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H.知的財産権の出願・登録状況

なし

〔研究協力者〕

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表1. 主な食事因子等のHbA1c上昇の多変量調整オッズ比（大阪）

男　性

	オッズ比	95%信頼区間	有意確率
Body Mass Index （+1kg/m²）	1.089	0.989 - 1.199	P=0.084
ｱﾙｺｰﾙ摂取量 46g/日以上	2.173	1.020 - 4.627	P=0.044
魚介類週 3 以上	2.278	1.088 - 4.772	P=0.029
麺類の汁全部飲む	1.774	1.015 - 3.102	P=0.044

女　性

	オッズ比	95%信頼区間	有意確率
Body Mass Index （+1kg/m²）	1.074	0.995 - 1.160	P=0.068
菓子ｴﾈﾙｷﾞｰ（150kcal 以上）	1.680	1.046 - 2.698	P=0.032
油料理毎日	1.736	0.920 - 3.274	P=0.088
醤油ｿｰｽかける	2.078	1.112 - 3.885	P=0.022
野菜・海藻毎日食べる	0.597	0.367 - 0.972	P=0.038
運動あり※)	0.623	0.382 - 1.015	P=0.057

調整因子：ベースライン時の年齢、HbA1c 値

※) 週 1 回以上かつ 15 分/回以上の運動を 3 ヵ月以上継続している者

注）いずれも生活習慣が該当しない群に対する該当する群のオッズ比

表2.主な食事因子等のHbA1c上昇の多変量調整オッズ比(秋田)

	男　性		
	オッズ比	95%信頼区間	有意確率
Body Mass Index (+1kg/m²)	1.156	1.045 - 1.278	P=0.005
炭水化物ｴﾈﾙｷﾞｰ比率(60%以上)	0.317	0.090 - 1.111	P=0.073
間食・夜食食べる	2.261	1.070 - 4.778	P=0.033
塩蔵品週３以上	1.965	1.036 - 3.726	P=0.038

	女　性		
	オッズ比	95%信頼区間	有意確率
Body Mass Index (+1kg/m²)	1.145	1.071 - 1.223	P=0.000
ｱﾙｺｰﾙ摂取量 46g/日以上	11.001	0.739 - 163.700	P=0.082
脂肉類週３以上	1.852	1.091 - 3.143	P=0.022
汁物１日２杯以上	1.782	1.053 - 3.017	P=0.032

調整因子：ベースライン時の年齢、HbA1c値

注）いずれも生活習慣が該当しない群に対する該当する群のオッズ比

研究成果の刊行に関する一覧表

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地域住民におけるnon-HDL-コレステロールレベルと虚血性心疾患発症との関連について

＜目的＞

わが国の一般住民を対象として、non-HDL-コレステロール値（non-HDL-C）と虚血性心疾患(CHD)発症との関連を追跡研究にて検討するとともに、CHD発症リスクを上昇させるnon-HDL-Cの閾値について明らかにする。

＜方法＞

1975～1987年に循環器健診を受診した4地域の40～69歳の一般住民8158人（男性3201人，女性4957人）のうち，冠動脈疾患または脳卒中の既往のある26人を除いた8132人(男性3178人，女性4954人)を21.9年間追跡(中央値)し、健診時のnon-HDL-C（総コレステロール値とHDL-C値の差)のレベルごとにＣＨＤ発症リスクを検討した。

＜結果＞

追跡期間中にCHDを発症したのは155人（心筋梗塞は91人，狭心症は36人，心臓突然死は28人）であった。

non-HDL-Cのカテゴリーごとの CHD発症の多変量調整ハザード比（95%信頼区間）を算出した結果、100 mg/dL 未満の区分に対して、140～159 mg/dL では 2.49 (1.35-4.61)、≧180 mg/dL では 3.13 (1.58-6.21) のハザード比を示し、140 mg/dL前後に閾値がある可能性が示唆された。

次いで、integrated discrimination improvement (IDI) 赤池情報量基準 (AIC)，多変量調整ハザード比の3つの指標により，CHD発症リスクを予測するためのnon-HDL-Cの最適なカットオフ値を検討した。その結果，IDIがもっとも高くなるカットオフ値は140 mg/dL，AICがもっとも低くなるカットオフ値は141 mg/dL，多変量調整ハザード比がもっとも高くなるカットオフ値は≧141 mg/dLであった。

＜結論＞

わが国の地域住民において、non-HDL-C高値はCHD発症リスクの増加と有意に関連しており，CHD発症リスク上昇を予測するための最適なカットオフ値は140 mg/dL前後と考えられた。

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Association between dietary behavior and risk of hypertension among Japanese male workers.

Umesawa M, Kitamura A, Kiyama M, Okada T, Shimizu Y, Imano H, Ohira T, Nakamura M, Maruyama K, Iso H.

Hypertens Res. 2013;36(4):374-80.

日本人勤務者男性における、食習慣と高血圧発症リスク

＜目的＞

本研究の目的は、高血圧の頻度が高い日本人において、食習慣と高血圧発症リスクとの関連を、前向きコホート研究の手法を用いて評価することである。

＜方法＞

対象は、2001 年から 2011 年にかけて、2 回以上大阪府立健康科学センターによる健康診断（健診）を受診し、初回の健診時に高血圧でなかった成人男性 3486 人（30-71 歳、平均年齢 42.9 歳）とした。ベースラインは初回の健診受診時とし、追跡終了は高血圧の発症もしくは最終の健診受診時とした。食習慣の調査は全期間を通じて同一の質問紙を用い、健診時に実施した。

＜結果＞

平均追跡期間は 4.6 年であった。追跡中、846 件の高血圧の発症を認めた。食習慣のうち、「脂身付の肉類を週 2-3 回以上食べる」ことと「乳製品を毎日摂る」ことが高血圧の発症に有意な関連を示した。前者については、ベースライン時および追跡終了時の両方で「いいえ」と回答した者では、両方で「はい」と回答した者に比べ、高血圧発症のオッズ比が 1.26（95%信頼区間 1.00-1.59）と有意に高かった。また、後者についても両方で「いいえ」と回答した者では、両方で「はい」と回答した者に比べ、高血圧発症のオッズ比が 1.39（95%信頼区間 1.13-1.71）と有意に高かった。

＜結論＞

日本人勤務者男性において、肉類の摂取頻度が少ない、乳製品を毎日摂らないことと高血圧発症リスクとの間に正の関連が認められた。

代表文献３の要約

Shimizu Y, Imano H, Ohira T, Kitamura A, Kiyama M, Okada T, Ishikawa Y, Shimamoto T, Yamagishi K, Tanigawa T, Iso H; CIRCS Investigators. Adult Height and Body Mass Index in Relation to Risk of Total Stroke and its Subtypes: The Circulatory Risk in Communities Study. J Stroke Cerebrovasc Dis. 2013;S1052-3057:00230-9.

日本人の身長及びBody Mass Indexと脳卒中発症リスク：the Circulatory Risk in Communities Study(CIRCS)

＜目的＞
身長が脳卒中の発症リスクと関係することが報告されている。これは身長が小児期におかれた環境を反映する指標と考えられているためである。しかしながら、身長に加えて、現在の体格も含めて脳卒中の発症リスクとの関連を調べた研究は少ない。そこで、本研究では脳卒中の発症リスクについて、身長及びBody Mass Index(BMI)の関連を検討した。

＜方法＞
Prospective cohort studyの手法を用いた。対象者は、CIRCS研究グループに含まれる日本国内4地域の一般住民男女で、一定の期間内（2つの地域が1985年から1990年、1つの地域が1985年から1991年、残る一つが1985年から1994年）に健診を受診した40-69歳の12,222人である。対象者を性別に身長で4分位に分け、身長が最も低い群に対する他の群の脳卒中発症リスクを、Cox比例ハザードモデルを用いて算出した。

＜結果＞17年間の追跡の間に565人が脳卒中を発症した（脳梗塞326人、出血性脳卒中186人）。身長は男女ともに全脳卒中の発症リスクと負の関連を示した。特にBMIが23kg/m^{2}未満の者ではその傾向が顕著であった。一方、BMIが23kg/m^{2}以上の者では、身長と全脳卒中の発症リスクとの間に有意な関連は認められなかった。BMIが23kg/m^{2}未満の者について病型別に身長との関連を分析したが、男女ともに身長は脳梗塞、出血性脳卒中のいずれとも有意な負の関連を示した。

＜結論＞
日本人の男女において、身長と脳卒中の発症リスクに負の関連が認められた。また、その傾向はBMI23 kg/m^{2}未満の者で顕著であった。

VI. 研究成果の刊行物・別刷

（統合研究と受賞論文からの抜粋）

（一覧は各個別研究の末尾に記載）

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Influence of Smoking Combined with Another Risk Factor on the Risk of Mortality from Coronary Heart Disease and Stroke: Pooled Analysis of 10 Japanese Cohort Studies

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Key Words
Smoking · Blood pressure · Cholesterol · Coronary heart disease · Stroke

Abstract
Background: In spite of the importance of a multifactorial approach to preventing cardiovascular disease in smokers, most information on the combined adverse effects of smoking and hypertension or high serum cholesterol on cardiovascular disease has been derived from Western populations, and coronary heart disease was often used as the only endpoint. Therefore, the present large-scale pooled analysis attempted to provide reliable information on the adverse effects of the coexistence of smoking and hypertension or high serum cholesterol on the risk of mortality from coronary heart disease and stroke in both, individuals and the entire population in Japan. ***Methods:*** A total of 27,385 male and 39,207 female participants aged 40–89 years were enrolled from 10 well-qualified Japanese 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. ***Results:*** The multivariate-adjusted hazard ratios in male and female current smokers with hypertension, compared with those with neither factor were 2.57 (95% confidence intervals, 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. The fractions of deaths attributable to the coexistence of current smoking and hypertension in men and women were 24.6 and 9.6% for coronary heart disease and 28.1 and 2.0% for cerebral infarction, respectively. Smokers with high serum cholesterol were broadly comparable to hypertensive smokers only with respect to coronary

The members of the EPOCH-JAPAN Research Group are listed in the Appendix.

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mortality risk; the hazard ratios, compared with those with neither factor were 4.19 (2.33–7.53) for men and 3.90 (1.57–9.67) for women. The fraction of coronary deaths attributable to the coexistence of current smoking and high serum cholesterol was 6.3% in men and 2.2% in women. There was no interaction between smoking habit and blood pressure or serum total cholesterol for these two subtypes in both men and women. ***Conclusions:*** Particular attention should be given to smokers who have concomitant hypertension or high serum cholesterol for preventing deaths due to cardiovascular disease. From a public health perspective in Japan, priority should be given to hypertensive smokers, since this group makes a large contribution to the burden of both coronary and cerebral infarction deaths.

Introduction

Cardiovascular disease, including coronary heart disease and stroke, is a major cause of death worldwide [1]. This is also true in Japan, where the life expectancy of the population is fairly high [2]. 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 [3–11]. 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 [4, 6–10, 12].

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 [13–18]. Hypertension is also a prevalent cardiovascular risk factor [19] and 20–25% of Japanese men are estimated to have both hypertension and a smoking habit [20, 21]. Although high serum cholesterol was less prevalent in Asia than in the West in the past two decades [22], 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, 24]. 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 [25–31]. Relevant information is scarce for stroke [30–33], the predominant subtype of cardiovascular disease in Asian populations [23, 24].

The goal of the present large-scale pooled analysis, called Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN), was 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 in both, individuals and the entire population in Japan.

Participants and Methods

Participating Studies

Details of EPOCH-JAPAN are described elsewhere [34, 35]. In brief, EPOCH-JAPAN is a pooled analysis of 13 well-qualified cohort studies in Japan 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.

Endpoints

The majority of participating studies classified the underlying causes of death according to the ninth revision of the International Classification of Diseases (ICD-9) or the tenth revision of the International Classification of Diseases (ICD-10). Endpoints in this report were cardiovascular diseases (ICD-9 codes 390–459, ICD-10 codes I00-I99), which were further classified into coronary heart disease (ICD-9 codes 410-414, ICD-10 codes I20–I25) and stroke (ICD-9 codes 430–438, ICD-10 codes I60-I69). Stroke was also further classified into cerebral infarction (ICD-9 codes 433, 434, and 437.8a-8b, ICD-10 codes I63 and I69.3) and intracerebral hemorrhage (ICD-9 codes 431-432, ICD-10 codes I61 and I69.1).

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 [36]. 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 following formula: PAF = proportion × (hazard ratio – 1)/hazard ratio [37], 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 (i.e. the absence or presence of hypertension, defined as a systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg), 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 ≥6.21 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 [36]. 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 are summarized in table 1. 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) (table 1). 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 2 and 3 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 (≤10%) than men.

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 (table 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–

Table 1. Baseline characteristics of the entire study population and the participants grouped by cohort (EPOCH-JAPAN)

Cohort name	Geographic location prefecture	Year of baseline survey	Follow-up period years	Participants n	Age at study entry years	Smoking habit						Blood pressure, mm Hg		Serum total mmol/l	BMI kg/m^2
						never-smoker		former smoker		current smoker		systolic	diastolic		
			mean ± SD		mean ± SD	%	n	%	n	%	n	mean ± SD	mean ± SD	mean ± SD	mean ± SD
Men															
Tanno-Sobetsu	Hokkaido	1977	19 ± 4	745	50 ± 7	30.5	227	NA[a]		69.5	518	131 ± 19	82 ± 10	4.81 ± 1.05	23.1 ± 2.7
Osaki	Miyagi	1994	6 ± 1	6,246	62 ± 10	21.6	1,350	29.6	1,848	48.8	3,048	132 ± 17	80 ± 11	5.02 ± 0.87	23.6 ± 2.9
Ohasama	Iwate	1997	10 ± 3	877	59 ± 11	49.6	435	NA[a]		50.4	442	134 ± 17	76 ± 11	4.84 ± 0.89	23.1 ± 2.8
Oyabe	Ishikawa	1988	10 ± 2	1,461	60 ± 10	45.2	661	NA[a]		54.8	800	131 ± 20	79 ± 11	4.69 ± 0.85	22.6 ± 2.7
YKK workers	Toyama	1990	11 ± 3	1,970	47 ± 5	27.7	545	15.4	303	57.0	1,122	121 ± 16	76 ± 12	5.21 ± 0.88	22.7 ± 2.6
RERF cohort	Hiroshima	1986	15 ± 4	650	55 ± 11	14.6	95	28.0	182	57.4	373	122 ± 13	79 ± 8	5.11 ± 0.91	21.8 ± 2.7
Hisayama	Fukuoka	1988	11 ± 3	1,107	58 ± 12	20.4	226	29.5	327	50.1	554	135 ± 20	81 ± 11	5.09 ± 1.07	22.8 ± 3.0
JACC study	Nationwide[b]	1988–90	9 ± 2	9,176	58 ± 10	22.9	2,100	24.0	2,206	53.1	4,870	135 ± 19	81 ± 11	4.86 ± 0.90	22.8 ± 2.8
NIPPON DATA80	Nationwide[b]	1980	16 ± 5	2,741	55 ± 11	17.9	492	20.4	558	61.7	1,691	142 ± 21	85 ± 12	4.83 ± 0.87	22.5 ± 2.9
NIPPON DATA90	Nationwide[b]	1990	9 ± 2	2,412	57 ± 11	21.7	524	24.8	597	53.5	1,291	140 ± 20	85 ± 12	5.14 ± 0.96	23.0 ± 3.0
Total			10 ± 4	27,385	58 ± 11	24.3	6,655	22.0	6,021	53.7	14,709	134 ± 19	81 ± 12	4.95 ± 0.91	23.0 ± 2.9
Women															
Tanno-Sobetsu	Hokkaido	1977	19 ± 4	867	50 ± 7	92.5	802	NA[a]		7.5	65	133 ± 20	82 ± 10	5.02 ± 0.91	24.2 ± 3.4
Osaki	Miyagi	1994	6 ± 1	6,967	61 ± 9	93.4	6,509	1.7	115	4.9	343	130 ± 18	77 ± 11	5.48 ± 0.88	24.1 ± 3.2
Ohasama	Iwate	1997	11 ± 2	1,363	58 ± 9	97.5	1,329	NA[a]		2.5	34	129 ± 16	73 ± 11	5.3 ± 0.93	23.9 ± 3.3
Oyabe	Ishikawa	1988	10 ± 1	3,166	58 ± 10	97.4	3,085	NA[a]		2.6	81	126 ± 20	75 ± 11	5.23 ± 0.94	23.2 ± 3.1
YKK workers	Toyama	1990	11 ± 3	1,036	47 ± 5	98.9	1,025	0.2	2	0.9	9	117 ± 16	72 ± 12	5.31 ± 0.95	22.3 ± 2.7
RERF cohort	Hiroshima	1986	16 ± 3	1,447	58 ± 10	87.1	1,261	2.4	35	10.4	151	121 ± 14	76 ± 8	5.57 ± 0.99	22.3 ± 3.3
Hisayama	Fukuoka	1988	11 ± 2	1,515	59 ± 12	91.0	1,379	2.1	31	6.9	105	133 ± 22	76 ± 11	5.53 ± 1.07	22.9 ± 3.3
JACC study	Nationwide[b]	1988–90	10 ± 2	16,151	56 ± 9	95.3	15,394	1.2	188	3.5	569	132 ± 19	78 ± 11	5.26 ± 0.94	23.3 ± 3.2
NIPPON DATA80	Nationwide[b]	1980	17 ± 4	3,420	56 ± 11	89.4	3,057	2.1	73	8.5	290	138 ± 22	81 ± 12	5.05 ± 0.87	23.1 ± 3.4
NIPPON DATA90	Nationwide[b]	1990	10 ± 1	3,275	57 ± 12	89.3	2,925	2.2	72	8.5	278	137 ± 20	81 ± 12	5.49 ± 0.98	23.1 ± 3.3
Total			10 ± 4	39,207	57 ± 10	93.8	36,766	1.3	516	4.9	1,925	131 ± 20	78 ± 11	5.32 ± 0.95	23.4 ± 3.2

BMI = Body mass index; SD = standard deviation; NA = not available.

[a] Former smoking was included in never-smoking in 3 cohort studies (Tanno-Sobetsu, Ohasama and Oyabe).

[b] Study participants in 3 nationwide cohort studies were selected from all areas of Japan.

Table 2. Hazard ratios for cardiovascular mortality and the PAF of deaths in 27,385 men grouped according to age and smoking habit (EPOCH-JAPAN)

	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					

HR = Hazard ratio; CI = confidence interval; NC = not calculated; ref. = reference.

[a] From a Cox proportional hazards regression model with multivariate adjustment for age, systolic blood pressure, serum total cholesterol, body mass index and cohort. [b] PAFs were calculated as proportion × (HR – 1)/HR, using the proportion of deaths in each smoking group and the HR. [c] The heterogeneity for the cardiovascular mortality risk due to smoking between the younger group and the older group was assessed using likelihood ratio tests.

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.

Table 3. Hazard ratios for cardiovascular mortality and the PAF of deaths in 39,207 women grouped according to age and smoking habit (EPOCH-JAPAN)

	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					

HR = Hazard ratio; CI = confidence interval; NC = not calculated; ref. = reference.

[a] From a Cox proportional hazards regression model with multivariate adjustment for age, systolic blood pressure, serum total cholesterol, body mass index and cohort. [b] PAFs were calculated as proportion × (HR – 1)/HR, using the proportion of deaths in each smoking group and the HR. [c] The heterogeneity for the cardiovascular mortality risk due to smoking between the younger group and the older group was assessed using likelihood ratio tests.

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.

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 (table 5). 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

Table 4. Hazard ratios for cardiovascular mortality in 27,385 men and 39,207 women grouped according to blood pressure and smoking habit (EPOCH-JAPAN)

	Men						Women					
	normal blood pressure			hypertension[a]			normal blood pressure			hypertension[a]		
	never-smoker	former smoker	current smoker	never-smoker	former smoker	current smoker	never-smoker	former smoker	current smoker	never-smoker	former smoker	current smoker
Participants, n	3,999	3,363	9,091	2,656	2,658	5,618	24,373	313	1,289	12,393	203	636
Person-years of follow-up	39,718	30,933	91,722	26,210	24,779	57,108	248,032	3,083	13,902	127,784	1,972	6,788
Cardiovascular disease												
Cases, n	67	74	203	121	130	393	284	10	32	507	17	55
Adjusted HR[b]	1.00	1.07	1.43	1.52	1.70	2.83	1.00	1.49	1.70	1.69	2.56	2.70
95% CI	ref.	0.76–1.50	1.08–1.89	1.13–2.06	1.25–2.31	2.17–3.69	ref.	0.79–2.81	1.18–2.46	1.45–1.98	1.56–4.20	2.00–3.64
PAF[c], %		0.5	6.2	4.2	5.4	25.7		0.4	1.5	22.9	1.1	3.8
	p value for interaction[d] = 0.22						p value for interaction[d] = 0.96					
Coronary heart disease												
Cases, n	17	16	55	19	22	87	44	3	7	89	4	19
Adjusted HR[b]	1.00	0.90	1.58	1.00	1.12	2.57	1.00	2.96	2.43	1.86	3.86	6.14
95% CI	ref.	0.45–1.82	0.91–2.74	0.52–1.95	0.59–2.16	1.51–4.38	ref.	0.91–9.60	1.09–5.42	1.27–2.72	1.36–10.97	3.49–10.79
PAF[c], %		NC	9.3	NC	1.1	24.6		1.2	2.5	24.8	1.8	9.6
	p value for interaction[d] = 0.40						p value for interaction[d] = 0.71					
Stroke												
Cases, n	28	30	85	64	67	189	138	6	16	247	6	17
Adjusted HR[b]	1.00	1.04	1.43	1.86	2.10	3.19	1.00	1.99	1.81	1.76	1.97	1.82
95% CI	ref.	0.61–1.76	0.93–2.20	1.19–2.92	1.33–3.31	2.12–4.78	ref.	0.88–4.53	1.08–3.05	1.41–2.19	0.86–4.50	1.09–3.04
PAF[c], %		0.2	5.5	6.4	7.6	28.0		0.7	1.7	24.8	0.7	1.8
	p value for interaction[d] = 0.77						p value for interaction[d] = 0.21					
Cerebral infarction												
Cases, n	15	23	44	35	45	110	65	4	6	104	4	10
Adjusted HR[b]	1.00	1.38	1.45	1.61	2.29	3.28	1.00	2.30	1.33	1.25	1.92	1.61
95% CI	ref.	0.71–2.68	0.80–2.63	0.87–2.98	1.25–4.18	1.89–5.71	ref.	0.83–6.36	0.58–3.09	0.90–1.73	0.69–5.36	0.81–3.18
PAF[c], %		2.3	5.0	4.9	9.3	28.1		1.2	0.8	10.8	1.0	2.0
	p value for interaction[d] = 0.49						p value for interaction[d] = 0.86					
Intracerebral hemorrhage												
Cases, n	10	3	24	23	15	40	24	2	3	70	0	1
Adjusted HR[b]	1.00	0.30	1.04	2.23	1.58	2.00	1.00	4.23	2.08	3.33	0.00	0.75
95% CI	ref.	0.08–1.11	0.49–2.19	1.04–4.75	0.69–3.63	0.98–4.07	ref.	0.99–18.08	0.62–6.95	2.04–5.44		0.10–5.63
PAF[c], %		NC	NC	NC	NC	NC		NC	NC	NC	NC	NC
	p value for interaction[d] = 0.29						p value for interaction[d] = 0.01					

HR = Hazard ratio; CI = confidence interval; NC = not calculated; ref = reference.

[a] Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg.[b] From a Cox proportional hazards regression model with multivariate adjustment for age, body mass index, serum total cholesterol and cohort. [c] PAFs were calculated as proportion × (HR – 1)/HR, using the proportion of deaths in each smoking group and the HR. [d] The interaction between smoking habit and blood pressure was assessed using likelihood ratio tests.

Table 5. Hazard ratios for cardiovascular mortality in 27,385 men and 39,207 women grouped according to serum total cholesterol and smoking habit (EPOCH-JAPAN)

	Men						Women					
	normal serum cholesterol			high serum cholesterol[a]			normal serum cholesterol			high serum cholesterol[a]		
	never-smoker	former smoker	current smoker	never-smoker	former smoker	current smoker	never-smoker	former smoker	current smoker	never-smoker	former smoker	current smoker
Participants, n	6,030	5,387	13,559	625	634	1,150	30,513	392	1,622	6,253	124	303
Person-years of follow-up	59,933	49,733	137,259	5,996	5,979	11,571	313,809	3,860	17,556	62,007	1,195	3,133
Cardiovascular disease												
Cases, n	177	181	552	11	23	44	646	18	71	145	9	16
Adjusted HR[b]	1.00	1.06	1.63	0.81	1.28	1.94	1.00	1.27	1.58	0.97	1.74	1.87
95% CI	ref.	0.86–1.31	1.37–1.94	0.44–1.49	0.82–1.98	1.39–2.71	ref.	0.80–2.04	1.23–2.03	0.81–1.17	0.90–3.37	1.14–3.09
PAF[c], %		1.0	21.6	NC	0.5	2.2		0.4	2.9	NC	0.4	0.8
	p value for interaction[d] = 0.48						p value for interaction[d] = 0.60					
Coronary heart disease												
Cases, n	32	32	124	4	6	18	103	3	21	30	4	5
Adjusted HR[b]	1.00	1.02	1.96	1.56	1.77	4.19	1.00	1.38	3.04	1.30	5.17	3.90
95% CI	ref.	0.62–1.69	1.32–2.91	0.55–4.44	0.73–4.28	2.33–7.53	ref.	0.43–4.36	1.89–4.90	0.86–1.97	1.88–14.18	1.57–9.67
PAF[c], %		0.3	28.1	0.7	1.2	6.3		0.5	8.5	4.2	1.9	2.2
	p value for interaction[d] = 0.82						p value for interaction[d] = 0.40					
Stroke												
Cases, n	99	87	263	4	10	11	320	8	26	65	4	7
Adjusted HR[b]	1.00	1.04	1.60	0.59	1.17	1.02	1.00	1.19	1.20	0.88	1.61	1.70
95% CI	ref.	0.76–1.41	1.25–2.06	0.22–1.62	0.60–2.26	0.54–1.91	ref.	0.59–2.41	0.80–1.80	0.67–1.15	0.60–4.33	0.80–3.61
PAF[c], %		0.7	21.3	NC	0.3	0.05		0.3	1.0	NC	0.4	0.7
	p value for interaction[d] = 0.40						p value for interaction[d] = 0.49					
Cerebral infarction												
Cases, n	49	63	145	1	5	9	144	6	13	25	2	3
Adjusted HR[b]	1.00	1.35	1.73	0.28	1.10	1.72	1.00	1.73	1.20	0.79	1.67	1.60
95% CI	ref.	0.92–1.99	1.24–2.42	0.04–2.03	0.44–2.78	0.84–3.52	ref.	0.76–3.93	0.68–2.13	0.51–1.21	0.41–6.77	0.51–5.05
PAF[c], %		6.0	22.5	NC	0.2	1.4		1.3	1.1	NC	0.4	0.6
	p value for interaction[d] = 0.39						p value for interaction[d] = 0.75					
Intracerebral hemorrhage												
Cases, n	30	13	64	3	5	0	76	1	4	18	1	0
Adjusted HR[b]	1.00	0.46	1.04	1.26	1.66	0.00	1.00	0.68	0.83	1.01	1.76	0.00
95% CI	ref.	0.24–0.90	0.66–1.62	0.38–4.16	0.63–4.36		ref.	0.09–4.88	0.30–2.29	0.60–1.70	0.24–12.78	
PAF[c], %		NC	NC	NC	NC	NC		NC	NC	NC	NC	NC
	p value for interaction[d] = 0.001						p value for interaction[d] = 0.39					

HR = Hazard ratio; CI = confidence interval; NC = not calculated; ref. = reference.

[a] High serum cholesterol was defined as serum total cholesterol ≥6.21 mmol/l. [b] From a Cox proportional hazards regression model with multivariate adjustment for age, body mass index, systolic blood pressure and cohort. [c] PAFs were calculated as proportion × (HR – 1)/HR, using the proportion of deaths in each smoking group and the HR. [d] The interaction between smoking habit and serum total cholesterol was assessed using likelihood ratio tests.

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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 in Japanese 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 Japanese 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 [11], and these risks were broadly comparable with our results although these estimates are for men and women combined. Honjo et al. [5] 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. 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. [5] 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 nonsignificant increment in the corresponding risk. Our results are in accordance with the results of the Japan Public Health Center Study [38] and the results of the previous Korean male study [10] that found that smoking, even heavy smoking, had little effect on incident intracerebral hemorrhage. We suggest that the discrepant results of intracerebral hemorrhage come from the inappropriate adjustment for confounders in their study.

In previous studies [4], 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 [4], 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 [4]. Although these discrepant results may have resulted in part from different characteristics of the two study populations, our results suggest a potentially larger burden of stroke deaths, especially cerebral infarction deaths, due to smoking in Japanese men than previously reported. Our estimated PAF of stroke due to smoking among Japanese men is comparable to the corresponding PAF in Korean men [8, 10], but is larger than the corresponding PAF in Chinese men (approximately 10%) [6, 7]. Although this may be due to the large proportion of fatal intracerebral hemorrhage among total strokes in China [7], and to a difference in background mortality rate between Japanese and Chinese never-smokers [6, 35], this international comparison indicates the importance of tobacco control for preventing stoke in Japan.