代表文献の要約３

Chei CL, Yamagishi K, Kitamura A, Kiyama M, Imano H, Ohira T, Cui R, Tanigawa T, Sankai T, Ishikawa Y, Sato S, Iso H. C-reactive protein levels and risk of stroke and its subtype in Japanese: The Circulatory Risk in Communities Study (CIRCS). Atherosclerosis. 2011 Jul;217(1):187-93

日本人の高感度CRP値と脳卒中発症リスク：The Circulatory Risk in Community Study (CIRCS)

＜目的＞

これまでに行われてきた疫学研究では、高感度CRP(hsCRP)が循環器疾患発症の予測因子であることが報告されている。しかし、hsCRPと脳卒中の発症、特に病型別にみた脳卒中の発症リスクに関する研究は少ない。そこで、本研究では全脳卒中及び病型別の脳卒中の発症リスクについて、hsCRP値との関連を分析した。

＜方法＞

Nested case-control 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3地域の一般住民男女で、一定の期間内（一つの地域が1984年から2001年、他の地域が1989年から1998年）に健診を受診し、血清を冷凍保存している40－85歳の13,521人とした。この中で、脳卒中の発症例と性、年齢、受診年、地域をマッチさせた対照例を1対3の割合でとり、分析を行った。

＜結果＞

2005年までの追跡で、261人が脳卒中を発症した（脳梗塞165人、出血性脳卒中96人）。hsCRP値の1SDの変化と脳卒中、脳梗塞および穿通枝系脳血栓の発症リスクの間には正の関連が認められた。これらの関連は既知の循環器疾患のリスク因子を調整しても、有意なままであった。多変量調整を行ったLog transformed hsCRPの1SDあたりのオッズ比は、脳卒中が1.17(1.01-1.35)、脳梗塞が1.27(1.06-1.52)、穿通枝系脳血栓が1.24(1.00-1.55)であった。hsCRPと脳梗塞の発症リスクは、性、年齢、BMI、喫煙で層別しても、相異は見られなかった。hsCRPと出血性脳卒中の発症リスクは関連を認めなかった。

＜結論＞

日本人の男女において、hsCRPが脳卒中および脳梗塞発症の予測因子であることが認められた。

代表文献の要約４

Shimizu Y, Maeda K, Imano H, Ohira T, Kitamura A, Kiyama M, Okada T, Ishikawa Y, Shimamoto T, Yamagishi K, Tanigawa T, Iso H. Chronic kidney disease and drinking status in relation to risks of stroke and its subtypes: the Circulatory Risk in Communities Study (CIRCS). Stroke. 42: 2531-2537, 2011.

地域住民における飲酒習慣と慢性腎臓病（CKD）が脳卒中のタイプ別病型の発症に及ぼす影響について

＜背景＞

GFRの推定値により定義された慢性腎臓病（CKD）は脳卒中の危険因子となることが、幾つかの先行疫学研究により報告されているが、CKDと脳卒中のタイプ別の病型との関連やその関連の性差に関しては限られた報告しかない。

＜方法＞

我々は40から69歳までの、12,222人の日本人男女を対象とした、4地域における脳卒中サーベイランスを用いて、前向きコホート研究を行い、CKDと脳卒中、及び脳卒中のタイプに関係について検討を行った。

＜結果＞

17年にわたる経過観察において、566例の脳卒中（内訳327例の脳虚血と186例の脳出血）を認めた。脳卒中の年齢-地域-調整ハザード比は、男性においても女性においてもGFRの値と負の相関関係を示した。非CKD群（GFR≥60ml/min/1.73m^2）に比較し年齢-地域-調整脳卒中ハザード比はCKD（GFR<60ml/min/1.73m^2）において、男性では1.63（95％信頼区間：1.22-2.17）を、女性においては1.51（95％信頼区間：1.13-2.02）を認めた。CKDによる過剰リスクは男性においては主に脳出血に、女性においては主に脳虚血において認めた。これらの関係は、既知の心血管病危険因子を調整変数として加え解析を行っても有意であった。飲酒習慣により層別化し解析を行ったところ、CKDの脳出血過剰リスクは飲酒者にのみ認められた。CKDの脳出血における多変量調整ハザード比は、飲酒男性においては4.18（95％信頼区間：2.31-7.57）、飲酒女性においては7.00（95％信頼区間：1.92-25.56）であった。

＜結果＞

CKDは男性においては脳出血リスク上昇と関係を示し、女性においては脳虚血のリスク上昇と関係を示した。これらの性差の一部は男女における飲酒率の違いにより説明し得る。

Ⅳ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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Ⅴ．研究成果の刊行物・別刷

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Population attributable numbers and fractions of deaths due to smoking: A pooled analysis of 180,000 Japanese

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ABSTRACT

Objective. Age- and sex-specific population attributable fraction (PAF) and premature deaths attributable to smoking were estimated from a pooled analysis of cohort studies in Japan.

Methods. A pooled analysis of individual participant data from 13 well-qualified cohort studies throughout Japan (a total of 183,251 Japanese aged 40–89, 69,502 men and 113,749 women; the baseline years between 1987 and 1995 with average 10 years of follow-up) was performed. Poison regression model was used to estimate age- and sex-specific hazard ratios, and their PAFs of all-cause deaths and number of annual premature deaths attributable to smoking were estimated.

Results. Overall PAF attributable to smoking was 24.6% in men and 6.0% in women. The estimated number of annual premature deaths due to smoking was 121,854 (men: 109,998; women: 11,856) in Japan. The age-specific PAF was largest in men aged 60–69 (47.7%) and in women aged 50–59 (12.2%). In the older group aged 70–79 and 80–89, PAF was 15.4% and 8.0% in men and 3.5% and 1.5% in women, respectively.

Conclusions. Age-specific PAFs attributable to smoking in Japanese men are much larger than that reported from other Asian countries.

Introduction

Cigarette smoking is one of the most important, established risk factors for diseases that threaten human life (Peto et al., 1999). A large volume of evidence on the harm of smoking has been published (Ezzati and Lopez, 2003; Lopez et al., 2006), with challenges and programs to stop smoking being common in Western countries. The mortality attributable to smoking showed the substantial impact that smoking may have on people's health and has been reported from various countries (Centers for Disease Control and Prevention (CDC), 2008; Gu et al., 2009; Hara et al., 2002; Honjo et al., 2010; Hozawa et al., 2004; Katanoda et al., 2008; Peto et al., 2006; Peto et al., 1992; Pham et al., 2007). However, smoking rates still remain high in Asian countries (Martiniuk et al., 2006) and incentive measures for smoking cessation are urgently required.

A recent study from China reported the number of deaths attributable to smoking (Gu et al., 2009). We expect that the impact of smoking on total mortality may be different in Japan; a more economically developed Asian country with the highest life expectancy in the world (World Health Organization, 2005) but with a high smoking rate in men. Moreover, few studies from Asia have performed age- and sex-specific investigations on the contribution of smoking to mortality, as such investigations need large-scale data from cohort studies.

In this pooled analysis of 180,000 Japanese men and women from 13 well-qualified cohort studies in Japan, we examined age- and sex-specific population attributable fraction (PAF) of mortality by smoking and the annual number of premature deaths attributable to smoking.

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Methods

Study participants

The EPOCH-JAPAN (Evidences for Cardiovascular Prevention from Observational Cohorts in Japan) is the pooling project of a number of well-qualified cohort studies which investigates the relationship between health examination measures (laboratory measures and lifestyle factors) and mortality in the Japanese population. The EPOCH-JAPAN consists of 13 cohort studies in Japan and includes a total number of 188,321 participants followed up for an average of 10 years. The year range of baseline survey in the cohort was between 1987 and 1995. The details of this project have been described previously (Murakami et al., 2008). In the EPOCH-JAPAN database, the age range of the participants at study entry was set between 40 and 89 years and the termination of the follow-up was fixed at age 90. A total of 5070 participants were excluded from the analysis; missing information of variables (smoking habit, 4984; blood pressure, 74), few participants within a sparse age and sex strata in the cohort ($n = 12$). Finally, data for 183,251 participants were included in the analyses.

Hazard ratio estimation

We estimated age- and sex-specific hazard ratios for total mortality according to smoking habits. The statistical model was applied to each age group stratified by decades (40–49, 50–59, 60–69, 70–79, 80–89). Smoking habit was classified as either never smoked, former smokers or current smokers, with the group who had never smoked acting as the reference level. A Poisson regression model was used with adjustment for systolic blood pressure, body mass index, drinking status (drinkers/ex-drinkers/non-drinkers) and study cohort. To examine graded increases in the hazard ratios in the smoking categories, a score (1, 2, or 3) was assigned to each category and the statistical significance of increases in this score examined using the trend test.

Impact of smoking on the total deaths in Japan

The age- and sex-specific PAF (Hanley, 2001; Kleinbaum et al., 1982) for smoking was calculated by multiplying the estimated hazard ratio with the prevalence of smoking status among the Japanese population. We used the current age- and sex-specific smoking prevalence from the National Health and Nutrition Survey in Japan, 2006 (Ministry of Health Labour and Welfare, 2009). The estimated annual number of premature deaths due to smoking in the Japanese population was estimated from above PAFs. We used the age- and sex-specific number of all-cause deaths in the year 2008 (Japan Health and Welfare Statistics Association, 2005), with the corresponding PAFs multiplied by the total number of deaths to calculate the number of premature deaths in each category.

All statistical analysis was performed using SAS release 9.13 (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 shows the baseline characteristics of the participants in this study. The total number of participants in this analysis was 183,251 (69,502 men and 113,749 women) and the total number of all-cause deaths was 17,224 (9612 men and 7612 women) during follow-up. The mean age at study entry was 59.6 years for men and 58.4 years for women and the mean follow-up period was 9.6 years for men and 9.9 years for women. As reported previously, the distribution of baseline characteristics was not different between the cohorts (Murakami et al., 2008).

Table 2 shows the age- and sex-specific mortality rates, hazard ratios and PAFs for all-cause deaths according to smoking status. Crude mortality rate was generally the highest in current smokers of the three smoking categories in each age and sex group. A significant graded increasing trend in multivariate-adjusted hazard ratios according to smoking status was observed in all age and sex groups, except for men and women aged 40–49. The adjusted hazard ratio in current smokers was highest in men aged 60–69 (hazard ratio 1.96) and women aged 50–59 (hazard ratio 2.21) compared with people who had never smoked. The PAF for smoking was consistently larger in current smokers than in former smokers. In men, the PAF in current smokers was largest in men aged 60–69 (33.4%), and for men aged 40–49 and 50–59 was more than 25%. In women, the PAF was largest in women aged 50–59 (11.1%).

Table 3 shows the PAF for smokers (former and current smokers combined) in each age and sex group and the estimated numbers of premature deaths attributable to smoking in Japan in 2008. The PAFs by age groups ranged from 8.0% (age 80–89) to 47.7% (age 60–69) in men and from 1.5% (age 80–89) to 12.2% (age 50–59) in women. Overall PAF in participants aged 40–89 was 24.6% in men and 6.0% in women. A total of 109,998 men and 11,856 women were estimated to have died attributable to smoking in Japan in 2008. These numbers were greatest in men aged 60–69 (45,409 deaths per year) and aged 70–79 (27,259 deaths per year).

Discussion

This large-scale pooled analysis of 180,000 Japanese from 13 well-qualified cohort studies showed that estimated annual premature deaths attributable to smoking habits were 110,000 for men and 12,000 for women in Japan. The proportion of premature all-cause deaths was 24.6% for men, with this proportion reaching 47.7% in men aged 60–69. This considerable loss of health attributable to smoking was confirmed in this analysis in Japan, a developed country with the greatest longevity in the world, but with a high smoking rate, especially in men.

The comprehensive global assessments of premature deaths attributable to smoking had been taken among developed countries (Peto et al., 1992). This report is the only one that we can find sex- and age-specific PAFs of developed countries. The report was focused on the global assessment of smoking harm so that the age group only divided into two categories (age from 35 to 69/age 70 and over). The updated report in year 2006 (Peto et al., 2006) showed that PAFs due to smoking in the developed countries are 30% (men aged 35–69), 19% (men age 70 and over), 11% (women aged 35–69) and 8% (women age 70 and over), respectively. Compared with our result, these numbers were lower in men and higher in women. In the country specific section in this report, they showed that the annual number of premature deaths due to smoking in Japan, year 2000 was estimated 90,000 in men and 24,000 in women, which were also lower in men and higher in women compared with our results. Particularly, this discrepancy is quite obvious in women aged 70 and over, where 20,000 in Peto et al. and 6000 in our study. We found that their smoking prevalence estimated from their method was quite different from the current smoking prevalence in Japanese women. We believe that our direct approach is more appropriate to show the current status of premature deaths due to smoking in Japan.

There have been several reports on PAF due to smoking in Asian countries including Japan (Hara et al., 2002; Hozawa et al., 2004; Katanoda et al., 2008; Pham et al., 2007). A report from north-east Japan (Miyagi) showed a larger PAF (34%) for men (Hozawa et al., 2004), whereas a report from southern Japan (Fukuoka) showed a smaller PAF (16.0%) (Pham et al., 2007). The PAFs reported from other nationwide cohort studies in Japan were similar to our results (Hara et al., 2002; Katanoda et al., 2008). For women, previously reported PAFs ranged from 4% to 8% in Japan (Hara et al., 2002; Hozawa et al., 2004; Katanoda et al., 2008; Pham et al., 2007) and our results come in the middle (6.0%). One reason for these variations in PAF may be the difference in hazard ratios of current smokers (ranged from 1.30 to 1.72), and it is important to note that the hazard ratio of current smokers played a dominant role in determination of PAF values in previous Japanese studies.

Although there have been only a few studies on PAF due to smoking in other Asian countries, a large-scale study was recently conducted in China (Gu et al., 2009). That study showed that overall

Table 1
Baseline characteristics of the study participants in each cohort (EPOCH-JAPAN).

Men

Cohort name	Geographic location (Prefecture)	Year of baseline survey	Follow up periods (years)		Number of participants	Age at study entry (years)		Blood pressure (mm Hg)				Smoking* status				Drinking† status				BMI (kg/m^2)		Number of all-cause mortality
								Systolic		Diastolic												
			Average	SD		Average	SD	Average	SD	Average	SD	Never	Past	Current	%	Never	Past	Current	Missing	Average	SD	
Tanno-Sobetsu	Hokkaido	1977	19	4	750	51	7	131	19	82	10	228	0	522	70	214	0	533	3	23.1	2.7	88
Osaki	Miyagi	1994	6	1	6,597	63	10	133	17	80	11	1,413	1,996	3,188	48	1,016	535	4,936	110	23.6	2.9	509
Ohasama	Iwate	1987	10	3	1,122	61	11	135	17	76	11	585	0	537	48	459	0	663	0	23.1	2.8	250
Oyabe	Ishikawa	1988	10	2	1,509	61	10	131	20	79	11	689	0	820	54	392	416	701	0	22.6	2.7	270
YKK workers	Toyama	1990	11	2	3,177	51	6	121	15	74	12	809	494	1,874	59	562	38	2,577	0	22.6	2.6	73
SPMI cohort	Shiga	1989–1991	9	3	1,937	54	8	133	18	82	11	544	229	1,164	60	398	0	1,528	11	22.6	2.7	149
Suita	Osaka	1989	6	2	2,300	60	11	131	21	80	12	423	772	1,105	48	504	99	1,694	3	22.7	2.9	164
RERF cohort	Hiroshima	1986	14	5	1,329	58	12	134	21	85	12	191	417	721	54	200	86	959	84	22.2	2.9	495
Hisayama	Fukuoka	1988	10	3	1,113	58	12	135	20	81	11	228	329	556	50	369	70	673	1	22.8	3.0	180
JACC study	Nationwide‡	1988–1990	9	2	10,621	58	10	135	19	81	11	2,392	2,639	5,590	53	2,020	547	7,811	243	22.8	2.9	1,342
NIPPON DATA80	Nationwide‡	1980	16	5	3,155	56	11	142	22	85	12	578	655	1,922	61	656	219	2,275	5	22.5	2.9	992
NIPPON DATA90	Nationwide‡	1990	9	2	2,759	58	12	140	20	85	12	605	708	1,446	52	962	206	1,591	0	23.0	3.0	412
Ibaraki	Ibaraki	1993	10	2	33,133	61	10	137	18	81	11	7,376	9,190	16,567	50	9,629	2,039	21,465	0	23.3	3.0	4,688
Total			10	3	69,502	60	10	135	19	81	11	16,061	17,429	36,012	52	17,381	4,255	47,406	460	23.1	2.9	9,612

Women

Cohort name	Geographic location (Prefecture)	Follow up periods (years)		Number of participants	Age at study entry (years)		Blood pressure (mm Hg)				Smoking* status				Drinking† status				BMI (kg/m^2)		Number of all-cause mortality
							Systolic		Diastolic												
		Average	SD		Average	SD	Average	SD	Average	SD	Never	Past	Current	%	Never	Past	Current	Missing	Average	SD	
Tanno-Sobetsu	Hokkaido	19	4	865	50	7	133	20	82	10	800	0	65	8	788	0	76	1	24.2	3.4	63
Osaki	Miyagi	6	2	7,181	62	9	130	18	78	11	6,706	120	355	5	5,209	196	1,407	369	24.1	3.2	225
Ohasama	Iwate	11	2	1,678	60	10	130	17	73	11	1,639	0	39	2	1,584	0	94	0	24.0	3.3	194
Oyabe	Ishikawa	10	1	3,208	58	10	126	20	75	11	3,126	0	82	3	2,770	399	39	0	23.2	3.1	255
YKK workers	Toyama	11	2	1,724	50	6	115	15	70	11	1,693	9	22	1	1,320	7	397	0	22.0	2.9	18
SPMI cohort	Shiga	9	3	2,568	54	8	132	17	79	10	2,467	14	87	3	2,048	0	514	6	23.0	3.0	63
Suita	Osaka	6	2	2,539	58	11	128	22	77	12	2,173	87	279	11	1,711	39	771	18	22.5	3.2	83
RERF cohort	Hiroshima	15	4	2,994	63	12	134	23	81	12	2,602	96	296	10	1,604	47	949	394	22.9	3.7	814
Hisayama	Fukuoka	11	3	1,518	60	12	133	22	76	11	1,382	31	105	7	1,366	17	133	2	22.9	3.3	123
JACC study	Nationwide ‡	10	2	17,853	57	10	132	19	78	11	16,989	208	656	4	14,143	195	3,273	242	23.3	3.2	913
NIPPON DATA80	Nationwide ‡	17	4	4,016	56	11	139	22	82	12	3,573	91	352	9	3,235	59	716	6	23.1	3.4	787
NIPPON DATA90	Nationwide ‡	10	2	3,697	58	12	138	20	81	12	3,284	87	326	9	3,443	35	219	0	23.1	3.3	312
Ibaraki	Ibaraki	10	2	63,908	59	10	132	18	78	11	60,357	462	3,089	5	57,784	125	5,999	0	23.6	3.2	3,762
Total		10	3	113,749	58	10	132	19	78	11	106,791	1,205	5,753	5	97,005	1,119	14,587	1,038	23.5	3.3	7,612

*Smoking status of ex-smokers was classified as never smokers in three cohort studies (Tanno-Sobetsu, Ohasama and Oyabe).
†Drinking status of ex-drinkers was classified as never drinkers in three cohort studies (Tanno-Sobetsu, Ohasama and Oyabe).
‡Study participants of the nationwide cohort study were selected from all areas of Japan.

Table 2
Age- and sex-specific mortality rates, adjusted hazard ratios and population attributable fractions of all-cause deaths according to smoking status (EPOCH-JAPAN).

Age groups (years)	Smoking status	Prevalence of smoking (%)‡	Person years of follow-up	Number of deaths	Crude mortality rate*	Adjusted hazard ratio†	95% Confidence interval	P for trend	PAF‡ (%)
Men									
40–49	Never	31.9	16,716	20	120	1.00			–
	Former	21.6	13,003	24	185	1.55	0.94 – 2.58		11.9
	Current	46.5	45,722	91	199	1.59	1.05 – 2.41	0.08	27.4
50–59	Never	28.9	39,736	105	264	1.00			–
	Former	24.9	30,583	95	311	1.16	0.91 – 1.47		4.0
	Current	46.2	90,304	396	439	1.64	1.36 – 1.97	<0.01	29.6
60–69	Never	39.2	51,521	285	553	1.00			–
	Former	26.0	52,616	471	895	1.55	1.36 – 1.76		14.3
	Current	34.8	118,131	1,350	1,143	1.96	1.76 – 2.19	<0.01	33.4
70–79	Never	51.7	36,982	695	1,879	1.00			–
	Former	28.4	53,893	1,190	2,208	1.17	1.08 – 1.27		4.8
	Current	19.9	81,197	2,422	2,983	1.53	1.42 – 1.65	<0.01	10.5
80–89	Never	51.7	10,511	620	5,899	1.00			–
	Former	28.4	12,238	749	6,120	1.07	0.97 – 1.17		2.0
	Current	19.9	13,795	1,099	7,967	1.30	1.20 – 1.42	<0.01	6.0
Overall	Never	38.4	155,466	1,725	1,110	1.00			–
	Former	25.5	162,333	2,529	1,558	1.20	1.26 – 1.14		5.1
	Current	36.2	349,149	5,358	1,535	1.54	1.62 – 1.47	<0.01	19.5
Women									
40–49	Never	81.4	126,961	117	92	1.00			–
	Former	4.8	1,557	2	128	1.52	0.46 – 4.95		2.5
	Current	13.8	9,624	9	94	0.95	0.53 – 1.71	0.96	−0.7
50–59	Never	86.8	278,258	455	164	1.00			–
	Former	4.0	2,371	5	211	1.26	0.60 – 2.65		1.0
	Current	9.2	17,193	62	361	2.21	1.75 – 2.80	<0.01	11.1
60–69	Never	91.1	351,145	1,338	381	1.00			–
	Former	2.6	3,368	22	653	1.64	1.14 – 2.34		1.6
	Current	6.4	15,547	100	643	1.70	1.42 – 2.03	<0.01	4.5
70–79	Never	94.8	247,653	2,710	1,094	1.00			–
	Former	2.4	3,201	63	1,968	1.59	1.28 – 1.98		1.4
	Current	2.8	10,973	222	2,023	1.74	1.54 – 1.96	<0.01	2.1
80–89	Never	94.8	55,577	2,264	4,074	1.00			–
	Former	2.4	1,003	54	5,384	1.16	0.92 – 1.47		0.4
	Current	2.8	3,109	189	6,079	1.39	1.22 – 1.59	<0.01	1.1
Overall	Never	89.2	1,059,594	6,884	650	1.00			–
	Former	3.3	11,500	146	1,270	1.39	1.61 – 1.21		1.3
	Current	7.5	56,446	582	1,031	1.63	1.75 – 1.51	<0.01	4.7

PAF, population attributable fraction.
*Rates per 100,000 person-years.
†A Poisson regression model was used to estimate hazard ratios adjusted for potential confoundings (systolic blood pressure, body mass index, drinking status and study cohort).
‡Each PAF of the former and current smokers showed the partial component of PAF in sex and age category. These PAFs were estimated from the hazard ratios of our study and the age- and sex-specific smoking prevalence from the National Health and Nurition Survey in Japan, 2008.

PAF of all-cause deaths due to smoking was 12.9% in men, which is considerably smaller than the value measured in our study, despite the smoking rate being rather higher in China (71.1% in men). Age-specific PAFs were also reported in that study and were also smaller than those calculated in our study. For example, the PAF in men aged 40–54 was 12.7% in China, less than half the PAF values measured in our study (39.3% for ages 40–49; 33.6% for ages 50–59). One possibility of this difference comes from the study period that studies were conducted. The baseline survey in the China study began at 1991 and the follow-up ended in 2000, although some of our cohorts started before 1990. In our study, the baseline survey of three cohorts were conducted before mid-1980s and their proportion among the study participants are 8% ($n=5234$) in men and 7% ($n=7875$) in women. We think the difference of the study period dose not totally explain PAF difference in Japan and China. These lower PAF values in China may be explained by the smaller hazard ratio (HR = 1.21) in male smokers (current and former combined), compared with hazard ratios of 1.54 in current smokers and 1.20 in former smokers measured in our study. All-cause mortality rate in people who had never smoked were also different between the two studies; 1279 per

Table 3
Age- and sex-specific population attributable fraction for all-cause deaths due to smoking in EPOCH-JAPAN and the estimated premature deaths due to smoking in Japan, 2008.

Age groups (years)	Population attributable fraction (%)*		Number of all-cause deaths in 2008, Japan†		Estimated premature deaths due to smoking	
	Men	Women	Men	Women	Men	Women
40–49	39.3	1.8	16,851	8,511	6,624	152
50–59	33.6	12.2	52,812	24,629	17,718	2,995
60–69	47.7	6.1	95,137	42,409	45,409	2,591
70–79	15.4	3.5	177,349	99,248	27,259	3,444
80–89	8.0	1.5	163,266	181,883	12,988	2,674
Overall	24.6	6.0	505,415	356,680	109,998	11,856

*Sum of population attributable fractions for former smokers and current smokers.
†Number of deaths in 2008 in Japan was obtained from the Vital Statistics of Japan, 2008.

100,000 person-years for men in the Chinese study, which was higher than that in our study (1110 per 10,0000 person-years). This higher background mortality rate, which is the denominator of hazard ratio, leads to smaller PAFs attributable to smoking in China. It would be expected that background mortality rate of Chinese non-smokers will decrease and the relative amounts of smoking-related causes of deaths (cancer and cardiovascular diseases) will increase in the future, like contemporary situation in Japan. Our results from Japan may become more common feature of health threat in Asian countries caused by smoking.

Age-specific analysis of PAF provided a clear picture of smoking harm. This harm persisted through the age categories and also substantially observed in people aged 70 and over in the Japanese population. A cohort study in an elderly population in Hong Kong also showed that the PAF for smoking in people aged 65 and over was 23.4% for men and 4.8% for women (Lam et al., 2007a, 2007b). Our findings in elderly people provide evidence that harm from smoking has a broad impact from young age to older age in developed Asian regions. The PAF for smoking in people aged 80–89 was only available in countries with longer life spans such as Japan, with our study being the only one in the Asian region able to estimate this figure.

The relatively high PAF among men aged 60–69 could partly be explained by the cohort effect. The baseline survey year of the cohort of EPOCH-JAPAN ranged from 1987 to 1995. This shows that the men aged in the 60–69 year in our study correspond to the generation who spent their 20s just after Japan defeated World War II. At that time, the smoking habit spread among Japanese men and the amount of lifetime smoking of age 60–69 in our study would be large compared to other age groups.

This study had several limitations. First, we only have all-cause death and a disease specific mortality was not available from the database. Second, the quantity of cigarettes smoking was not examined in our study. Only few cohorts collected the amount of smoking and every cohort used slightly different type of smoking category. To integrate several type of smoking classification of the 13 cohort studies into one, we finally set the smoking category as follows; never, former and current. Third, information of smoking status in the participants is based on the baseline survey of each cohort and changes in smoking status during follow-up were not considered in our study. As the smoking rate in Japanese men has been decreasing constantly, these misclassifications of smoking status during the follow-up may underestimate the relationships. Fourth, we focused mainly on individual smoking habits and did not take into account the effect of environmental tobacco smoke. Prior to 2000, smoking was not restricted in public places and environmental tobacco smoke was common in work places and homes in Japan. Passive smoking has been reported to increase mortality of non-smokers (Kurahashi et al., 2008; McGhee et al., 2005), although we were unable to estimate this impact in this pooled analysis.

Using the data of this pooled analysis, we estimate that approximately 110,000 men and 12,000 women die every year due to smoking in Japan. This number of deaths corresponds to 36% of annual deaths from cardiovascular diseases and lung cancer in Japan (364,547 deaths in year 2006) (Japan Health and Welfare Statistics Association, 2005). These large numbers therefore have a major impact on public health policy and the Japanese nation. Even though Japan accepted the WHO Framework Convention on Tobacco Control (FCTC) in June 2004, the smoking rate in Japan still remains high compared with Western countries. The Health Promotion Act was introduced in Japan in 2002. According to this law, smoking in public places was prohibited to protect non-smokers from passive smoking. In October 2010, the tobacco tax has drastically risen by the Japanese government and an urgent and an effective measure is now taken to accomplish lower smoking rate in the next decades. We believe the present study gives an important evidence to promote anti-smoking campaign to the policy makers in Japan. Our results also encourage promoting smoking ban campaign of other Asian countries with high smoking rates.

In conclusion, pooled data of 180,000 Japanese from well-qualified cohort studies in Japan revealed that there are a large number of deaths attributable to smoking in Japan and age-specific PAFs attributable to smoking in men are much larger than that reported from China.

Conflict of interest statement
No conflict of interest.

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Mild Retinopathy Is a Risk Factor for Cardiovascular Mortality in Japanese With and Without Hypertension : The Ibaraki Prefectural Health Study

Toshimi Sairenchi, Hiroyasu Iso, Kazumasa Yamagishi, Fujiko Irie, Yoshiro Okubo, Junko Gunji, Takashi Muto and Hitoshi Ota

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Mild Retinopathy Is a Risk Factor for Cardiovascular Mortality in Japanese With and Without Hypertension

The Ibaraki Prefectural Health Study

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Background—It is unclear whether mild hypertensive retinopathy is a risk factor for mortality. This study examined whether mild hypertensive retinopathy could be a risk factor for cardiovascular mortality in subjects with and without hypertension.

Methods and Results—In this cohort study, 87 890 individuals (29 917 men and 57 973 women) 40 to 79 years of age in 1993 were followed up until 2008. Retinal photography was classified as normal, grade 1, or grade 2 based on the Keith-Wagener-Barker system. Risk ratios for all-cause and cause-specific mortality for each classification were calculated with Cox proportional hazards regression models. Covariates included age, systolic blood pressure, antihypertensive medication use, and other cardiovascular risk factors. Multivariable hazard ratios for total cardiovascular disease mortality were 1.24 (95% confidence interval [CI], 1.12–1.38) and 1.23 (95% CI, 1.03–1.47) for grades 1 and 2 among men and 1.12 (95% CI, 1.01–1.24) and 1.44 (95% CI, 1.24–1.68) for grades 1 and 2 among women, respectively. Hazard ratios for total stroke mortality were 1.31 (95% CI, 1.13–1.53) and 1.38 (95% CI, 1.08–1.77) for grades 1 and 2 among men and 1.30 (95% CI, 1.12–1.50) and 1.70 (95% CI, 1.36–2.11) for grades 1 and 2 among women, respectively. For both hypertensive and normotensive subjects of each sex, multivariable hazard ratios for all-cause mortality, total cardiovascular mortality, and total stroke mortality were significantly higher for grade 1 or 2 compared with normal.

Conclusions—Mild hypertensive retinopathy is a risk factor for cardiovascular mortality independently of cardiovascular risk factors among men and women with and without hypertension. **(*Circulation*. 2011;124:2502-2511.)**

Key Words: cardiovascular diseases ■ cohort studies ■ hypertension ■ retinal diseases ■ stroke

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7),[1] the World Health Organization International Society of Hypertension (WHO-ISH) 2003 statement,[2] and the British Hypertension Society 2004 guidelines (BHS IV)[3] consider hypertensive retinopathy target-organ damage. The 2007 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension (ESH-ESC 2007)[4] stated that grade 3 and 4 hypertensive retinopathy as defined with the Keith-Wagener-Barker classification[5] was associated with cardiovascular events. In contrast, the ESH-ESC guidelines argued that the ability of grade 1 and 2 retinal changes detected by fundal analysis to be used for prognosis was questionable on the basis of results of several cross-sectional studies.[6–8] However, those cross-sectional studies had relatively small sample sizes and did not directly examine a temporal relationship.

Clinical Perspective on p 2511

Several population-based studies[9–12] have provided evidence that hypertensive retinopathy or optic fundus abnormalities were associated with risks for cardiovascular disease independently of blood pressure levels in the general population. Results of these studies imply that mild hypertensive retinopathy might be associated with a risk for cardiovascular disease even in normotensive individuals.

Examining the association between mild hypertensive retinopathy and risk of cardiovascular disease among a population with and without hypertension can yield important evidence to identify high-risk individuals. However, limited data are available regarding this association.

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The present study was conducted to examine whether mild hypertensive retinopathy graded by the Keith-Wagener-Barker classification could be a risk factor for cardiovascular mortality in individuals with and without hypertension.

Methods

Study Cohort and Population

In 1993, the Ibaraki prefectural government initiated a community-based large cohort study, known as the Ibaraki Prefectural Health Study, to obtain information on health status for the purpose of health education and policy making. The cohort included 97 042 individuals (33 130 men and 63 912 women) 40 to 79 years of age living in Ibaraki Prefecture who completed an annual health checkup, including an ophthalmoscopic examination in 1993.

We excluded 4067 persons (1133 men and 2934 women) from the analyses because of incomplete health checkup data. We also excluded 4996 persons (2043 men and 2953 women) because of a history of stroke or heart disease at baseline. Furthermore, we excluded 89 individuals (37 men and 52 women) because of grade 3 or 4 retinopathy, which was not considered mild retinopathy. Thus, 87 890 individuals (29 917 men and 57 973 women) were enrolled in the present study. Informed consent was obtained from community representatives to conduct an epidemiological study according to guidelines of the Council for International Organizations of Medical Science. The Ethics Committee of Ibaraki Prefecture approved this study.

Baseline Measurements

At baseline, nonmydriatic retinal photography of right eye was taken by a trained medical technologist using a CR6-45VAF device (Canon, Tokyo, Japan) and FUJICHROME TREBI 100C reversal film (Fujifilm, Tokyo, Japan). A photographic slide on the roll film was interpreted by a grader with information on the subject's sex, age, and systolic and diastolic blood pressures. In addition, a previous grade of Keith-Wagener-Barker classification[5] was included in the information if it was completed in the last health checkup. Approximately 20 trained graders evaluated all photographic slides for the presence or absence of microvascular abnormalities using the Keith-Wagener-Barker classification.[5]

Height in stocking feet and weight in light clothing were measured, and body mass index was calculated as weight (kg) divided by height squared (m^2). Blood pressure was measured on the right arm of seated subjects by trained observers using standard mercury sphygmomanometers.

Blood samples were drawn from seated subjects. Fasting was not needed. Serum total cholesterol and triglycerides were measured by enzymatic methods, and high-density lipoprotein cholesterol levels were measured by phosphotungstic acid magnesium methods. Plasma glucose level was measured by means of a glucose oxidase electrode method. A standard 12-lead ECG was obtained. Trained physicians evaluated the ECG for the presence or absence of atrial fibrillation and ST-T abnormality.

An interview was conducted to ascertain smoking status, number of cigarettes smoked per day, usual weekly intake of alcohol in *go* units (a Japanese traditional unit converted to grams of ethanol per day by 22 g ethanol per *go* unit), and history of stroke, heart disease, hypertension, dyslipidemia, and diabetes mellitus.

Follow-Up Surveillance

To ascertain deaths in the cohort, investigators conducted a systematic review of death certificates. Data from health checkups and date of death or moving were obtained from local governments. It is believed that all deaths that occurred in the cohort were ascertained, except for subjects who died after they had moved from their original community, in which case the subject was withdrawn from the study. Data on death are centralized at the Ministry of Health and Welfare, where the underlying causes of death are coded for the National Vital Statistics according to the *International Classification of Diseases* (ICD), 9th (1993–1994) and 10th (1995–2008) revisions. The underlying causes of death of this cohort were obtained from the Ministry of Health and Welfare. Record matching between the residence certificates and the underlying causes of death was done by residential area, sex, birthday, and death date.

Definitions

Subjects were classified with regard to their retinal photography based on the Keith-Wagener-Barker classification[5]: normal, grade 1, or grade 2. According to the classification, grade 1 is defined as mild narrowing or sclerosis of the retinal arterioles. Grade 2 is defined as moderate to marked sclerosis of the retinal arterioles, moderate narrowing of the retinal arterioles, or arteriosclerotic retinopathy or thrombosis of retinal veins. Grade 3 is defined as angiospastic retinopathy, characterized by edema, cotton-wool patches, and hemorrhages in the retina, in addition to marked sclerosis of the retinal arterioles. Grade 4 is defined as measurable edema of the disks in addition to grade 3 pictures. In the present study, subjects without retinopathy were graded as normal, and subjects with grade 3 or 4 retinopathy were excluded because these categories were not considered mild retinopathy.

Blood glucose level was divided into 3 categories: normal (6.1 mmol/L fasting or <7.8 mmol/L nonfasting), prediabetes (6.1–6.9 mmol/L fasting or 7.8–11.0 mmol/L nonfasting), and diabetes mellitus (≥7.0 mmol/L fasting or ≥11.1 mmol/L nonfasting). Smoking habits were divided into 4 categories: never smoker, ex-smoker, currently smoking <20 cigarettes a day, and currently smoking ≥20 cigarettes/d. Alcohol intake was divided into 4 categories: never, sometimes (not almost every day), almost every day (<44 g/d), and almost every day (≥44 g/d).

Cause-specific mortality was classified according to the ICD code of the underlying cause of death. Total cardiovascular disease deaths were identified as codes 393 through 459 in ICD-9 and as codes I00 through I99 in ICD-10. Total stroke deaths were identified as code 430 through 438 in ICD-9 and as code I60 through I69 in ICD-10. Cerebral infarction deaths were identified as codes 433 through 434 and 437.7 in ICD-9 and as code I63 and I69.3 in ICD-10. Intracerebral hemorrhage deaths were identified as codes 431 through 432 in ICD-9 and as codes I61 and I69.1 in ICD-10. Ischemic heart disease deaths were identified as codes 410 through 414 in ICD-9 and as codes I20 through I22 and I24-I25 in ICD-10.

Statistical Analysis

The *P* values for difference of baseline characteristics according to the Keith-Wagener-Barker classification were calculated by an ANOVA for age, body mass index, systolic blood pressure, diastolic blood pressure, serum total cholesterol level, and serum high-density lipoprotein cholesterol level and by χ^2 text for antihypertensive medication use, antidyslipidemic medication use, diabetes mellitus, antidiabetic medication use, atrial fibrillation, ST-T abnormality, smoking status, and alcohol intake.

Risk ratios and 95% confidence intervals (CIs) for all-cause and cause-specific mortality according to the Keith-Wagener-Barker classification were calculated with reference to the normal grade by use of Cox proportional hazards regression models. Covariates included age, body mass index, systolic blood pressure, antihypertensive medication use (yes or no), serum total cholesterol level, serum high-density lipoprotein cholesterol level, antidyslipidemic medication use (yes or no), blood glucose level (normal, prediabetes, and diabetes mellitus), antidiabetic medication use (yes or no), atrial fibrillation (yes or no), ST-T abnormality (yes or no), smoking status (never smoker, ex-smoker, currently smoking <20 cigarettes a day, currently smoking ≥20 cigarettes/d), and alcohol intake (never, sometimes, <44 g/d almost every day, and ≥44 g/d almost every day). The analysis was also stratified by hypertension status: hypertensive subjects (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, and/or use of hypertensive medication) and normotensive subjects (systolic blood pressure <140 mm Hg, diastolic blood pressure <90 mm Hg, and no use of hypertensive medication). The *P* values for trend were calculated by multivariable Cox proportional hazard models adjusted for the variables described above. All statistical tests were 2 sided, and values of $P<0.05$ were

considered statistically significant. All statistical analyses were conducted with SAS version 9.1.3 (SAS Institute, Inc, Cary, NC).

Results

Sex-specific baseline characteristics of this study subjects according to the Keith-Wagener-Barker classification of ophthalmoscopy are shown in Table 1. Statistically significant differences according to the Keith-Wagener-Barker classification were found for all covariables at baseline except antidyslipidemic medication use in men. Mean age was higher with higher grades of the Keith-Wagener-Barker classification in both sexes. The means of systolic and diastolic blood pressures and the proportion of antihypertensive medication use were also higher with the higher grades in both sexes.

During follow-up through 2008, a mean of 14.1 years (13.6 years in men and 14.3 years in women), 12 946 total deaths (7001 in men and 5945 in women), 3697 cardiovascular deaths (1801 in men and 1896 in women), 1746 total stroke deaths (841 in men and 905 in women), 990 cerebral infarction deaths (546 in men and 444 in women), 453 intracerebral hemorrhage deaths (206 in men and 247 in women), and 957 ischemic heart disease deaths (511 in men and 446 in women) were observed.

Table 2 shows hazard ratios of all-cause and cause-specific mortality according to the Keith-Wagener-Barker classification among all study subjects. The multivariable hazard ratios for all-cause mortality, total cardiovascular disease, total stroke, and cerebral infarction were higher with higher grades of the Keith-Wagener-Barker classification in both sexes (P for trend <0.01). In addition, the multivariable hazard ratios for intracerebral hemorrhage were higher with higher grades of the Keith-Wagener-Barker classification among women (P for trend <0.01). Compared with normal grade, the multivariable hazard ratios for all-cause mortality were significantly high for grades 1 and 2 among men and for grade 2 among women. The multivariable hazard ratios for total cardiovascular disease mortality, total stroke mortality, and cerebral infarction mortality were significantly higher for grades 1 and 2 among men and women. In addition, a significantly high hazard ratio for intracerebral hemorrhage mortality for grade 2 was found among women but not among men. The multivariable hazard ratios for ischemic heart disease mortality were not statistically significant in both sexes.

Table 3 shows the multivariable hazard ratios of all-cause and cause-specific death according to Keith-Wagener-Barker classification of ophthalmoscopy, stratified by hypertensive status. Compared with the normal grade, both hypertensive and normotensive subjects with grade 1 or 2 showed a significantly higher multivariable hazard ratios for all-cause mortality, total cardiovascular mortality, and total stroke mortality for both sexes. In hypertensive subjects, the multivariable hazard ratio for total cardiovascular mortality was significantly high for grade 1 among men and for grades 1 and 2 among women. The multivariable hazard ratios for total stroke mortality were significantly high for grades 1 and 2 among hypertensive men and women. In nonhypertensive subjects, the multivariable hazard ratios for total cardiovascular mortality and total stroke mortality were significantly high for grade 2 in both sexes. In addition, a significantly high multivariable hazard ratio for ischemic heart disease mortality was found among nonhypertensive men with grade 2 disease.

Discussion

To the best of our knowledge, the results of the present study are the first to show that mild hypertensive retinopathy classified by the Keith-Wagener-Barker classification is a risk factor for cardiovascular mortality independently of other cardiovascular risk factors in both sexes with and without hypertension.

In 1939, Keith et al[5] reported a graded decline in survival during an 88-month follow-up period from grade 1 to grade 4 among 219 hypertensive patients. Their cumulative all-cause mortality rates at 5 years after baseline survey were 30% for grade 1, 46% for grade 2, 80% for grade 3, and 99% for grade 4. Several follow-up studies[13–16] confirmed the association between hypertensive retinopathy classified by the Keith-Wagener-Barker classification and all-cause mortality among hypertensive patients. Kato et al[17] reported that the cumulative all-cause mortality rates at 5 years after baseline survey were 2.4% for grade 1 and 16.6% for grade 2 among 170 Japanese patients with fundus hypertonicus.

The ESH-ESC 2007[4] states that patients with grade 3 and 4 retinopathy are at high risk for cardiovascular events, and the WHO-ISH 2003 statement[2] and the BHS IV[3] regard retinopathy of grades 3 and 4 as target-organ damage. The JNC-7[1] also indicates that retinopathy (without grading) is target-organ damage. However, the ESH-ESC 2007[4] questioned the ability of grade 1 and 2 retinopathy detected by fundal analysis to predict prognosis on the basis of several cross-sectional studies.[6–8] Those cross-sectional studies[6–8] had a relatively small sample size and did not directly examine a temporal relationship. In contrast, the present large prospective cohort study supports that mild degrees of retinopathy can predict the risk of stroke mortality in individuals with hypertension.

The Atherosclerosis Risk in Communities (ARIC) Study,[10,12] a population-based cohort study of ≈10 000 men and women 51 to 72 years of age in 4 US communities, provided evidence that the multivariable hazard ratio of retinopathy (no use of the Keith-Wagener-Barker classification) was 2.58 (95% CI, 1.59–4.20) for incident total stroke and 2.60 (95% CI, 1.55–4.34) for incident ischemic stroke.[10] In that study, a 6-year mean arterial blood pressure was included as a covariate. The Shibata Study,[9] a cohort study of 2302 residents ≥40 of age in a Japanese provincial city, provided evidence that an association between optic fundus abnormality and incident stroke in men (multivariable hazard ratio, 3.42 [95% CI, 1.03–11.31] for all stroke, 4.54 [95% CI, 1.05–19.57] for cerebral infarction, and 8.53 [95% CI, 1.04–69.21] for intracerebral hemorrhage) but not in women. The Beaver Dam Eye Study,[11] a nested case-control study of 413 cases and 1198 controls 43 to 84 years of age, provided evidence that the multivariable odds ratio of retinopathy was 1.8 (95% CI, 1.2–2.7) for total cardiovascular mortality after adjustment for cardiovascular risk factors, including systolic blood pressure. The present study is consistent with previous