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A Prospective Study of Cigarette Smoking and Risk of Incident Hypertension in Women

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Objectives We undertook this study to prospectively evaluate whether cigarette smoking was associated with an increased risk of developing hypertension.

Background Smoking is a well-recognized risk factor for cardiovascular disease. Few prospective cohort studies have examined the relationship between smoking and hypertension.

Methods We conducted a prospective cohort study among 28,236 women in the Women's Health Study who were initially free of hypertension, cardiovascular disease, and cancer. Detailed risk factor information, including smoking status, was collected from self-reported questionnaires. We used Cox proportional hazards survival models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) of incident hypertension (defined as either new diagnosis, the initiation of antihypertensive medication, systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg).

Results At baseline, 51% of women were never smokers, 36% were former smokers, 5% smoked 1 to 14 cigarettes, and 8% smoked ≥15 cigarettes per day. During a median of 9.8 years, there were 8,571 (30.4%) cases of incident hypertension. The age-adjusted HRs of developing hypertension among never, former, and current smokers of 1 to 14 and ≥15 cigarettes per day were 1.00 (reference), 1.04 (95% CI 0.99 to 1.09), 1.00 (95% CI 0.90 to 1.10), and 1.10 (95% CI 1.01 to 1.19), respectively. In multivariable models further adjusting for lifestyle, clinical, and dietary variables, the corresponding HRs were 1.00 (reference), 1.03 (95% CI 0.98 to 1.08), 1.02 (95% CI 0.92 to 1.13), and 1.11 (95% CI 1.03 to 1.21), respectively. Among women who smoked ≥25 cigarettes per day, the multivariable HR was 1.21 (95% CI 1.06 to 1.39).

Conclusions In this large cohort of women, cigarette smoking was modestly associated with an increased risk of developing hypertension, with an effect that was strongest among women smoking at least 15 cigarettes per day. (J Am Coll Cardiol 2007;50:2085–92) © 2007 by the American College of Cardiology Foundation

Hypertension is a common, chronic condition, and an improved understanding of its etiology could lead to new prevention and treatment efforts (1,2). Although cigarette smoking is a strong risk factor for cardiovascular disease (CVD) (3), its relationship with hypertension remains unclear (4). Cigarette smoking causes sympathetic activation, oxidative stress, and acute vasopressor effects (5) that are associated with increases in markers of inflammation (6,7) that are linked with hypertension (8). Chronic smoking may also lead to endothelial dysfunction (9), vascular injury, plaque progression (10), and increased arterial stiffness (11) that leads to the development of hypertension (12). The long-term effect of cigarette smoking on hypertension has not been fully elucidated, and abstinence from smoking is not included in current clinical guidelines for the prevention of hypertension (13).

A recent population-based study of middle-aged men reported that current cigarette smoking was independently associated with an elevated risk of developing hypertension (14). However, other studies have reported lower blood pressure (BP) levels among smokers (15) and increases in BP after smoking cessation (16). As a result, it remains unclear to what extent cigarette smoking is a risk factor for the development of hypertension (4). Therefore, we conducted a prospective cohort study among 28,236 middle-aged and older women initially free of hyperten-

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Abbreviations and Acronyms

BMI = body mass index
BP = blood pressure
CI = confidence interval
CVD = cardiovascular disease
DBP = diastolic blood pressure
HR = hazard ratio
MI = myocardial infarction
SBP = systolic blood pressure
WHO = World Health Organization

sion from the Women's Health Study (WHS) for the association between baseline smoking status and risk of incident hypertension.

Methods

Study population. We analyzed data from the WHS, a randomized 2 × 2 factorial trial of low-dose aspirin, beta-carotene, and vitamin E in the primary prevention of cardiovascular disease and cancer. Between September 1992 and May 1995, letters of invitation and baseline health questionnaires were sent to more than 1.7 million female health professionals in the U.S. The eligibility criteria included age ≥45 years and no history of coronary heart disease, cerebrovascular disease, cancer (except nonmelanoma skin cancer), or other major illness. Additional criteria consisted of no current aspirin or nonsteroidal anti-inflammatory medication use more than once a week, and no current anticoagulants or corticosteroids. A total of 453,787 women completed the questionnaires, and 65,169 were willing and able to participate. These women began a 3-month run-in period, and a total of 39,876 women who remained willing, eligible, and compliant were subsequently enrolled in the trial, which had morbidity and mortality follow-up rates of 97.2% and 99.4%, respectively (17–20). All participants gave written, informed consent, and the study was approved by the Institutional Review Board of the Brigham and Women's Hospital in Boston, Massachusetts.

Baseline information was self-reported by mailed questionnaire for demographic, lifestyle, and medical history information. Every 12 months, participants were mailed follow-up questionnaires to evaluate compliance, side effects, clinical end points, and risk factors. For our analysis, the baseline study population was restricted to women with no self-reported prebaseline or baseline diagnosis of hypertension, no prebaseline or baseline antihypertensive treatment, a systolic blood pressure (SBP) <140 mm Hg, and a diastolic blood pressure (DBP) <90 mm Hg. As a result of these exclusions, we followed 28,236 women for the development of incident hypertension.

Body mass index (BMI) at baseline was calculated as weight in kilograms divided by the square of height in meters. Participants provided information on BP from 9 ordinal SBP categories ranging from <110 to ≥180 mm Hg, and from 7 ordinal DBP categories ranging from <65 to ≥105 mm Hg. Among health professionals, self-reported BP is greatly correlated with measured SBP (r = 0.72) and DBP (r = 0.60) (21).

Ascertainment of cigarette smoking status and other covariates. Cigarette smoking status was provided on the baseline questionnaire. Participants were asked to classify themselves as never smokers (<100 cigarettes in a lifetime), former smokers, or current smokers. Former smokers reported whether they quit within the last year. Current smokers were categorized into 6 groups based upon number of cigarettes smoked per day (1 to 4, 5 to 14, 15 to 24, 25 to 35, 36 to 44, or ≥45 cigarettes/day). Self-reported smoking status among health care professionals has been shown to be accurate in a previous meta-analysis (22) and in a subsequent population-based study (23,24). Baseline self-reported risk factors included age, height, weight, history of high cholesterol or diabetes, exercise level, alcohol use, and parental history of myocardial infarction (MI) before the age of 60 years. A self-administered semiquantitative food frequency questionnaire (25) also was provided by participants and included information on dietary intake of fruits and vegetables (26) and individual energy-adjusted dietary factors, such as saturated fat, sodium, and potassium (27).

Evaluation of incident hypertension. Incident cases of hypertension were defined by meeting at least 1 of the following 4 criteria provided by self-reports: 1) a new physician diagnosis of hypertension on questionnaires at years 1 and 3 and then annually thereafter; 2) starting antihypertensive treatment during follow-up; 3) SBP ≥140 mm Hg during follow-up; or 4) DBP ≥90 mm Hg during follow-up (8). Participants reporting a new hypertension diagnosis also were asked to provide the month and year that it occurred. Any missing date for incident hypertension was assigned a date by randomly selecting a date between the current and previous annual questionnaire. All participants were followed for CVD events, and all relevant medical information was reviewed by the WHS Endpoints Committee composed of physicians (19). Participants who developed a CVD event (including MI, stroke and revascularization) that may have affected their BP or BP management were censored at the date of diagnosis and not considered an incident case of hypertension.

Statistical analysis. We first divided the baseline population into 4 groups based upon cigarette smoking status (never, past, currently smoking <15 cigarettes per day, and currently smoking ≥15 cigarettes per day) and computed means or proportions of baseline variables for each group and for the entire cohort. Categories were compared using analysis of variance or chi-square tests. We determined the number of incident hypertension cases and calculated follow-up time in person-years. To determine the effect of higher levels of smoking, we also evaluated participants who smoked 15 to 24, ≥25, and ≥45 cigarettes/day.

We used Cox proportional hazards survival models to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for risk of incident hypertension, using never smokers as the reference group. The crude model included only smoking status. We then adjusted for baseline age (in years). The multivariable model additionally adjusted for

BMI (in kg/m^2), exercise level (rarely/never, <1 per week, 1 to 3 per week, ≥4 per week), alcohol use (rarely/never, 1 to 3 per month, 1 to 6 per week, ≥1 per day), history of diabetes, history of high cholesterol ≥240 mg/dl or use of cholesterol-lowering medication, and energy-adjusted dietary intake of fruits and vegetables (servings/day), saturated fat (g/day), sodium (mg/day), and potassium (mg/day). For exercise level and alcohol use, we did not take into account their ordinality because there is no established graded relationship between these variables and risk of hypertension. Because our variable for parental history of MI before age 60 years (yes/no) had missing data in 9.7% of participants, we included those missing this information with an indicator variable in our multivariable models. In supplementary analyses, we assessed the effect of including both SBP and DBP category in the multivariable model.

Because the relationship between smoking status and hypertension may be affected by body weight, we stratified our population by baseline BMI using World Health Organization (WHO) criteria and evaluated the risk of hypertension among normal (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), and obese (≥30 kg/m^2) participants (28). A test for interaction between smoking status, BMI category, and the risk of developing hypertension was assessed where both smoking status and WHO category were ordinal variables.

We also stratified the cohort according to baseline SBP and DBP levels to determine whether smoking has differential effects on the risk of developing hypertension based upon initial BP level. The test for interaction was assessed for baseline smoking status and SBP and DBP category using ordinal variables. All HRs are presented with 95% CIs, and all reported p values are 2-sided. All data analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina).

Results

Among the 28,236 women in our study, the mean (±SD) age at baseline was 53.7 ± 6.6 years, and 13.3% of participants were current smokers (Table 1). The mean (±SD) BMI was 25.2 ± 4.5 kg/m^2, with 30% of participants classified as overweight and 13% as obese. When we stratified the cohort by smoking status, there were 14,377 never smokers, 10,115 former smokers, 1,409 participants who currently smoked 1 to 14 cigarettes/day, and 2,335 participants who currently smoked ≥15 cigarettes per day. Current smokers had slightly greater levels of baseline SBP ($p < 0.01$) and DBP ($p < 0.05$). Current smokers had a lower average BMI, greater intake of saturated fat, exercised less, and were more likely to drink alcohol (all $p < 0.01$). After a median follow-up of 9.8 years, (228,933 person-years), there were 8,571 cases of incident hypertension defined by medical diagnosis (36.7%), elevations in BP (20.6%), initiation of antihypertensive treatment (3.1%), or a combination of the aforementioned (39.2%).

In Cox proportional hazard survival models using never smokers as the reference group, former smokers had an age-adjusted HR of 1.04 (95% CI 0.99 to 1.09) and multivariable-adjusted HR of 1.03 (95% CI 0.98 to 1.08) (Table 2). Participants who smoked 1 to 14 cigarettes/day had an age-adjusted HR of 1.00 (95% CI 0.90 to 1.10) and multivariable-adjusted HR of 1.02 (95% CI 0.92 to 1.13), whereas those who smoked ≥15 cigarettes/day had an age-adjusted HR of 1.10 (95% CI 1.01 to 1.19) and multivariable-adjusted HR of 1.11 (95% CI 1.03 to 1.21). When we considered the addition of randomized aspirin, beta-carotene, and vitamin E treatment to our multivariable models, the HRs for smoking status remained unchanged. We then evaluated the 702 women who currently smoked ≥25 cigarettes/day and the 53 women who smoked ≥45 cigarettes/day, and the age-adjusted HRs were 1.22 (95% CI 1.07 to 1.39) and 1.26 (95% CI 0.81 to 1.98), whereas the multivariable-adjusted HRs were 1.21 (95% CI 1.06 to 1.39) and 1.16 (95% CI 0.74 to 1.82), respectively.

We next considered the additional adjustment by baseline SBP or DBP in our multivariable models, which only slightly affected the multivariable HRs. For example, former smokers and those currently smoking 1 to 14 cigarettes/day had a slight increase in their HRs of hypertension, whereas the HRs among women smoking ≥15 cigarettes/day did not materially change.

When we stratified the cohort by baseline WHO category, participants with a normal BMI (18.5 to <25 kg/m^2) had the greatest HRs of developing hypertension (p interaction = 0.04) (Table 3). Among these participants, the multivariable HRs for former smokers and those currently smoking 1 to 14 cigarettes/day and ≥15 cigarettes/day were 1.04, 1.11, and 1.21, respectively. Among women in the normal weight category who were currently smoking ≥25 cigarettes/day, the multivariable HR was 1.31 (95% CI 1.07 to 1.61). Among participants in the overweight (25 to <30 kg/m^2) and obese (≥30 kg/m^2) categories, there was no statistical association between cigarette smoking and hypertension.

We next stratified the cohort by baseline SBP and DBP category and evaluated smoking status and the risk of developing hypertension (Table 4). In age-adjusted and multivariable-adjusted models, the highest HRs were among those patients with a lower baseline BP. Former and current smokers with an initial DBP <75 mm Hg were at a greater relative risk of developing hypertension compared with those with a DBP that was ≥75 mm Hg (p interaction <0.01). Former and current smokers with a SBP <120 mm Hg also had greater HRs compared with those with a SBP ≥120 mm Hg, but this finding did not reach statistical significance (p interaction=0.13).

JACC Vol. 50, No. 21, 2007
November 20, 2007:2085–92

Table 1 Baseline Characteristics of 28,236 Women, According to Baseline Cigarette Smoking Status

Characteristic	Cigarette Smoking Status				
	Never	Past	1–14/day	≥15/day	Total
n	14,337	10,115	1,409	2,335	28,236
Age, yrs*	53.6 (6.7)	54.1 (6.5)	53.6 (6.3)	53.2 (6.1)	53.7 (6.6)
BMI, kg/m^2*	25.2 (4.5)	25.3 (4.4)	24.7 (4.4)	24.9 (4.5)	25.2 (4.5)
WHO category*					
Normal	56.1	55.5	61.0	56.8	56.2
Overweight	29.3	30.5	25.3	29.1	29.5
Obese	13.4	13.0	11.9	12.0	13.1
Physical activity, %*					
Rarely/never	34.5	32.8	42.5	54.4	36.0
<1 per week	20.4	18.9	22.3	23.2	20.2
1–3 per week	33.6	34.7	28.9	19.2	32.6
≥4 per week	11.5	13.5	6.3	3.1	11.3
Alcohol use, %*					
Rarely/never	50.7	31.8	40.0	44.2	42.9
1–3 drinks/month	13.6	13.3	12.3	13.2	13.4
1–6 drinks/week	29.6	40.1	33.9	27.9	33.4
≥1 drink/day	6.1	14.8	13.8	14.8	10.3
Parental history of MI before age 60 yrs, %*	11.9	12.5	14.6	14.6	12.4
Diabetes, %	1.3	1.3	1.0	1.7	1.3
History of hyperlipidemia, %	24.2	25.1	23.1	26.2	24.6
Fruit and vegetables, servings/day*	6.2 ± 3.6	6.2 ± 3.6	5.6 ± 3.5	4.9 ± 3.1	6.1 ± 3.6
Dietary saturated fat, g/day*	19.3 ± 4.6	19.2 ± 4.7	20.7 ± 4.9	22.3 ± 5.4	19.6 ± 4.8
Dietary sodium, g/day*	1.86 ± 0.33	1.87 ± 0.34	1.85 ± 0.35	1.90 ± 0.38	1.87 ± 0.34
Dietary potassium, g/day*	3.20 ± 0.58	3.25 ± 0.58	3.18 ± 0.62	3.12 ± 0.63	3.21 ± 0.59
SBP, mm Hg*					
<110	20.3	20.2	21.5	20.5	20.3
110–119	37.2	38.0	41.0	35.6	37.6
120–129	29.4	28.2	25.6	29.5	28.8
130–139	13.1	13.6	11.9	14.5	13.3
DBP, mm Hg†					
<65	11.7	12.3	13.8	12.3	12.0
65–74	40.9	40.9	44.1	40.7	41.1
75–84	39.2	38.7	34.9	39.0	38.8
85–89	8.2	8.2	7.2	8.0	8.1

Values are mean ± SD. *$p < 0.01$. †$p < 0.05$.

BMI = body mass index; DBP = diastolic blood pressure; MI = myocardial infarction; SBP = systolic blood pressure; WHO = World Health Organization.

Discussion

In this large prospective cohort study of 28,236 women initially free of hypertension and followed for a median of 9.8 years, we found a significantly increased risk of developing hypertension among women currently smoking at least 15 cigarettes per day. The magnitude of effect from cigarette smoking was modest, and an increased risk of hypertension was most pronounced among women with a normal BMI or low initial BP.

In the U.S., 21% of adults (44.5 million individuals) were current smokers in 2004, despite a national health objective to reduce the prevalence of smoking to <12% by 2010 (29). Among U.S. women in 2004, 18.5% were current smokers (29), a proportion similar to our study cohort in whom 15.3% of women were current smokers at baseline in 1992. Currently, there are at least 65 million people with hypertension in the U.S. (30), and the lifetime risk of developing hypertension is estimated at 90% (31). In our cohort, 30.2% of women became hypertensive over 10 years, a rate similar to that among 379 men followed for 11 years where 32.7% developed hypertension (14).

Although cigarette smoking has many well-established detrimental health effects (32), smoking has variable effects on BP. For example, quitting smoking decreases inflammation (6) but may also lead to weight gain (14) that causes greater BPs and increased rates of hypertension (33,34). Smoking also may reduce weight gain and affect the relationship between smoking and hypertension among overweight and obese women. Although the HRs of hypertension among women currently smoking 1 to 14 cigarettes/day did

Table 2 Hazard Ratios (95% Confidence Intervals) From Cox Proportional Hazards Survival Models of Incident Hypertension, According to Baseline Cigarette Smoking Status Among 28,236 Participants

	Baseline Smoking Status				Higher Categories	
	Never	Former	1 to 14/day	≥15/day	15 to 24/day	≥25/day
n	14,377	10,115	1,409	2,335	1,633	702
Person-yrs	117,020	81,898	11,523	18,491	13,120	5,371
Cases	4,273	3,150	417	731	493	238
Crude	1.00 (ref)	1.06 (1.01–1.11)	0.99 (0.90–1.10)	1.08 (1.00–1.17)	1.03 (0.94–1.13)	1.20 (1.06–1.37)
Age-adjusted	1.00 (ref)	1.04 (0.99–1.09)	1.00 (0.90–1.10)	1.10 (1.01–1.19)	1.05 (0.95–1.15)	1.22 (1.07–1.39)
Multivariable*	1.00 (ref)	1.03 (0.98–1.08)	1.02 (0.92–1.13)	1.11 (1.03–1.21)	1.07 (0.97–1.18)	1.21 (1.06–1.39)
Multivariable+systolic and diastolic blood pressure	1.00 (ref)	1.05 (1.00–1.10)	1.09 (0.98–1.21)	1.11 (1.02–1.20)	1.08 (0.98–1.18)	1.18 (1.03–1.35)

*Adjusted for age, body mass index, exercise level, alcohol use, parental history of myocardial infarction before age 60 years, diabetes and high cholesterol (self-reported history or current treatment), and intake of energy-adjusted dietary factors (fruits and vegetables, saturated fat, sodium, and potassium). Note: The further consideration of randomized treatment assignment (aspirin, beta-carotene, vitamin E) in the multivariable model did not change the hazard ratios for smoking status.

not reach statistical significance, the multivariable risk estimates were >1.0 and consistent with a slightly increased risk of hypertension.

Inflammation also may mediate the relationship between smoking and high BP. In a nationally representative sample, cigarette smoking was associated with elevated inflammatory biomarkers and chronic systemic inflammation (7). In the WHS, both former and current smokers had increased levels of inflammatory biomarkers (35), and higher baseline levels of C-reactive protein have been associated with an increased risk of subsequent hypertension (8). In a large population-based study in England, the independent association between smoking and BP was small, but causality could not be addressed in this cross-sectional study (36). A prospective study among middle-aged men in Finland supported the idea that smoking may be a risk factor for hypertension, however the study size was small (n = 379) and requires confirmation in other cohorts (14).

There are several other potential biological mechanisms through which exposure to cigarette smoke may lead to high BP. Long-term smoking leads to abnormalities of myocardial blood flow, which may be due to impairment of the vascular endothelium (37). Cigarette smoking also increases BP by stiffening arteries, with particularly deleterious effects on chronic smokers (38). Smoking in youth is associated with arterial changes and increased common carotid artery intima-media thickness in adulthood (39). Smoking in adults is also associated with progression of atherosclerosis, and these adverse effects may be cumulative and irreversible (40).

Study limitations. Our study has several strengths, including the prospective collection of data, large number of participants and events, and long follow-up. Some potential

Table 3 Hazard Ratios (95% Confidence Intervals) From Cox Proportional Hazards Survival Models* of Incident Hypertension According to Baseline Cigarette Smoking Status Among 28,236 Participants, Stratified by Baseline WHO Category

WHO category	Never	Former	Current, 1 to 14/day	Current, ≥15/day
Normal (18.5 to <25.0 kg/m^2)				
n	8,058	5,616	860	1,326
Cases	1,806	1,353	219	345
Age-adjusted	1.00 (ref)	1.06 (0.99–1.14)	1.14 (0.99–1.31)	1.23 (1.09–1.38)
Multivariable*	1.00 (ref)	1.04 (0.97–1.12)	1.11 (0.96–1.28)	1.21 (1.07–1.36)
Overweight (25.0 to <30.0 kg/m^2)				
n	4,213	3,088	357	679
Cases	1,522	1,149	121	235
Age-adjusted	1.00 (ref)	1.02 (0.95–1.11)	0.96 (0.80–1.16)	1.00 (0.87–1.15)
Multivariable*	1.00 (ref)	1.03 (0.95–1.12)	0.97 (0.80–1.17)	0.99 (0.86–1.14)
Obese (≥30 kg/m^2)				
n	1,927	1,313	167	281
Cases	916	627	70	141
Age-adjusted	1.00 (ref)	1.00 (0.90–1.11)	0.88 (0.69–1.12)	1.10 (0.92–1.31)
Multivariable*	1.00 (ref)	0.99 (0.89–1.11)	0.86 (0.67–1.11)	1.13 (0.94–1.36)

*Adjusted for age, body mass index, exercise level, alcohol use, parental history of myocardial infarction before age 60 years, diabetes and high cholesterol (self-reported history or current treatment), and intake of energy-adjusted dietary factors (fruits and vegetables, saturated fat, sodium, and potassium).

WHO = World Health Organization.

JACC Vol. 50, No. 21, 2007
November 20, 2007:2085–92

Table 4 Hazard Ratios (95% Confidence Intervals) From Cox Proportional Hazards Survival Models* of Incident Hypertension According to Baseline Cigarette Smoking Status Among 28,236 Participants, Stratified by Baseline SBP and DBP

	Never	Former	Current, 1 to 14/day	Current, ≥15/day
SBP category (mm Hg)				
<110				
n	2,914	2,041	303	478
No. cases	288	218	38	49
Age-adjusted	1.00 (ref)	1.06 (0.89–1.26)	1.29 (0.92–1.80)	1.03 (0.76–1.39)
Multivariable*	1.00 (ref)	1.11 (0.92–1.34)	1.33 (0.94–1.88)	1.06 (0.77–1.46)
110–119				
n	5,354	3,846	577	830
No. cases	1,075	834	137	185
Age-adjusted	1.00 (ref)	1.09 (0.99–1.19)	1.21 (1.01–1.44)	1.15 (0.99–1.35)
Multivariable*	1.00 (ref)	1.05 (0.96–1.16)	1.18 (0.98–1.42)	1.15 (0.98–1.36)
120–129				
n	4,227	2,853	361	688
No. cases	1,653	1,178	129	279
Age-adjusted	1.00 (ref)	1.07 (0.99–1.15)	0.89 (0.75–1.07)	1.07 (0.95–1.22)
Multivariable*	1.00 (ref)	1.09 (1.01–1.18)	0.92 (0.77–1.11)	1.09 (0.95–1.24)
130–139				
n	1,882	1,375	168	339
No. cases	1,257	920	113	218
Age-adjusted	1.00 (ref)	0.99 (0.91–1.08)	1.01 (0.83–1.22)	0.99 (0.85–1.14)
Multivariable*	1.00 (ref)	0.99 (0.91–1.09)	1.05 (0.86–1.28)	1.03 (0.89–1.20)
DBP category (mm Hg)				
<65				
n	1,679	1,242	194	286
No. cases	171	127	37	37
Age-adjusted	1.00 (ref)	0.97 (0.77–1.22)	1.98 (1.39–2.83)	1.30 (0.91–1.85)
Multivariable*	1.00 (ref)	1.06 (0.83–1.35)	2.00 (1.38–2.90)	1.23 (0.84–1.80)
65–74				
n	5,885	4,135	622	951
No. cases	1,150	931	116	213
Age-adjusted	1.00 (ref)	1.16 (1.06–1.26)	0.96 (0.79–1.16)	1.22 (1.05–1.41)
Multivariable*	1.00 (ref)	1.14 (1.04–1.25)	0.96 (0.79–1.17)	1.27 (1.09–1.48)
75–84				
n	5,634	3,909	492	911
No. cases	2,188	1,567	201	369
Age-adjusted	1.00 (ref)	1.03 (0.96–1.10)	1.06 (0.92–1.23)	1.08 (0.97–1.21)
Multivariable*	1.00 (ref)	1.02 (0.96–1.10)	1.10 (0.95–1.28)	1.10 (0.98–1.24)
85–89				
n	1,179	829	101	187
No. cases	764	525	63	112
Age-adjusted	1.00 (ref)	0.97 (0.86–1.08)	0.92 (0.71–1.18)	0.91 (0.74–1.11)
Multivariable*	1.00 (ref)	0.97 (0.86–1.09)	0.94 (0.72–1.23)	1.01 (0.82–1.24)

*Adjusted for age, body mass index, exercise level, alcohol use, parental history of myocardial infarction before age 60 years, diabetes and high cholesterol (self-reported history or current treatment), and intake of energy-adjusted dietary factors (fruits and vegetables, saturated fat, sodium, and potassium).

DBP = diastolic blood pressure; SBP = systolic blood pressure.

limitations include self-reported smoking status; however, both a population-based study (23,24) and a meta-analysis using serum cotinine have confirmed that self-reports of smoking are accurate (22), and self-reported medical information from health professionals is reliable (41). For self-reported hypertension in the WHS, there is an 86% validation rate, which is consistent with other studies (41,42), and any potential misclassification would be random and likely bias our HRs to the null. Our participants were all apparently healthy female health professionals, possibly affecting this study's generalizability to other populations; however, we have no reason to believe that the biological mechanisms by which chronic cigarette smoking may be associated with developing hypertension is unique to our study population (7,14). In the WHS, loss to follow-up was minimal regardless of smoking status and should not appreciably affect our risk estimates. We adjusted for many potential confounders in

our multivariable models and although residual confounding may be present in this observational study, given the relatively small impact of adjusting for other confounders, we believe that any residual confounding would only marginally impact the HRs.

Conclusions

Among apparently healthy women followed for a median of 9.8 years, an increased risk of developing hypertension was found among women currently smoking at least 15 cigarettes per day. Whether the magnitude of effect is susceptible to confounding or reflects a true association requires an improved understanding of the biological mechanisms through which smoking may lead to the development of hypertension.

Although the risk estimates were modest and found mainly among women with a normal BMI and lower initial BPs, the population-attributable risk of hypertension associated with cigarette smoking may potentially be substantial given the high prevalence of hypertension. Therefore, public health efforts to reduce the burden of smoking remain a potentially clinically relevant and effective strategy for preventing hypertension and reducing the impact of smoking on CVD.

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