9) years), 54% of men and 11.9% of women were current smokers and few were former smokers (25 men and 3 women) (1). Subjects were enrolled in the study from January 1 to March 1, 1994. Through July 1, 2011, a total of 1,006 (602 men and 404 women) of the 1,494 subjects that we included from the 1994 follow-up were alive and 488 (359 men and 129 women) had died. In 1994, the mean age of the cohort members was 60.5 (standard deviation, 5.2) years (range, 51.5–87.8 years). The number of person-years of follow-up since 1994 was 22,076, and the mean duration of follow-up was 14.8 years.

During 1976–1994, the percentage of participants who were current smokers in 1976 and who quit was 38.7% (38.3% in men, 41.9% in women). In the 226 new quitters in 1994, the mean time since quitting was 8.4 (standard deviation, 3.5) years (range, 2.2–16.1 years), and the mean age at quitting was 52.3 (standard deviation, 6.5) years (range, 38–81 years).

Table 1 shows that in 1994, there were 910 never smokers (60.9%), 226 new quitters (15.1%), and 358 continuing current smokers (24.0%). New quitters had lower systolic and diastolic blood pressures and lower prevalences of hypertension, CHD, stroke, diabetes, and COPD than did continuing current smokers.

Compared with never smokers, ever smokers (new quitters plus continuing current smokers) had increased risks of lung cancer (relative risk (RR) = 2.91; 95% CI: 1.47, 5.79), CHD (RR = 1.97; 95% CI: 1.24, 3.15), thrombotic stroke (RR = 2.25; 95% CI: 1.24, 4.07), COPD (RR = 1.91; 95% CI: 1.15, 3.19), all tobacco-related diseases (RR = 2.07; 95% CI: 1.62, 2.66), and all-cause mortality (RR = 1.66; 95% CI: 1.36, 2.02) (Web Table 1). Because most interaction terms between sex and smoking on these deaths were not significant (except for hemorrhagic stroke and all stroke), data for men and women were pooled.

Table 2 shows dose-response associations of increasing smoking categories with all-cause mortality and mortality from the following causes: lung cancer, all tobacco-related cancers, CHD, thrombotic stroke, cardiovascular disease, COPD, all respiratory diseases, and all tobacco-related causes (P for trend from 0.010 to <0.001). Compared with never smokers, the relative risk of CHD mortality was 1.36 (95% CI: 0.57, 3.26) in new quitters with a history of less than 20 pack-years of smoking, 1.58 (95% CI: 0.72, 3.47) in new quitters with a history of 20 or more pack-years of smoking, 2.13 (95% CI: 1.15, 3.95) in continuing current smokers with a history of less than 35 pack-years of smoking, and 2.73 (95% CI: 1.44, 5.16) in continuing current smokers with a history of 35 or more pack-years of smoking. The corresponding relative risks were 1.06, 2.96, 2.44, and 5.34, respectively, for lung cancer and 1.27, 1.85, 2.05 and 2.20, respectively, for COPD (all P for trend <0.01).

Table 3 shows a significant reduction in the risk of all-cause mortality and cause-specific mortality in new quitters. Compared with continuing current smokers, new quitters who had stopped smoking for 2–7 years had a relative risk for all tobacco-related mortality of 0.68 (95% CI: 0.46, 0.99), and those who had stopped at least 8 years had a relative risk of 0.56 (95% CI: 0.37, 0.85). The corresponding relative risks were 0.69 and 0.45 for lung cancer, 0.78 and 0.51 for CHD, 0.76 and 0.84 for thrombotic stroke, and 0.89 and 0.61 for COPD, respectively (all P for trend <0.01). Kaplan-Meier survival function curves for CHD, COPD, all tobacco-related causes, and all causes by smoking status and years since quitting are shown in Figure 1 (for all log-rank tests, $P < 0.05$).

The stratification analysis by age (<60 years and ≥60 years) in 1994 showed the same patterns of decreased risks of all-cause mortality and cause-specific mortality both

Table 1. Characteristics of 1,494 Subjects by Smoking Status at 1994, Xi'an, China, 1994–2011

Characteristic	Never Smokers ($n = 910$)		New Quitters ($n = 226$)		Continuing Current Smokers ($n = 358$)		*P* Value
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	
Age, years	60.2 (5.0)		60.8 (5.2)		61.2 (5.4)		0.007
Systolic blood pressure, mm Hg	127.6 (18.0)		126.9 (17.3)		127.6 (17.8)		0.85
Diastolic blood pressure, mm Hg	83.1 (10.4)		82.9 (10.0)		83.7 (10.2)		0.59
Total cholesterol concentration, mmol/L	5.3 (1.0)		5.1 (0.9)		5.1 (0.9)		0.004
Triglyceride concentration, mmol/L	1.6 (1.1)		1.4 (0.9)		1.4 (1.0)		0.036
Body mass index[a]	23.5 (2.7)		23.0 (2.7)		22.6 (3.1)		<0.001
Waist circumference, cm	87.1 (9.4)		88.0 (9.9)		87.8 (9.0)		0.32
Sex							<0.001
Male		48.2		88.5		89.9	
Female		51.8		11.5		10.1	
Educational level, years							0.47
0–6		33.8		28.8		32.7	
7–9		37.8		41.2		36.3	
10–12		17.3		21.2		18.4	
≥13		11.1		8.8		12.6	
Marital status							0.43
Married		88.7		89.8		88.8	
Single or divorced		1.4		2.2		2.8	
Widowed		9.9		8.0		8.4	
Occupation							0.009
Technical		14.9		11.1		10.6	
Cadre		25.1		35.0		31.0	
Worker		60.0		54.0		58.4	
Current alcohol drinking		8.9		18.6		30.4	
Existing diseases							<0.001
Hypertension		30.4		19.5		31.3	
CHD		16.8		17.3		27.1	0.003
Stroke		5.6		3.1		7.5	<0.001
Diabetes mellitus		6.7		8.0		14.0	0.077
COPD		3.6		4.4		8.7	<0.001
Cancer		1.2		1.7		1.6	0.001

Abbreviation: CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; SD, standard deviation.
[a] Weight (kg)/height $(m)^2$.

in middle-aged new quitters and older new quitters (Table 4). Compared with continuing current smokers, new quitters less than 60 years of age had a relative risk for all tobacco-related mortality of 0.67 (95% CI: 0.40, 1.13), and those 60 years of age or older had a relative risk of 0.59 (95% CI: 0.38, 0.90). The corresponding relative risks were 0.51 and 0.72 for CHD, 0.69 and 0.84 for thrombotic stroke, 0.63 and 0.53 for lung cancer, and 0.83 and 0.67 for COPD, respectively.

The results in 1,020 subjects who did not have 5 existing diseases (CHD, stroke, diabetes, COPD, and cancer) at the 1994 follow-up were similar (Table 5 and Web Table 2). Sensitivity analyses that were conducted after excluding the deaths that occurred during the first 2 years (40 deaths) and 5 years (120 deaths) of follow-up and that were adjusted for exposure to SHS showed results consistent with those in Table 3. The adjusted relative risks of COPD were 1.77 (95% CI: 0.89, 3.49) in new quitters and 2.26 (95% CI: 1.26, 4.06) in continuing current smokers after we excluded deaths that occurred in the first 2 years (Web Table 3). The corresponding relative risks were 1.52 (95% CI: 0.68, 3.38) and 2.04 (95% CI: 1.04, 4.02), respectively, after excluding deaths that occurred in the first 5 years (Web Table 4) and 1.61 (95% CI: 0.82, 3.16) and 1.86 (95% CI: 1.03, 3.33), respectively, after adjustment for exposure to SHS (Web Table 5).

Table 2. Adjusted Relative Risks of Major Causes of Death by Smoking Status and Pack-years of Smoking in 1,494 Subjects, Xi'an, China, 1994–2011

Cause of Death	Never Smokers ($n = 910$)		New Quitters						Continuing Current Smokers						*P* for Trend
			<20 Pack-years ($n = 114$)			≥20 Pack-years ($n = 112$)			<35 Pack-years ($n = 188$)			≥35 Pack-years ($n = 170$)			
	No. of Deaths	RR	No. of Deaths	RR[a]	95% CI	No. of deaths	RR[a]	95% CI	No. of Deaths	RR[a]	95% CI	No. of Deaths	RR[a]	95% CI	
All causes	238	1.00	41	1.48	1.06, 2.08	43	1.32	0.94, 1.84	68	1.49	1.13, 1.98	98	2.29	1.77, 2.96	<0.001
All tobacco-related causes[b]	136	1.00	24	1.59	1.02, 2.48	28	1.52	1.00, 2.32	51	2.03	1.45, 2.85	71	3.00	2.18, 4.12	<0.001
All vascular diseases	95	1.00	16	1.40	0.82, 2.42	16	1.23	0.71, 2.12	24	1.30	0.82, 2.08	37	2.23	1.47, 3.38	0.001
CHD	43	1.00	6	1.36	0.57, 3.26	8	1.58	0.72, 3.47	15	2.13	1.15, 3.95	16	2.73	1.44, 5.16	0.001
All stroke	52	1.00	11	1.57	0.80, 3.06	8	1.02	0.47, 2.18	9	0.79	0.38, 1.64	21	1.93	1.11, 3.34	0.153
Hemorrhagic stroke	28	1.00	2	0.42	0.10, 1.80	6	1.14	0.46, 2.82	3	0.40	0.12, 1.32	6	0.76	0.30, 1.90	0.296
Thrombotic stroke	24	1.00	9	3.53	1.58, 7.89	2	0.69	0.16, 2.99	6	1.44	0.57, 3.64	14	3.76	1.78, 7.95	0.008
All cancers	68	1.00	13	1.47	0.80, 2.70	14	1.45	0.80, 2.62	23	1.55	0.94, 2.54	32	2.38	1.50, 3.78	<0.001
All tobacco-related cancers[c]	33	1.00	5	1.11	0.43, 2.90	9	1.82	0.85, 3.90	17	2.30	1.24, 4.25	24	3.66	2.05, 6.54	<0.001
Lung cancer	15	1.00	2	1.06	0.24, 4.75	6	2.96	1.09, 8.05	8	2.44	0.98, 6.06	14	5.34	2.33, 12.21	<0.001
All respiratory diseases	37	1.00	5	1.39	0.54, 3.61	9	1.63	0.76, 3.48	13	2.12	1.09, 4.10	17	2.29	1.22, 4.27	0.003
COPD	32	1.00	4	1.27	0.44, 3.66	9	1.85	0.85, 4.02	11	2.05	1.00, 4.19	14	2.20	1.11, 4.35	0.008

Abbreviations: CHD, coronary heart disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; RR, relative risk.

[a] Adjusted for age, sex, marital status, occupation, educational level, alcohol drinking, diastolic blood pressure, triglyceride and total cholesterol levels, and body mass index (weight (kg)/height $(m)^2$).

[b] All tobacco-related causes included CHD, ischemic stroke, COPD, pneumonia, and cancer of lung, stomach, esophagus, larynx, nose, pancreas, and bladder.

[c] All tobacco-related cancers included cancer of lung, stomach, esophagus, larynx, nose, pancreas, and bladder.

Table 3. Adjusted Relative Risks of Major Causes of Death by Smoking Status and Number of Years Since Quitting in 1,494 Subjects, Xi'an, China, 1994–2011

Cause of Death	Continuing Current Smokers ($n = 358$)		New Quitters by Years Since Quitting						Never Smokers ($n = 910$)			*P* for Trend
			2–7 ($n = 96$)			≥8 ($n = 130$)						
	No. of Deaths	RR	No. of Deaths	RR[a]	95% CI	No. of Deaths	RR[a]	95% CI	No. of Deaths	RR[a]	95% CI	
All causes	166	1.00	41	0.89	0.63, 1.16	43	0.64	0.46, 0.90	238	0.53	0.42, 0.65	<0.001
All tobacco-related causes	122	1.00	24	0.68	0.46, 0.99	28	0.56	0.37, 0.85	136	0.40	0.31, 0.53	<0.001
All vascular diseases	61	1.00	14	0.82	0.46, 1.47	18	0.71	0.42, 1.20	95	0.58	0.41, 0.82	0.002
CHD	31	1.00	7	0.78	0.34, 1.78	7	0.51	0.22, 1.16	43	0.42	0.25, 0.70	0.001
All stroke	30	1.00	7	0.86	0.38, 1.97	12	0.99	0.52, 1.99	52	0.75	0.46, 1.22	0.27
Hemorrhagic stroke	9	1.00	3	1.24	0.33, 4.63	5	1.48	0.49, 4.45	28	1.73	0.79, 3.79	0.16
Thrombotic stroke	20	1.00	4	0.76	0.26, 2.24	7	0.84	0.35, 1.99	24	0.41	0.21, 0.79	0.009
All cancers	55	1.00	12	0.82	0.44, 1.53	15	0.71	0.40, 1.25	68	0.52	0.35, 0.77	0.001
All tobacco-related cancers	41	1.00	5	0.45	0.18, 1.45	9	0.54	0.26, 1.12	33	0.34	0.21, 0.57	<0.001
Lung cancer	22	1.00	4	0.69	0.24, 2.02	4	0.45	0.16, 1.33	15	0.28	0.13, 0.57	<0.001
All respiratory diseases	30	1.00	8	0.88	0.40, 2.00	6	0.54	0.22, 1.30	37	0.45	0.27, 0.77	0.002
COPD	25	1.00	7	0.89	0.40, 2.21	6	0.61	0.26, 1.54	32	0.47	0.27, 0.83	0.007

Abbreviations: CHD, coronary heart disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; RR, relative risk.

[a] Adjusted for age, sex, marital status, occupation, educational level, alcohol drinking, diastolic blood pressure, triglyceride and total cholesterol levels, and body mass index (weight (kg)/height (m)^2).

DISCUSSION

The benefits of smoking cessation in reducing the rate of deaths from all causes and many specific causes have been confirmed by numerous studies, and quitting by 40 years of age eliminated nearly all the excess smoking related deaths in previous studies (9–13). However, most studies on COPD and smoking cessation in Asia, especially in China and other populations with higher prevalences of COPD, have not shown the beneficial effects of stopping smoking on COPD (15–17). One explanation is that the reasons for quitting are different in developed versus developing countries. In the former, smokers are more likely to quit in order to reduce disease risks while they are still relatively healthy, whereas in developing countries in which the hazards of smoking are much less widely known, the main reason for quitting is ill health (15, 17, 28). Consequently, the beneficial effects of smoking cessation are likely to be underestimated (the "sick-quitter" effect).

Also, previous cohort studies in Asia, as well as many conducted elsewhere, had a major methodological limitation in that smoking status was recorded only at baseline, with no repeated measures. Other limitations were the short duration of follow-up, the inclusion of subjects with the diseases of interest at baseline, and the lack of adjustment for exposure to SHS and/or other environmental air pollutants (15–17).

An important advantage of our study is that we collected repeated measures at the 1994 follow-up of subjects who were recruited in 1976, including ascertainment of smoking status, and the never and current smokers in 1976 were reconfirmed in 1994. We excluded 28 subjects who were former smokers in 1976 (13 of them died from 1976 to 1994) because their deaths could have been due to the sick-quitter effect. We also excluded 41 subjects with other changes in smoking status from 1994 to 1976 to avoid misclassification of exposure. Hence, we were able to focus on new quitters to examine the effect of quitting at middle age (the mean age at quitting was approximately 52 years). It is interesting that new quitters in the present study were healthier than were continuing current smokers. They also had lower systolic and diastolic blood pressures and lower prevalences of chronic disease histories. Most previous cohort studies on smoking cessation compared existing former and current smokers based on smoking status only at baseline, and hence the beneficial effects of quitting on COPD and other diseases could have been underestimated or an unexpected greater risk in quitters could have been observed.

So far, there have been 6 cohort studies that examined the relationship between changes in smoking status assessed using repeated measures of tobacco use and subsequent mortality: 2 in the United States (19, 21) and 1 each in Singapore, Norway, Israel, and Scotland (14, 18, 20, 22). On each subsequent repeated questionnaire, participants reported whether they currently smoked cigarettes, and at the beginning of each follow-up cycle, they were reclassified by smoking status (never, former, or current), by the number of cigarettes smoked and duration of smoking among current smokers, and by the time since quitting among former smokers. Two studies that categorized smoking behaviors as increased, maintained, reduced, or stopped found that there

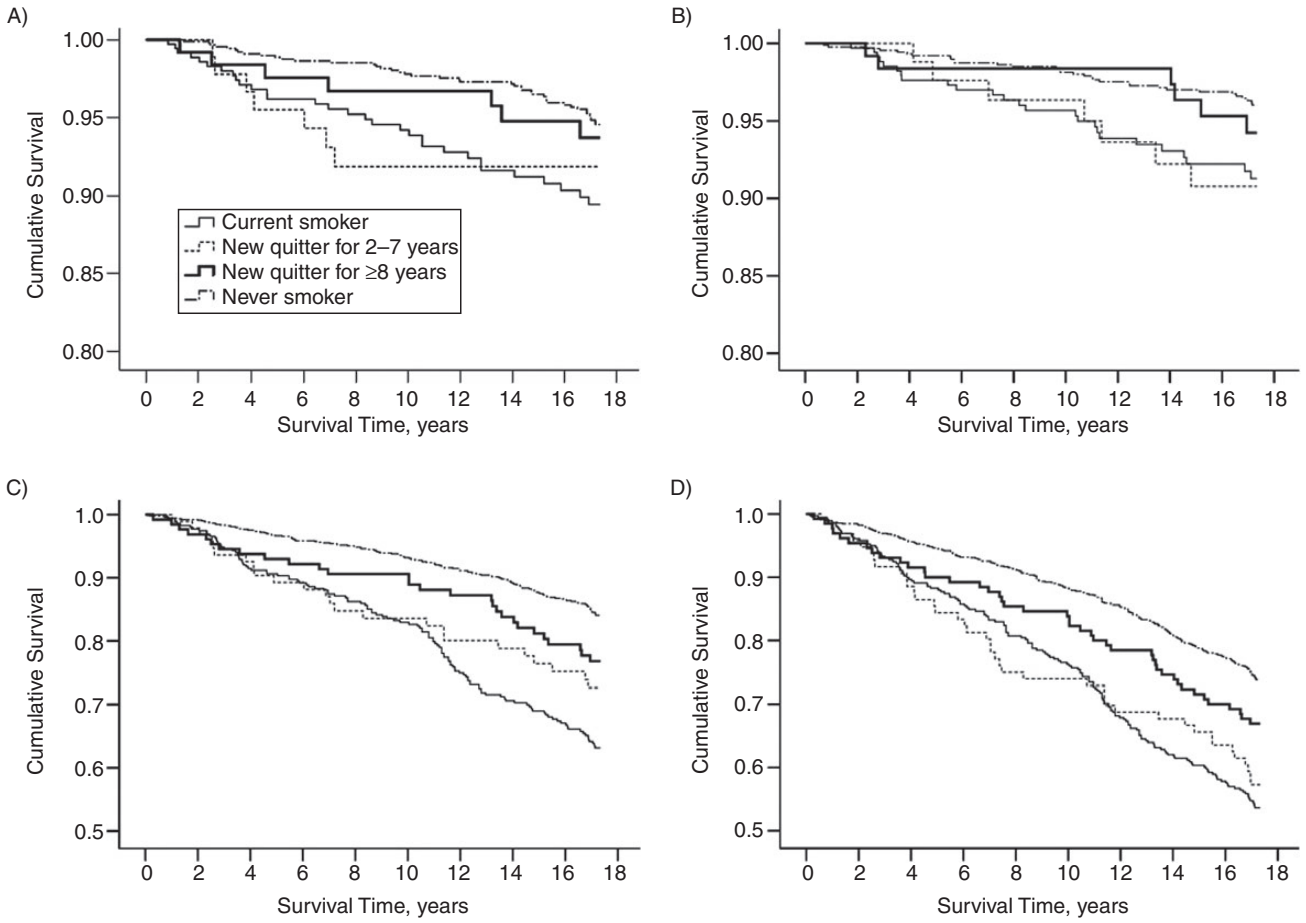

Figure 1. Survival curves for A) coronary heart disease ($P = 0.001$), B) chronic obstructive pulmonary disease ($P = 0.001$), C) all tobacco-related causes ($P < 0.001$), and D) all causes ($P < 0.001$) by smoking status and the years since smoking cessation, Xi'an, China, 1994–2011. *P* values are for the log-rank test.

were benefits associated with smoking reduction and cessation (20, 22). Two studies found that among former smokers, a greater number of years since quitting was associated with a reduction in the risk of death from most of the tobacco-related diseases and that the excess risk for all-cause mortality decreased after quitting for 20 years to the level of a never smoker, with different time frames for risk reduction observed across different outcomes (19, 21). The Norwegian population-based cohort study reported that continuing to smoke strongly increased and quitting smoking decreased the risk of death in both women and men who were between 40 and 70 years of age (18). In 2013, a report from Singapore (14), like our study, classified smoking status as current smokers, new quitters (reassessed at an interval of 5 years), long-term quitters (former smokers at baseline), and never smokers and showed that new quitters had a 16% reduction in total and CHD mortality and a 24% reduction in lung cancer mortality. With the exception of the US Nurses Study (19) and the study from Singapore (14), none the above observed a reduction in COPD mortality after quitting.

Most previous prospective studies of persons from mainland China did not examine mortality rates in former smokers (1–4, 6, 7). Four population-based cohort studies from China (5, 15, 29, 30) and 1 cohort study of Chinese people from Singapore (31) reported on the rate of COPD mortality in former smokers (not new quitters). Three of them showed that COPD mortality rates were higher in former smokers than in never and current smokers, results that were strikingly in opposition to the findings that quitting had beneficial effects on the risk of other major causes of death (15, 29, 30). Only 2 large cohorts studies, one on elderly Chinese persons in Hong Kong (5) and the other from Singapore Chinese Health Study (31), found that the relative risks of all-cause mortality in former smokers lay between those of never and current smokers. However, 4 studies included only participants who were 60 years of age or older, had short follow-up periods (less than 10 years in 3 studies), and had small numbers of COPD deaths (5, 29–31). Our study was the only cohort study in China that started with current smokers at baseline (in 1976) and compared persons who continued to smoke with those who had quit subsequently during follow-up (1976–1994); it is also

Table 4. Adjusted Relative Risks of Major Causes of Death by Smoking Status and Age in 1994, Xi'an, China, 1994–2011

Cause of Death	Continuing Current Smokers		New Quitters				Never Smokers				*P* for Trend
	No.	RR	No.	RR[a]	95% CI	*P* Value	No.	RR[a]	95% CI	*P* Value	
Subjects <60 Years of Age (n = 835)											
Total subjects	177		117				541				
Cause of death											
All causes	65	1.00	35	0.78	0.52, 1.19	0.251	93	0.47	0.33, 0.67	<0.001	<0.001
All tobacco-related causes	47	1.00	22	0.67	0.40, 1.13	0.131	51	0.34	0.22, 0.54	<0.001	<0.001
All vascular diseases	26	1.00	14	0.80	0.42, 1.54	0.504	42	0.58	0.34, 1.00	0.048	0.046
CHD	13	1.00	5	0.51	0.18, 1.44	0.201	23	0.45	0.21, 0.96	0.038	0.043
Thrombotic stroke	9	1.00	4	0.69	0.21, 2.28	0.545	8	0.37	0.13, 1.09	0.071	0.070
All cancers	22	1.00	12	0.80	0.40, 1.64	0.548	30	0.46	0.25, 0.86	0.014	0.013
Lung cancer	10	1.00	4	0.63	0.19, 2.06	0.448	3	0.18	0.10, 0.48	0.001	0.001
All respiratory diseases	9	1.00	5	0.81	0.27, 2.43	0.700	8	0.28	0.09, 0.83	0.022	0.021
COPD	8	1.00	5	0.83	0.30, 2.29	0.745	7	0.30	0.10, 0.96	0.042	0.041
Subjects ≥60 Years of Age (n = 659)											
Total subjects	181		109				369				
Cause of death											
All causes	101	1.00	49	0.72	0.51, 1.02	0.062	145	0.59	0.45, 0.78	<0.001	<0.001
All tobacco-related causes	75	1.00	30	0.59	0.38, 0.90	0.015	85	0.44	0.32, 0.62	<0.001	<0.001
All vascular diseases	35	1.00	18	0.73	0.41, 1.30	0.291	53	0.59	0.37, 0.94	0.025	0.026
CHD	18	1.00	9	0.72	0.32, 1.62	0.423	20	0.41	0.20, 0.82	0.012	0.011
Thrombotic stroke	11	1.00	7	0.84	0.32, 2.18	0.718	16	0.42	0.18, 0.98	0.045	0.038
All cancers	33	1.00	15	0.73	0.39, 1.35	0.310	38	0.58	0.35, 0.97	0.037	0.038
Lung cancer	12	1.00	4	0.53	0.17, 1.67	0.278	12	0.50	0.21, 1.21	0.123	0.128
All respiratory diseases	21	1.00	9	0.62	0.28, 1.38	0.242	29	0.51	0.28, 0.93	0.029	0.032
COPD	17	1.00	8	0.67	0.29, 1.59	0.364	25	0.53	0.27, 1.03	0.061	0.064

Abbreviations: CHD, coronary heart disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; RR, relative risk.

[a] Adjusted for age, sex, marital status, occupation, educational level, alcohol drinking, diastolic blood pressure, triglyceride and total cholesterol levels, and body mass index (weight (kg)/height $(m)^2$).

the only one that had a long duration (17 years) of further follow-up for mortality. Our results showed that the benefits of quitting at middle age (approximately 50 years of age) for 2–7 years to 8 or more years were substantial, with risk reductions of 32% and 44%, respectively, for all tobacco-related causes and of 11% and 39%, respectively, for COPD when compared with continuing current smokers. CHD and lung cancer had greater risk reductions (22% and 49%, respectively; Table 3), which are consistent with previous studies (5, 9–15, 19, 21). We also noted that the risk reduction in subjects with COPD associated with having stopped smoking for least 8 years should be greater than that for subjects with 7 years or less since cessation (Figure 1) and suggest that benefits from smoking cessation on COPD might be delayed more than those for cardiovascular diseases. Our finding was consistent with the results from the studies in the United States and Singapore (14, 19). The American Cancer Society Cancer Prevention Study (CPS-II) also showed that the reduction in risk was observed only in former smokers who had quit for more than 10 years (10). Our stratification analysis by age (<60 years and ≥60 years) at 1994 showed that there were benefits to smoking cessation at both middle and older age. Although cessation at middle age appeared to show a greater protective effect on cardiovascular disease and cessation at older age seemed more protective for lung cancer and COPD, the differential effects of quitting at different ages need to be confirmed in large cohort studies. Such results are especially relevant for health education of middle-aged and elderly Chinese and Asians.

In the past few decades, most people in China have been unaware of the health hazards due to smoking (23, 28, 32), and thus bias due to over-reporting of smoking or quitting in our subjects, including those with some chronic diseases, should be minimal. Sensitivity analyses showed that bias due to the sick-quitter effect was minimal (Web Tables 3 and 4). After adjustment for SHS exposure (72.7% in present study), we found similar results (Web Table 5). Another advantage of the cohort design is the lack of recall bias, as information about exposure was collected before follow-up of disease outcomes. Moreover, our results regarding the excess risks

Table 5. Adjusted Relative Risks of Major Causes of Death by Smoking Status in 1,020 Subjects Without 5 Existing Diseases[a], Xi'an, China, 1994–2011

Cause of Death	Never Smokers ($n = 657$)		New Quitters ($n = 165$)				Continuing Current Smokers ($n = 198$)				*P* for Trend
	No. of Deaths	RR	No. of Deaths	RR[b]	95% CI	*P* Value	No. of Deaths	RR[b]	95% CI	*P* Value	
All causes	131	1.00	46	1.39	0.98, 1.98	0.07	70	1.81	1.32, 2.49	<0.001	<0.001
All tobacco-related causes	62	1.00	27	1.86	1.15, 2.99	0.011	45	2.68	1.74, 4.11	<0.001	<0.001
All vascular diseases	51	1.00	17	1.36	0.77, 2.42	0.29	24	1.66	0.97, 2.82	0.06	0.046
CHD	24	1.00	6	1.18	0.46, 3.03	0.73	10	1.84	0.81, 4.18	0.15	0.04
All stroke	27	1.00	12	1.69	0.83, 3.45	0.15	14	1.61	0.80, 3.24	0.19	0.14
Hemorrhagic stroke	17	1.00	5	0.89	0.32, 2.47	0.82	7	0.99	0.39, 2.52	0.99	0.95
Thrombotic stroke	10	1.00	7	2.69	1.05, 9.15	0.04	7	3.38	1.24, 9.24	0.02	0.013
All cancers	45	1.00	13	1.12	0.59, 2.13	0.73	30	2.11	1.26, 3.52	0.004	0.006
All tobacco-related cancers	21	1.00	9	1.53	0.68, 3.44	0.31	23	3.23	1.68, 6.20	<0.001	<0.001
Lung cancer	9	1.00	7	3.06	1.08, 8.69	0.04	14	5.06	1.99, 12.86	0.001	0.001
All respiratory diseases	8	1.00	5	2.40	0.70, 8.19	0.16	6	3.37	1.09, 10.45	0.04	0.01
COPD	6	1.00	5	2.81	1.02, 9.25	0.047	6	4.93	1.46, 16.57	0.01	0.02

Abbreviations: CHD, coronary heart disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; RR, relative risk.

[a] CHD, stroke, diabetes, COPD, and cancer.

[b] Adjusted for age, sex, marital status, occupation, educational level, alcohol drinking, diastolic blood pressure, triglyceride and total cholesterol levels, and body mass index (weight (kg)/height $(m)^2$).

of mortality (from causes such as CHD, stroke, lung cancer, and COPD) and the dose-response relationships are consistent with those from previous prospective studies on people from mainland China (1–4, 6, 7, 15), 3 Hong Kong studies (5, 8, 29), and a study from Taiwan of elderly Chinese people (30). Hence, our data and results on smoking status and mortality should be quite robust. Furthermore, our results that show that stopping smoking at middle age was associated with decreased risks of mortality can provide further and strong evidence that the associations observed between smoking, quitting, and mortality in Chinese people are causal.

A limitation of the present study was the lack of data on changes in smoking behaviors after 1994 through 2011. Another limitation was that our sample was derived persons recruited in 1976 who survived until 1994, and as there was no comparable information on the general Chinese population during that time, the representativeness of the sample was uncertain. Few subjects in this cohort from a machinery factory were exposed to occupational hazards (1), and this factor could not be examined; however, we adjusted for occupation. Given that younger smokers could have died from smoking either before the 1976 baseline or before the 1994 follow-up, the subjects in the present cohort were older survivors. As the relative risks for younger deaths are higher (7), our risk estimates for smoking in older people were expectedly lower. Other limitations included the relatively small sample size and small number of deaths that did not allow for additional subgroup analysis, as well as the fact that exposure to other air pollutants was not included.

To the best of our knowledge, this is the first prospective study in China and developing countries that used repeated measures of tobacco use to compare new quitters with continuing current smokers during follow-up. We found that quitting smoking reduced the risks of death from CHD, thrombotic stroke, lung cancer, and COPD and that there were dose-response relationships with quitting duration after adjustment for potential confounders. Our findings on COPD are particularly important, as COPD is the most important cause of tobacco-induced deaths in most developing countries (16, 17). In China, of all deaths that are attributable to tobacco, 45% are related to COPD, compared with 15% for lung cancer and 5%–8% each for esophageal cancer, stomach cancer, liver cancer, tuberculosis, stroke, and CHD (7). Smoking cessation reduced all-cause and major tobacco-related mortality, and it remains the only proven strategy for reducing the pathogenetic processes leading to COPD, as stated in the 2010 US Surgeon General's report (33). Furthermore, compared with the United States, United Kingdom, and other Western countries, the tobacco epidemic is at an early stage in China and other middle- and low-income countries in which smoking prevalence has been increasing in the past 3 decades. Because there is a delay of several decades between the peak of tobacco-induced deaths and the peak of smoking prevalence, the burden of disease due to smoking will likely increase sharply in the next 10–20 years unless there is massive smoking cessation. Urgent and stringent tobacco control measures need to highlight the fact that 1 out of 2 smokers (and potentially up to 2 out of 3 smokers, as shown by recent studies in the United States and United Kingdom (9–11)) will be killed by smoking and that there are substantial benefits to quitting in order to motivate smokers to quit early so as to prevent this growing epidemic in China and in other developing countries (32, 34).

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