Population attributable risks of cigarette smoking for deaths of all causes, all cancers and other chronic diseases among adults aged 40-74 years in urban Shanghai, China

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Objective: To evaluate the population attributable risks (PARs) between cigarette smoking and deaths of all causes, all cancers, lung cancer and other chronic diseases in urban Shanghai.

Methods: In total, 61,480 men aged 40-74 years from 2002 to 2006 and 74,941 women aged 40-70 years from 1997 to 2000 were recruited to undergo baseline surveys in urban Shanghai, with response rates of 74.0% and 92.3%, respectively. A Cox proportional hazards regression model was used to estimate relative risks (RRs) and 95% confidence intervals (95% CIs) of deaths associated with cigarette smoking. PARs and 95% CIs for deaths were estimated from smoking exposure rates and the estimated RRs.

Results: Cigarette smoking was responsible for 23.9% (95% CI: 19.4-28.3%) and 2.4% (95% CI: 1.6-3.2%) of all deaths in men and women, respectively, in our study population. Respiratory disease had the highest PAR in men [37.5% (95% CI: 21.5-51.6%)], followed by cancer [31.3% (95% CI: 24.6-37.7%)] and cardiovascular disease (CVD) [24.1% (95% CI: 16.7-31.2%)]. While the top three PARs were 12.7% (95% CI: 6.1-19.3%), 4.0% (95% CI: 2.4-5.6%), and 1.1% (95% CI: 0.0-2.3%), for respiratory disease, CVD, and cancer, respectively in women. For deaths of lung cancer, the PAR of smoking was 68.4% (95% CI: 58.2-76.5%) in men.

Conclusions: In urban Shanghai, 23.9% and 2.4% of all deaths in men and women could have been prevented if no people had smoked in the area. Effective control programs against cigarette smoking should be strongly advocated to reduce the increasing smoking-related death burden.

Keywords: Population attributable risk (PAR); smoking; mortality; cohort study; all causes death; cancer death; lung cancer

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Introduction

Cigarette smoking is a major risk factor for deaths from any cause and has led to 5 million deaths currently worldwide (1-3). An estimated about 15.8% deaths in men and 3.3% deaths in women were attributable to cigarette smoking in Asia (4).

Cigarette smoking is highly prevalent and is associated with substantially increased morbidity and mortality as well as economic development in China (5,6). As the biggest country of tobacco production and consumption in the world, China produces about 2.66 million tons of tobacco leaves each year, which accounts for one-third of the world's tobacco leaf production per year (7). In addition, about 30% of the world's cigarettes are consumed in China (8). It is estimated that China has an estimated 350 million smokers by 2002 (9). The third national retrospective sampling death survey shows that, cardio-cerebrovascular disease, cancer and respiratory disease are the top three causes of death in China (10), and cigarette smoking was responsible for 12.9% deaths for men and 3.1% deaths for women (11). The smoking rates are increasing among the young population and women (12). The World Health Organization (WHO) predicts that China's annual tobacco-related deaths could rise to 2 million by the year 2025, and smoking-related mortality will be significantly increased (13).

Several studies have estimated the burden of deaths due to cigarette smoking in Chinese population (11,14-18), however, almost these studies used a less-than-optimal statistical method or relative risk (RR) and smoking exposure rates were derived from other studies in one study. In the present study, we used the accurate statistical method to estimate population attributable risks (PARs) of cigarette smoking on deaths of all causes, all cancers, lung cancer and other certain specific chronic diseases in two large prospective cohorts: the Shanghai Men's Health Study (SMHS) and the Shanghai Women's Health Study (SWHS).

Materials and methods

Study population

The SMHS and the SWHS are both population-based, prospective cohort studies conducted in urban Shanghai, China. Previous publications have described the designs and methods in detail (19,20). Briefly, the SMHS recruited 61,480 men aged 40-74 years from 2002 to 2006, with a participation rate of 74.0% (19). The SWHS recruited 74,941 women aged 40-70 years from 1997 to 2000, with a participation rate of 92.3% (20). For the present analysis, we excluded 377 cases whose diagnosis of cancer could not be confirmed (170 in men and 207 in women); 19 cases who were lost to follow-up (14 in men and 5 in women); 91 cases who were diagnosed with cancer in situ (10 in men and 81 in women); 1,598 cases who were diagnosed with cancer at baseline interviews in women; and 1 participant who had incomplete smoking data in men. Ultimately, 134,335 participants were included in the analysis (61,285 in the SMHS and 73,050 in the SWHS).

Data on demographic characteristics, physical activity, personal habits, family cancer history, diet, and other

characteristics were acquired in-person interviews with the use of a standard questionnaire administered by trained interviewers at baseline. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Cigarette smoking was defined as at least one cigarette per day for more than 6 months continuously. Alcohol drinking was defined as at least three times per week for more than 6 months continuously. Physical activity was defined as at least once a week for more than 3 months continuously.

Outcome ascertainment

To obtain the information on the causes of death among study subjects, a combination of annual record linkage with the Shanghai Cancer Registry and the Shanghai Vital Statistics databases and active follow-up surveys conducted every 2-3 years was used. For cohort members who were diagnosed with cancer, medical charts from the diagnostic hospital and detailed information on the pathology characteristics of the tumor were collected to verify the diagnosis. The present study included 8,270 deaths (3,506 men and 4,764 women) diagnosed between the date of baseline enrollment and September 2013. All of the causes of death were classified according to the International Classification of Diseases (ICD-9) coding scheme. We divided the deaths into cancer (ICD codes from 140 to 208), cardiovascular disease (CVD) (ICD codes from 390 to 459), respiratory disease (ICD codes from 460 to 519), and diabetes (ICD code is 250).

Statistical analysis

A Cox proportional hazards regression model was used to examine age-adjusted and multivariable-adjusted RRs and their 95% confidence intervals (95% CIs) of deaths associated with cigarette smoking. The confounders adjusted included age at baseline (continuous), BMI (it was categorized into quartiles based on the distribution of alive population: \leq 21.67, ~23.67, ~25.68, and >25.68 kg/m² for men; \leq 21.60, ~23.63, ~26.00, and >26.00 kg/m² for women), education (primary school or less, middle school, high or technical school and professional education or above), income level (low, middle and high), physical activity (yes or no), and alcohol drinking (yes or no). We estimated RRs and 95% CIs of smokers compared with nonsmokers.

In order to express the burden of cigarette smoking attributable to deaths, the PAR was calculated using the

following equation (21):

$$PAR = \frac{\sum_{s=1}^{S} \sum_{t=1}^{T} p_{st}RR_{1s}RR_{2t} - \sum_{s=1}^{S} \sum_{t=1}^{T} p_{st}RR_{2t}}{\sum_{s=1}^{S} \sum_{t=1}^{T} p_{st}RR_{1s}RR_{2t}}$$
$$= 1 - \frac{\sum_{t=1}^{T} p_{st}RR_{2t}}{\sum_{s=1}^{S} \sum_{t=1}^{T} p_{st}RR_{1s}RR_{2t}}$$

In which, *t* denotes a stratum of unique combinations of levels of all background risk factors which are not under study, *t*=1, ..., *T*, and *RR*_{2*i*} is the relative risk in combination *t* relative to the lowest risk level, where *RR*_{2,1}=1. As previously, *s* indicates an index exposure group defined by each of the unique combinations of the levels of the index risk factors, that is, those risk factors to which the *PAR* applies, *s*=1, ..., *S*, and *RR*_{1s} is the relative risk corresponding to combinations relative to the lowest risk combination, *RR*_{1,1}=1. The joint prevalence of exposure group *s* and stratum *t* is denoted by *p*_{st}, and *p.t* = $\sum_{s=1}^{s} p_{st}$. This partial PAR equation is preferred over other PAR equations, such as $p_{MR} = \frac{P(RR-1)}{P(RR-1)+1}$ (22) when the set of risk factors includes some factors which cannot be modified, such as age and family history of the disease.

All analyses were conducted using SAS statistical software, version 9.2 (SAS Institute Inc., Cary, USA). SAS macro package was used for PAR point estimation and interval estimation (21). All quoted probability (P) values were based on two-sided tests.

Results

During the 1,395,486 person-years of follow-up for 134,335 cohort participants, a total of 3,506 men deaths and 4,764 women deaths were recorded. The top four deaths were cancer (1,430 men and 1,950 women), CVD (1,209 men and 1,537 women), respiratory disease (229 men and 165 women), and diabetes (143 men and 328 women). The baseline characteristics of the study population are shown in *Table 1*. Totally, 42,665 men (69.62%) and 2,028 (2.78%) women were smokers. Male smokers were younger and had a lower education, lower income and lower BMI than nonsmokers. Female smokers were older and had a lower education, lower income and less physical exerciser in male smokers than nonsmokers, and more drinkers and physical exerciser in female smokers than nonsmokers.

Table 2 shows age-adjusted and multivariable-adjusted RRs of deaths associated with cigarette smoking in this study. Smokers had a 1.54- and 1.45-fold higher multivariable-

adjusted RR of mortality from all causes compared with nonsmokers in men and women, respectively. Among the cigarette-related diseases, respiratory disease had the highest RR [2.05 (95% CI: 1.50-2.80)] in men, followed by cancer [1.77 (95% CI: 1.56-2.01)] and CVD [1.56 (95% CI: 1.37-1.78)]. While the top three RRs were 3.10 (95% CI: 2.05-4.68), 1.67 (95% CI: 1.41-1.99) and 1.24 (95% CI: 1.02-1.52), for respiratory disease, CVD and cancer in women, respectively. The RRs of lung cancer were 4.43 (95% CI: 3.27-6.01) and 2.54 (95% CI: 1.83-3.52) in men and women, respectively. There was no statistical significance for the multivariable-adjusted RRs of diabetes in our study.

Table 3 shows age-adjusted and multivariable-adjusted PARs of deaths due to cigarette smoking in this study. Cigarette smoking was responsible for 23.9% (95% CI: 19.4-28.3%) deaths in men and 2.4% (95% CI: 1.6-3.2%) deaths in women in Shanghai after multivariable-adjustment. When divided into cigarette-related sites, respiratory disease had the highest PAR in men [37.5% (95% CI: 21.5-51.6%), followed by cancer [31.3% (95% CI: 24.6-37.7%)] and CVD [24.1% (95% CI: 16.7-31.2%)]. While the top three PARs were 12.7% (95% CI: 6.1-19.3%), 4.0% (95% CI: 2.4-5.6%) and 1.1% (95% CI: 0.0-2.3%), for respiratory disease, CVD and cancer in women, respectively. The PARs of lung cancer were 68.4% (95% CI: 58.2-76.5%) and 6.5% (95% CI: 2.4-10.7%) in men and women, respectively.

Discussion

Our study provides a systematic estimate of the burden of cigarette smoking on total, cancer and other causespecific deaths observed in our two cohorts during 2002-2013 and 1997-2013 for middle aged and elderly men and women in urban Shanghai. The results indicate that cigarette smoking causes an increased risk of mortality of cancer, CVD and respiratory disease for both among men and women. To our knowledge, the results provide perhaps the best estimates of smoking-associated deaths so far in a Chinese population.

The RRs of cigarette smoking for all deaths in our study are substantially lower than those from studies conducted in Europe and North America (23-25). Among specific causes of mortality evaluated in this study, lung cancer showed the strongest association with tobacco smoking, with estimated RRs of 4.43 and 2.54 in men and women, respectively. Ezzati and Lopez estimated that the leading causes of death

Table 1 Baseline characteristics of SMHS and SWHS								
	Men			Women				
Characteristics	No. of	No. of	Р	No. of	No. of	Р		
	nonsmokers (%)	smokers (%)		nonsmokers (%)	smokers (%)	·		
Age (year, $\bar{x}\pm s$)	59.05±9.79	53.74±9.25	<0.001	52.33±8.98	58.57±9.63	<0.001		
Education level			<0.001			< 0.001		
Primary school or less	1,678 (9.01)	3,224 (7.56)		14,446 (20.34)	1,138 (56.11)			
Middle school	4,305 (23.12)	15,974 (37.44)		26,650 (37.52)	538 (26.53)			
High or technical school	5,552 (29.82)	16,247 (38.08)		20,124 (28.33)	293 (14.45)			
Professional education or	7.085 (38.05)	7.220 (16.92)		9.802 (13.80)	59 (2.91)			
above	.,,	.,,		-,()	()			
Family income, per person p		<0.001			<0.001			
Low	8,713 (46.79)	25,019 (58.64)		19,171 (26.99)	991 (48.87)			
Middle	7,440 (39.96)	14,164 (33.20)		27,710 (39.02)	699 (34.47)			
High	2,467 (13.25)	3,482 (8.16)		24,141 (33.99)	338 (16.67)			
Ever alcohol drinker			<0.001			< 0.001		
No	15,574 (83.64)	25,061 (58.74)		69,646 (98.06)	1,761 (86.83)			
Yes	3,046 (16.36)	17,604 (41.26)		1,376 (1.94)	267 (13.17)			
BMI (kg/m ²)*			<0.001			<0.001		
≤21.67 (≤21.60)	3,788 (20.36)	11,669 (27.35)		17,580 (24.75)	492 (24.26)			
~23.67 (~23.63)	4,779 (25.67)	10,506 (24.62)		17,611 (24.80)	378 (18.64)			
~25.68 (~26.00)	5,048 (27.11)	10,086 (23.64)		17,737 (24.97)	459 (22.63)			
>25.68 (>26.00)	5,005 (26.88)	10,404 (24.39)		18,094 (25.48)	699 (34.47)			
Regular physical activity during past 5 years			<0.001			< 0.006		
No	9,497 (51.00)	30,023 (70.37)		46,202 (65.05)	1,259 (62.08)			
Yes	9,123 (49.00)	12,642 (29.63)		24,820 (34.95)	769 (37.92)			
* cut points for the quartiles	of BMI are shown in	narentheses for wo	omen SMHS	the Shandhai Me	n's Health Study:	SWHS the		

*, cut points for the quartiles of BMI are shown in parentheses for women. SMHS, the Shanghai Men's Health Study; SWHS, the Shanghai Women's Health Study; BMI, body mass index.

from smoking worldwide in 2000 were CVD, cancer and respiratory disease (26). The three leading causes of death attributable to smoking were cancer, CVD and respiratory disease in American men and CVD, cancer and respiratory disease in American women (27). Our findings among urban Shanghai populations are similar to the studies in world and America regard to three leading causes of death attributable to smoking: respiratory disease, cancer and CVD in men and respiratory disease, CVD and cancer in women. Overall, 23.9% men deaths and 2.4% women deaths were attributable to cigarette smoking. In particular, 37.5% respiratory disease and 31.3% cancer deaths in Shanghai males could have been prevented if no man had smoked in Shanghai. Our study reported a higher PAR of cigarette smoking for death of all causes in men, and a lower PAR in women than those of studies in Japanese and other Chinese population (11,18,28,29). However, previous studies did not adjust for potential confounders adequately when estimating relative risks or used the following equations to estimate PARs [$_{PAR} = \frac{P(RR-1)}{P(RR-1)+1}$], while this equation is only used in no confounding factors existing (11,18,28,29). The PARs of deaths related to cigarette smoking may be underestimated in our study, because the length of the follow-up period of men was shorter than that of other studies (11,18,28), and due to the long latency of chronic diseases, most of the smoking-related diseases tend to occur later in life.

This study had several strengths. First is the cohorts who are followed with a well-established and tested protocol, including record linkage with multiple sources of routinely collected data and biennial home visits, are likely to provide

Death Cigarette Person-year Gender No. of deaths RR1 (95% CI)* RR₂ (95% CI)** cause smoking of follow-up Men All causes Never 1,034 4,590 1.00 1.00 Ever 2,472 10,978 1.76 (1.64-1.90) 1.54 (1.43-1.67) Cancer Never 374 1,735 1.00 1.00 Ever 1,056 4,705 2.02 (1.79-2.28) 1.77 (1.56-2.01) Lung cancer Never 50 246 1.00 1.00 Ever 375 1,632 5.50 (4.09-7.40) 4.43 (3.27-6.01) CVD Never 370 1,611 1.00 1.00 Ever 839 3.759 1.75 (1.55-1.98) 1.56 (1.37-1.78) Respiratory disease 58 259 1.00 1.00 Never Ever 171 816 2.52 (1.87-3.40) 2.05 (1.50-2.80) Diabetes Never 48 228 1.00 1.00 399 1.40 (0.97-2.02) Ever 95 1.54 (1.09-2.19) All causes Women Never 4,415 34,719 1.00 1.00 Ever 349 2,736 1.61 (1.44-1.79) 1.45 (1.30-1.62) Cancer Never 1,846 14,603 1.00 1.00 Ever 104 813 1.30 (1.06-1.58) 1.24 (1.02-1.52) Lung cancer Never 370 2,977 1.00 1.00 Ever 44 356 2.69 (1.96-3.68) 2.54 (1.83-3.52) CVD 11,275 1,392 1.00 1.00 Never Ever 145 1.154 1.87 (1.57-2.22) 1.67 (1.41-1.99) Respiratory disease Never 135 1.183 1.00 1.00 Ever 30 263 3.93 (2.63-5.86) 3.10 (2.05-4.68) Diabetes Never 304 2,202 1.00 1.00 Ever 24 174 1.38 (0.91-2.10) 1.15 (0.75-1.75) *, adjusted for age; **, adjusted for age, BMI, education level, family income per person per year, ever alcohol drinker, regular

Table 2 Association of cigarette smoking with risk of death from all causes, cancer, lung cancer, CVD, or respiratory disease in SMHS and SWHS

*, adjusted for age; **, adjusted for age, BMI, education level, family income per person per year, ever alcohol drinker, regula physical activity during past 5 years; CVD, cardiovascular disease; SWHS, the Shanghai Women's Health Study.

high follow-up rate and more credible data. Secondly, we use the relative risk of smoking and smoking exposure rate derived from our own cohorts and then to estimate PAR, theoretically, which should provide more reliable PAR estimates of disease burden due to cigarette smoking in the study population than using data from external sources, while in other studies, RR or smoking exposure rate was abstracted from external sources (11,18). Finally, we adjusted known confounding sufficiently, which ensured the potential bias of overestimating the PAR was minimized in our study. Despite the strengths, our study also had some limitations. Firstly, some estimates among women are unstable because smoking exposure rate in women was traditionally very low. Secondly, as the cohorts included in this study were conducted among adults aged 40 years old and over, we were unable to estimate the impact of tobacco smoking in people younger than 40 years old. Therefore, there is a need for continuous studies to consider these factors when estimating the burden of deaths attributable to tobacco smoking.

Approximately one in four deaths in men and one in forty deaths in women in urban Shanghai could have been prevented if no people had smoked in Shanghai. Furthermore, the exposure rate of cigarette smoking has been continuously high in adult men and has been increasing over the last decade in women and young people (12,30). The average age of smoking initiation has been

SMHS and SWHS	;	, , , 0	, , <u>i</u>	0 0
Gender	Death cause	No. of deaths	PAR ₁ (95% CI)*	PAR ₂ (95% CI)**
Men	All causes	3,506	0.295 (0.259-0.330)	0.239 (0.194-0.283)
Cancer		1,430	0.366 (0.311-0.419)	0.313 (0.246-0.377)
	Lung cancer	425	0.723 (0.644-0.786)	0.684 (0.582-0.765)
	CVD	1,209	0.288 (0.228-0.347)	0.241 (0.167-0.312)
	Respiratory disease	229	0.444 (0.314-0.557)	0.375 (0.215-0.516)
	Diabetes	143	0.210 (0.023-0.382)	0.170 (-0.032-0.359)
Women	All causes	4,764	0.030 (0.022-0.038)	0.024 (0.016-0.032)
	Cancer	1,950	0.014 (0.003-0.024)	0.011 (0.000-0.023)
	Lung cancer	414	0.068 (0.035-0.100)	0.065 (0.024-0.107)
	CVD	1,537	0.048 (0.032-0.064)	0.040 (0.024-0.056)
	Diabetes	328	0.024 (-0.006-0.054)	0.011 (-0.019-0.042)
	Respiratory disease	165	0.140 (0.075-0.205)	0.127 (0.061-0.193)

Table 3 PAR (%) and number of deaths fr	om all causes	s, cancer, lun	g cancer, (CVD,	or respiratory	disease	due to	cigarette	smoking ir	1
SMHS and SWHS										

*, adjusted for age; **, adjusted for age, BMI, education level, family income per person per year, ever alcohol drinker, regular physical activity during past 5 years; CVD, cardiovascular disease; BMI, body mass index; PAR, population attributable risk; SMHS, the Shanghai Men's Health Study; SWHS, the Shanghai Women's Health Study.

decreasing in past years (9,12,31,32), and the numbers of cases and deaths are expected to increase in the future. The present estimates have important public health implications, and these data guide policy-makers to make prevention and control strategies on issues of smoking. Considering the high exposure rate of smoking, effective control programs against cigarette smoking should be advocated in Shanghai to reduce the large and increasing smoking-related deaths burden.

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