CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3515727

Available online at: http://www.iajps.com ***Research Article***

"INFLUENCE OF SMOKING COMBINED WITH OTHER RISK ON MORTALITY FROM HEART DISEASE AND STROKE"

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Article Received: August 2019 **Accepted:** September 2019 **Published:** October 2019

Abstract:

Introduction: *Cigarette smoking is a well-established risk factor for all forms of stroke. While both the general public and the global healthcare system are aware of the vascular risks associated with smoking.*

Aim: *The goal of the present large-scale pooled analysis, called Evidence for Cardiovascular Prevention from Observational Cohorts, is to provide reliable information on smoking and the risk of mortality from each subtype of cardiovascular disease.*

Method: *A total of 27,385 male and 39,207 female participants aged 40–89 years were enrolled from 10 well-qualified cohort studies with a mean follow-up of 10.1 years. Hazard ratios and their corresponding 95% confidence intervals in smokers who had hypertension or high serum cholesterol were estimated for men and women separately using a Cox proportional hazards regression model that included age, body mass index, cohort and either serum total cholesterol or systolic blood pressure as covariates. Fractions of deaths attributable to the coexistence of these risk factors were also calculated.*

Conclusion: *Smoking is definitely an undesirable habit that can lead to an increased risk of mortality from both coronary heart disease and cerebral infarction. Furthermore, smoking increases the burden of cardiovascular disease due to its high popularity. Particular attention should be given to smokers who have another cardiovascular risk factor, such as hypertension or high serum cholesterol, because the combination of these risk factors substantially increases the mortality risk from coronary heart disease and cerebral infarction. Therefore, smokers with a concomitant risk factor should have rigorous counselling for smoking cessation and other lifestyle modifications.*

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Please cite this article in press Sehrish Iqbal et al., ***"Influence of Smoking Combined with Other Risk on Mortality from Heart Disease and Stroke".,*** *Indo Am. J. P. Sci, 2019; 06[10].*

INTRODUCTION:

Cigarette smoking is clearly identified as the chief preventable cause of death in our society and the most important public health issue of our time [1]. This statement was first articulated in 1982 by the then US Surgeon General C Everett Koop, and unfortunately it remains accurate today, over 25 years later[2]. Hence, over the last quarter of a century, one can argue that efforts regarding smoking prevention and cessation, and public awareness campaigns describing the associated health risks regarding smoking, have had only limited success.[3]

Current smoking is a known risk factor for stroke, with evidence of a strong dose-response relationship. The proportion of stroke attributable to current smoking is nearly 20 % [4]. Despite growing knowledge about the adverse health and economic consequences of smoking, the prevalence of smoking in the USA remains alarmingly high. According to the CDC, their most recent data indicates that 20.8% of the US adult population smokes. This represents only a 3% decline in smoking prevalence over the last 10 years [5]. Due to the current rates of population growth, even with a small percentage decline of tobacco consumption over the years, absolute consumption continues to grow and will continue to do so unless more aggressive measures are taken to promote smoking cessation [6]. In short, over 1 billion more cigarettes were consumed worldwide in 2000 compared with 1980.

The evidence linking smoking to stroke is extremely convincing. Some studies were performed across various ethnicities and populations demonstrate a strong association between smoking and stroke risk, with current smokers having at least a two- to fourfold increased risk of stroke compared with lifelong non-smokers or individuals who had quit smoking more than 10 years prior. In one study, the risk increased to six fold when this population was compared with non-smokers who had never been exposed to environmental tobacco smoke [i.e., second-hand smoke] [7]. In a separate study, this six fold increase in risk persisted when cigarette-smoking women with smoking spouses were compared with smoking women with non-smoking spouses, further demonstrating the effect of second-hand smoke on stroke risk [8].

More recently, the deleterious consequences of second-hand smoke have been at the forefront of public health organizations and the subject of numerous government reports [9]. These studies have convincingly shown that environmental [second-hand] smoke increases the risk of stroke even in non-smokers [10]. In an Australian study investigating the effect of spousal smoking, the risk of stroke was twice as high in individuals with spouses who smoked compared with sex-matched neighbourhood controls [11]. In New Zealand, second-hand smoke exposure at work was estimated to cause around 100 avoidable deaths per year from lung cancer, coronary heart disease and stroke collectively [12]. Finally, in the USA, a cohort study of over 27,000 individuals has shown a 1.50-fold increased risk of first ischemic stroke in women exposed to 20 h or more per week of environmental tobacco smoke at home compared with those exposed to less than 1 h per week [12].

Plausible mechanisms by which primary and environmental tobacco smoke exposure can increase the risk of stroke and heart disease are numerous and include carboxyhemoglobinemia, increased platelet aggregability, increased fibrinogen levels, reduced HDL-cholesterol, and direct toxic effects of compounds such as 1, 3-butadiene, a vapor phase constituent of environmental tobacco smoke that has been shown to accelerate atherosclerosis in animal models [13]. Environmental tobacco smoke exposure has also been linked to the progression of atherosclerosis as measured by B-mode ultrasound of the carotid wall [14], as well as to early arterial damage as assessed by endothelium-dependent brachial artery dilatation [15]. Last, the pathogenesis of increased stroke risk in populations exposed to cigarette smoke has been suggested to be that of advanced thermogenesis, potentially in relation to chronic infection [16].

Atherosclerosis and arterial damage thus explain how smoking predisposes individuals to large- and small-vessel lacunar stroke. Impaired endogenous fibrinolysis and reduced blood flow in the brain secondary to smoking-induced vasoconstriction may also contribute to lacunar stroke. While atrial fibrillation and hypertension may outweigh the risk of smoking for cardio embolic stroke, an association is believed to exist for this stroke subtype as well. The Atherosclerosis Risk in Communities [ARIC] study demonstrated a relative risk [RR] of 2.30, 1.61 and 1.94 for lacunar, no lacunar and cardio embolic strokes in current smokers, respectively [17].

Cardiovascular disease, including coronary heart disease and stroke, is a major cause of death worldwide. This is also true in Japan, where the life expectancy of the population is fairly high [18]. Large-scale cohort studies have demonstrated a causal relationship between smoking and both coronary heart disease and stroke in Asian populations, where intensive tobacco control is an

urgent public health policy issue due to the high popularity of smoking among men [19]. In fact, these studies have estimated that a major proportion of the morbidity and mortality from cardiovascular disease in Asian men is due to smoking [20]. Because of the importance of a multifactorial approach to the prevention of cardiovascular disease in smokers, information is necessary on the adverse effects of smoking combined with another cardiovascular risk factor such as hypertension or high serum cholesterol [21].

Hypertension is also a prevalent cardiovascular risk factor and 20–25% of Japanese men are estimated to have both hypertension and a smoking habit [22]. Although high serum cholesterol was less prevalent in Asia than in the West in the past two decades, the lipid profile has been worsening in urban areas in Asia due to adoption of a westernized diet that has a high fat content [23]. However, most information on the combined adverse effects of smoking and hypertension or high serum cholesterol has been derived from Western populations, and coronary heart disease was often used as the only endpoint. Relevant information is scarce for stroke, the predominant subtype of cardiovascular disease in Asian populations [24].

The goal of the present large-scale pooled analysis, called Evidence for Cardiovascular Prevention from Observational Cohorts, is to provide reliable information on smoking and the risk of mortality from each subtype of cardiovascular disease. In particular, we determined the adverse effects of the coexistence of smoking and hypertension or high serum cholesterol on the risk of death due to cardiovascular disease.

METHODOLOGY:

It is a pooled analysis of 13 well-qualified cohort studies in Pakistan which met the following criteria for inclusion: [1] participation of more than 1,000 individuals in each cohort; [2] follow-up of approximately 10 years; [3] measures of lifestyle, physical conditions and blood biochemistry at study entry, and [4] identification of diseases [mortality and incidence] during follow-up. Individuals aged 40–89 years at study entry were included, and follow-up was terminated at the age of 90 years, because the duration of follow-up varied across the cohorts. Of the 13 cohorts, 10 that had data on disease-specific mortality were used. From 80,000 individuals in 10 cohorts, 13,408 were excluded due to a history of cardiovascular disease [n = 5,160] or missing baseline information on sex, smoking habit [never, former or current smoker], body mass index, systolic and diastolic blood pressure, serum total cholesterol or a history of cardiovascular disease [n = 8,248]. The remaining 66,592 individuals were included in the analyses performed for this report.

Statistical Methods:

Initially, to compare the risk of mortality from all cardiovascular diseases as well as each disease subtype, hazard ratios and their corresponding 95% confidence intervals were estimated for current and former smokers, with never-smokers serving as the reference. The hazard ratios were determined from a Cox proportional hazards regression model that included the following variables as covariates: age [years], systolic blood pressure [mm Hg], serum total cholesterol [mmol/l], body mass index [kg/m 2] and cohort. All hazard ratios were estimated for men and women separately in the entire population as well as in two different age groups [40–64 and 65–89 years at study entry]. We assessed the heterogeneity for the cardiovascular mortality risk due to smoking between these two age groups for each outcome using likelihood ratio tests [25].

The population attributable fraction [PAF] of deaths was determined when a hazard ratio showed a significant increase in current smokers. The PAF, which represents the contribution of current and former smoking to cardiovascular deaths in the study population, was calculated according to the formula, using the proportion of deaths among current and former smokers and the hazard ratio. Next, we examined the adverse effects of smoking, when it was combined with either hypertension or high serum cholesterol, on cardiovascular mortality in both, individuals and in the entire population.

To compare the individual risk of cardiovascular mortality among participants grouped according to smoking habit [i.e. never, former or current smoker] and blood pressure, hazard ratios were calculated for each group, with never smoking without hypertension serving as the reference. Similarly, to compare the cardiovascular mortality risk among participants grouped according to smoking habit and serum total cholesterol [i.e. the absence or presence of high serum cholesterol, defined as a serum total cholesterol 6 6.21 mmol/l], hazard ratios were calculated for each group, with never-smoking without high serum cholesterol serving as the reference. We assessed the interaction between smoking habit and blood pressure and the interaction between smoking habit and serum total cholesterol for each outcome using likelihood ratio tests [26]. The PAF was also calculated in a similar manner. All statistical analyses were performed using SAS

version 9.13 [SAS Institute Inc., Cary, N.C., USA].

RESULTS:

Characteristics of the Study Population Baseline characteristics of the study participants in each of the 10 cohorts as well as in the overall population were summarized. The 10 cohorts included 66,592 participants [27,385 men and 39,207 women]. The mean age at study entry was 57.7 years in the male participants and 57.3 years in the female participants. The prevalence of never, former and current smoking was 24.3, 22.0 and 53.7% in men and 93.8, 1.3 and 4.9% in women, respectively.

Cardiovascular Disease Deaths:

There were a total of 672,031 person-years of follow-up. The mean follow-up period was 10.1 years [9.9 years in men and 10.2 years in women]. During follow-up, there were 1,893 deaths due to cardiovascular disease [988 in men and 905 in women]. These cases included 382 coronary heart disease deaths [216 in men and 166 in women] and 893 stroke deaths [463 in men and 430 in women]. Of the documented stroke deaths, 465 deaths [272 in men and 193 in women] were classified as cerebral infarction and 215 deaths [115 in men and 100 in women] as intracerebral hemorrhage.

Smoking Habits and Cardiovascular Mortality:

Tables 1 and 2 show the hazard ratios for the different mortality endpoints in male and female current and former smokers. Current smoking significantly increased the risk of mortality from cardiovascular disease in both men and women even after adjustment for age, body mass index, systolic blood pressure, serum total cholesterol and cohort. The adjusted hazard ratios [95% confidence intervals] were 1.68 [1.42–1.99] for men and 1.63 [1.31– 2.05] for women. When cardiovascular disease deaths were classified into subtypes, current smoking in both sexes significantly increased the mortality risk from both coronary heart disease and stroke, especially cerebral infarction. The adjusted hazard ratios in male and female current smokers were 2.07 [1.43–3.01] and 3.03 [1.98– 4.65] for coronary heart disease, and 1.82 [1.31–2.53] and 1.31 [0.78–2.19] for cerebral infarction, respectively.

These positive associations were more pronounced in participants aged 40–64 than in those aged 65–89 years although current smoking significantly increased the risk of mortality from coronary heart disease and cerebral infarction in both age groups. However, smoking had little effect on the risk of mortality from intracerebral hemorrhage. There was no heterogeneity between these two age groups for any outcome in both men and women. The fraction of deaths due to cardiovascular disease in men attributable to current and former smoking was 24.4 and 1.7%, respectively. The fraction of deaths due to coronary heart disease was 34.0 and 0.3%, respectively; the fraction of deaths due to cerebral infarction was 25.5 and 7.1%, respectively. The corresponding fraction for each endpoint was greater in men aged 40–64 than in those aged 65–89 years. However, the corresponding fraction for each endpoint was much smaller in women than men.

Table 1: Hazard ratio for cardiovascular mortality and the PAF of deaths in 27,385 men grouped according to age and screening lab.

	Overall men			40–64 years			65–89 years		
	never-smoker	former smoker	current smoker	never-smoker	former smoker	current smoker	never-smoker	former smoker	current smoker
Participants, n	6,655	6,021	14,709	4,878	3,627	11,106	1,777	2,394	3,603
Person-years of follow-up	65,929	55,712	148,830	51,280	37,221	120,330	14,649	18,491	28,499
Cardiovascular disease									
Cases, n	188	204	596	47	49	250	141	155	346
Adjusted HR[a]	1.00	1.09	1.68	1.00	1.20	2.08	1.00	1.08	1.57
95% CI	ref.	0.89–1.34	1.42–1.99	ref.	0.80–1.80	1.52–2.86	ref.	0.85–1.37	1.28–1.92
PAF[b], %		1.7	24.4		2.4	37.5		1.8	19.6
				p value for heterogeneity[c] = 0.61					
Coronary heart disease									
Cases, n	36	38	142	12	9	64	24	29	78
Adjusted HR[a]	1.00	1.02	2.07	1.00	0.83	2.25	1.00	1.11	2.01
95% CI	ref.	0.64–1.63	1.43–3.01	ref.	0.34–1.98	1.21–4.21	ref.	0.63–1.96	1.26–3.22
PAF[b], %		0.3	34.0		NC	41.8		2.2	29.9
				p value for heterogeneity[c] = 0.35					
Stroke									
Cases, n	92	97	274	17	20	115	75	77	159
Adjusted HR[a]	1.00	1.09	1.60	1.00	1.40	2.58	1.00	1.02	1.36
95% CI	ref.	0.81–1.46	1.25–2.04	ref.	0.72–2.71	1.54–4.33	ref.	0.73–1.43	1.02–1.81
PAF[b], %		1.7	22.2		3.8	46.3		0.5	13.5
				p value for heterogeneity[c] = 0.18					
Cerebral infarction									
Cases, n	50	68	154	4	9	48	46	59	106
Adjusted HR[a]	1.00	1.40	1.82	1.00	2.32	4.44	1.00	1.28	1.53
95% CI	ref.	0.96–2.04	1.31–2.53	ref.	0.70–7.68	1.58–12.45	ref.	0.85–1.91	1.07–2.18
PAF[b], %		7.1	25.5		8.4	61.0		6.1	17.4
				p value for heterogeneity[c] = 0.42					
Intracerebral hemorrhage									
Cases, n	33	18	64	10	6	34	23	12	30
Adjusted HR[a]	1.00	0.57	0.93	1.00	0.86	1.35	1.00	0.51	0.78
95% CI	ref.	0.32–1.04	0.60–1.43	ref.	0.30–2.45	0.66–2.78	ref.	0.24–1.05	0.44–1.38
PAF[b], %		NC	NC		NC	NC		NC	NC
				p value for heterogeneity[c] = 0.66					

Smoking Habits, Blood Pressure and Cardiovascular Mortality:

When current smokers had hypertension [20.5% of all the male and 1.6% of all the female participants], the risk of mortality from cardiovascular disease further increased in both men and women, compared with those that had just one of these risk factors [t able 4] . The adjusted hazard ratios for cardiovascular disease in male and female current smokers who had hypertension, compared with those that had neither risk factor, were 2.83 [2.17–3.69] for men and 2.70 [2.00–3.64] for women. A similar pattern was observed for both coronary heart disease and stroke, especially cerebral infarction. The adjusted hazard ratios in male and female current smokers who had hypertension were 2.57 [1.51–4.38] and 6.14 [3.49–10.79] for coronary heart disease, and 3.28 [1.89–5.71] and 1.61 [0.81–3.18] for cerebral infarction, respectively. There was no interaction between smoking habit and blood pressure for coronary heart disease and cerebral infarction in both men and women, whereas there was relevant interaction for intracerebral hemorrhage in women but not in men. The fraction of deaths due to cardiovascular disease attributable to the coexistence of current smoking and hypertension was 25.7% for men and 3.8% for women.

The corresponding fraction of deaths due to coronary heart disease was 24.6% for men and 9.6% for women, whereas the corresponding fraction of deaths due to cerebral infarction was 28.1% for men and 2.0% for women.

Table 2: Hazard ratios for cardiovascular mortality ansd the PAF of deaths in 39,267 women grouped according to age and screening lab.

	Overall women			40–64 years			65–89 years		
	never-smoker	former smoker	current smoker	never-smoker	former smoke	current smoker	never-smoker	former smoker	current smoker
Participants, n	36,766	516	1,925	27,909	296	1,462	8,857	220	220
Person-years of follow-up	375,816	5,055	20,689	296,791	3,178	16,460	16,460	1,877	4,230
Cardiovascular disease									
Cases, n	791	27	87	234	6	25	557	21	62
Adjusted HR[a]	1.00	1.41	1.63	1.00	2.08	1.86	1.00	1.33	1.60
95% CI	ref.	0.96–2.08	1.31–2.05	ref.	0.92–4.70	1.22–2.82	ref.	0.86–2.06	1.22–2.08
PAF[b], %		0.9	3.7		1.2	4.4		0.8	3.6
				p value for heterogeneity[c] = 0.73					
Coronary heart disease									
Cases, n	133	7	26	39	2	8	94	5	18
Adjusted HR[a]	1.00	2.18	3.03	1.00	4.25	3.52	1.00	1.90	2.89
95% CI	ref.	1.01–4.70	1.98–4.65	ref.	1.01–17.94	1.61–7.68	ref.	0.77–4.71	1.73–4.83
PAF[b], %		2.3	10.5		3.1	11.7		2.0	10.1
				p value for heterogeneity[c] = 0.67					
Stroke									
Cases, n	385	12	33	124	3	12	261	9	21
Adjusted HR[a]	1.00	1.35	1.31	1.00	2.11	1.79	1.00	1.25	1.17
95% CI	ref.	0.76–2.41	0.92–1.88	ref.	0.67–6.68	0.98–3.26	ref.	0.64–2.43	0.75–1.83
PAF[b], %		NC	NC		NC	NC		NC	NC
				p value for heterogeneity[c] = 0.55					
Cerebral infarction									
Cases, n	169	8	16	35	3	1	134	5	15
Adjusted HR[a]	1.00	1.79	1.31	1.00	5.62	0.44	1.00	1.30	1.52
95% CI	ref.	0.87–3.65	0.78–2.19	ref.	1.71–18.52	0.06–3.19	ref.	0.53–3.18	0.88–2.61
PAF[b], %		NC	NC		NC	NC		NC	NC
				p value for heterogeneity[c] = 0.06					
Intracerebral hemorrhage									
Cases, n	94	2	4	37	0	3	57	2	1
Adjusted HR[a]	1.00	1.01	0.68	1.00	0.00	1.52	1.00	1.44	0.27
95% CI	ref.	0.25–4.14	0.25–1.87	ref.		0.46–5.01	ref.	0.35–5.94	0.04–1.92
PAF[b], %		NC	NC		NC	NC		NC	NC
				p value for heterogeneity[c] = 0.12					

Smoking Habits, Serum Total Cholesterol and Cardiovascular Mortality:

The coexistence of current smoking and high serum cholesterol [4.2% of all the male and 0.8% of all the female participants] further increased the cardiovascular mortality risk in both men and women, compared with the presence of either risk factor. The adjusted hazard ratios for cardiovascular disease in participants with both risk factors was higher than in participants with neither risk factor: 1.94 [1.39–2.71] for men and 1.87 [1.14– 3.09] for women. A similar pattern was observed for coronary heart disease but not for stroke. The adjusted hazard ratios for coronary heart disease in men and women that were current smokers and had high serum cholesterol were 4.19 [2.33–7.53] and 3.90 [1.57–9.67], respectively.

Interaction was absent between smoking habit and serum total cholesterol for coronary heart disease and cerebral infarction in both sexes; however, there was interaction for intracerebral hemorrhage in men but not in women. The fraction of deaths due to cardiovascular disease attributable to the coexistence of current smoking and high serum cholesterol was 2.2% for men and 0.8% for women. The corresponding fraction of deaths due to coronary heart disease was 6.3% for men and 2.2% for women.

DISCUSSION:

The present study demonstrated that current smoking significantly increased the risk of mortality from both coronary heart disease and cerebral infarction men and women, even after adjustment for other major cardiovascular risk factors. These significant increments in risk were observed regardless of age, but were more pronounced in middle-aged than in elderly individuals. However, smoking had little adverse effect on mortality from intracerebral hemorrhage. Because of the high prevalence of smoking among Japanese men, approximately one-fourth of the total cardiovascular deaths in the male study population were attributable to ever smoking [current and former smoking combined], and this is important from a public health perspective.

There was a further increase in coronary risk in current smokers who also had hypertension or high serum cholesterol. In addition, hypertensive smokers were at further elevated risk of cerebral infarction. Neither hypertension nor high serum cholesterol modified the adverse effects of smoking on coronary heart disease and cerebral infarction. The results of a meta-analysis based on a systematic review of the relevant literature showed that the hazard ratios [95% confidence interval] in current smokers compared with never-smokers were 2.60 [2.19–3.09] for coronary heart disease and 1.39 [1.20–1.62] for total stroke [27], and these risks were broadly comparable with our results although these estimates are for men and women combined. Honjo et al. Conducted a pooled analysis similar to ours and reported that the hazard ratios for cardiovascular mortality in male and female current smokers were 2.19 [1.79–2.67] and 2.84 [2.24–3.60] for coronary heart disease and 1.15 [0.94–1.39] and 1.33 [0.99–1.81] for cerebral infarction, respectively, with adjustment only for age and cohort [28]. Although their study lacked adjustment for important confounders such as blood pressure and serum cholesterol, their results are also comparable with our results for coronary heart disease in both sexes and for cerebral infarction in women but are lower than our results for cerebral infarction in men. However, their results are inconsistent with our results for intracerebral hemorrhage.

Honjo et al. [29] reported that smoking significantly increased the risk of mortality from intracerebral hemorrhage, with a hazard ratio of 1.27 [1.00–1.62] for men and 1.87 [1.34–2.60] for women; however, our study showed a no significant increment in the corresponding risk. Our results are in accordance with the results of the Japan Public Health Centre Study [30] and the results of the previous Korean male study that found that smoking, even heavy smoking, had little effect on incident intracerebral hemorrhage [31]. We suggest that the discrepant results of intracerebral hemorrhage come from the inappropriate adjustment for confounders in their study. I n previous studies, as well as in our study, the impact of smoking on the global burden of total deaths from cardiovascular disease largely differed between sexes due to the much higher prevalence of smoking among men than women. A previous Japanese study estimated that the PAF of total cardiovascular deaths due to ever smoking was 23.0% in Japanese men and 8.0% in women [32], and these estimates were similar to ours. However, the estimated burden of coronary heart disease and stroke deaths in men differed between that study and ours. We observed a larger burden of stroke deaths [23.9 vs. 10.4%], especially cerebral infarction deaths [32.6 vs. 9.9%], due to ever smoking in men, but a smaller burden of coronary deaths [34.3 vs. 44.1%] compared with the previous Japanese study [33].

Our PAF estimates suggest that male hypertensive smokers are special targets for reducing the global burden of premature death and disability due to cardiovascular disease because of the large contribution of these smokers to the burden of cardiovascular disease deaths among men. NIPPON DATA80 estimated that the PAF of cardiovascular disease due to the coexistence of current smoking and hypertension in Japanese men was 42.4% for those less than 60 years and 18.6% for those 60 years or older, but did not estimate the PAF for coronary heart disease and stroke separately[34].

Our study indicates that male hypertensive smokers contribute significantly to the burden of deaths from both coronary heart disease and stroke. However, hypercholesterolemia smokers contribute less than hypertensive smokers to the total burden of cardiovascular disease deaths because of the lower prevalence of hypercholesterolemia smokers among Japanese men and their lower risk of cardiovascular mortality. Several limitations should be acknowledged in the present study. First, to maximize the availability of data on smoking habits from potentially participating cohorts, we defined the three categories of smoking habits without considering the number of cigarettes smoked. Second, we assumed that the smoking habit at baseline remained unchanged throughout the follow-up period although it is likely that some current smokers quit smoking during the follow-up period. Moreover, extensive passive exposure to environmental tobacco smoke either at home or in the workplace may have been common, due to the high prevalence of smoking among Japanese men and insufficient restriction of smoking in public places at that time. These limitations may have led to an underestimation of the true harm of active smoking [35]. Third, both hypertension and high serum cholesterol were defined without considering the use of medications that lower blood pressure or serum cholesterol. Furthermore, the levels of blood pressure and serum total cholesterol could have changed due to lifestyle modification and/or prescribed medications over the follow-up period although this was also present in other prospective studies in which the baseline levels of these factors were assumed to remain unchanged throughout the follow-up period.

As a whole, these limitations may also have led to misclassification of the blood pressure and serum

cholesterol categories, which may have resulted in an underestimation of the cardiovascular mortality risk due to the coexistence of smoking and hypertension or high serum cholesterol. Fourth, we could not calculate hazard ratios for subarachnoid hemorrhage mortality because there were only 75 documented deaths due to this subtype [20 in men and 55 in women]. Fifth, we could not determine the cardiovascular mortality risk in smokers who had both hypertension and high serum cholesterol, because of the small number of cardiovascular deaths in this group. Finally, due to limited baseline information, no adjustment was made for diabetes in our analyses.

In conclusion, smoking is definitely an undesirable habit that can lead to an increased risk of mortality from both coronary heart disease and cerebral infarction. Furthermore, smoking increases the burden of cardiovascular disease due to its high popularity. Particular attention should be given to smokers who have another cardiovascular risk factor, such as hypertension or high serum cholesterol, because the combination of these risk factors substantially increases the mortality risk from coronary heart disease and cerebral infarction. Therefore, smokers with a concomitant risk factor should have rigorous counselling for smoking cessation and other lifestyle modifications. From a public health perspective, priority should be given to hypertensive smokers since this group makes a large contribution to the burden of both coronary deaths and cerebral infarction deaths.

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