

Smoking, Smoking Status, and Risk for Symptomatic Peripheral Artery Disease in Women

A Cohort Study

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Background: Smoking has a well-documented detrimental effect on risk for myocardial infarction and stroke, but less information is available regarding peripheral artery disease (PAD), particularly among women.

Objective: To prospectively assess the association of current smoking status, cumulative smoking exposure, and smoking cessation with incident symptomatic PAD in women.

Design: Prospective cohort study.

Setting: U.S. female health care professionals in the Women's Health Study.

Participants: 39 825 women with no cardiovascular disease who were prospectively followed for a median of 12.7 years.

Measurements: Incidence of symptomatic PAD. Cox proportional hazards models were used to compare PAD risk across smoking categories.

Results: 178 confirmed PAD events occurred. Across the 4 smoking categories (never, former, <15 cigarettes/d, and \geq 15 cigarettes/d), age-adjusted incidence rates were 0.12, 0.34, 0.95, and 1.63 per 1000 person-years of follow-up, respectively. Multivariate adjustment had little effect on this relationship (adjusted hazard ratios [HRs], 3.14 [95% CI, 2.01 to 4.90], 8.93 [CI, 5.02 to 15.89], and 16.95 [CI, 10.77 to 26.67], respectively, vs. women who never smoked). Additional adjustment for high-sensitivity C-reactive pro-

tein and soluble intercellular adhesion molecule-1 levels among women with available blood samples (28 314 participants, 117 events) attenuated risk estimates (HR, 5.58 [CI, 2.61 to 11.93] for smoking <15 cigarettes/d and 9.52 [CI, 5.17 to 17.53] for smoking \geq 15 cigarettes/d). Lifetime exposure showed a strong dose-response relationship; fully adjusted HRs for smoking abstinence of fewer than 10, 10 to 29, and 30 or more pack-years were 2.52 (CI, 1.49 to 4.25), 6.75 (CI, 4.33 to 10.52), and 11.09 (CI, 6.94 to 17.72), respectively. Compared with current smokers, the adjusted HRs for fewer than 10 years, 10 to 20 years, more than 20 years, or lifelong abstinence were 0.39 (CI, 0.24 to 0.66), 0.28 (CI, 0.17 to 0.46), 0.16 (CI, 0.10 to 0.26), and 0.08 (CI, 0.05 to 0.12), respectively.

Limitation: The use of symptomatic PAD as the a priori primary end point excludes asymptomatic disease.

Conclusion: Among initially healthy women, smoking is a potent risk factor for symptomatic PAD and was associated with subclinical inflammation. Smoking cessation substantially reduces risk for PAD, but an increased occurrence of PAD persists even among former smokers who maintain abstinence.

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Despite the reduction in smoking prevalence achieved with recent aggressive tobacco control initiatives, 1 in 5 U.S. adults (22.9% of men and 18.2% of women) currently reports smoking cigarettes (1), and the prevalence of smoking is even higher in most European countries (2). Tobacco use therefore remains one of the leading preventable causes of morbidity and mortality worldwide (3–5). A British study (6) estimated a 10-year decrease in life expectancy among male smokers compared with lifelong smoking abstinence in this population. A similar effect of smoking on vascular diseases, cancer, and respiratory diseases has been documented in women (7).

Despite this vast body of literature, detailed analyses evaluating smoking as a risk factor for peripheral artery disease (PAD) have been limited because most studies have not focused on smoking as the main exposure variable (8–14). In one of the few prospective studies that provided a more comprehensive assessment, smoking more than 25 pack-years of cigarettes in a lifetime was associated with an adjusted hazard ratio (HR) for PAD of 2.72 (95% CI, 1.13 to 6.53) compared with lifelong abstinence. However, risk estimates were based on only

64 PAD events, fewer than one half of which occurred in women (13). In addition, the effect of smoking cessation on PAD incidence is unknown, and whether smoking confers heightened risk because of vascular inflammation has not been studied in detail (13).

To address these important issues, we evaluated the relationship of smoking and smoking cessation with symptomatic PAD, defined as intermittent claudication or lower-extremity artery revascularization, in a large cohort of initially healthy women.

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Conversion of graphics into slides

Context

Peripheral artery disease (PAD) is an important cause of morbidity and mortality that may be considered less frequently in women. The effect of smoking on a woman's risk for PAD is largely unknown.

Contribution

In this large, prospective cohort study, smoking significantly increased the risk for symptomatic PAD in women in a dose-dependent manner. Although smoking cessation greatly reduced the risk, risk remained elevated compared with never-smokers.

Caution

Only symptomatic PAD was studied.

Implication

Women should be made aware that smoking increases their risk for PAD and that smoking cessation will reduce that risk.

—The Editors

METHODS**Participants**

All study participants were part of the Women's Health Study, a completed randomized trial that evaluated the risks and benefits of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer. Details of the study design are described elsewhere (15–17). In brief, beginning in 1993, 39 876 female health professionals in the United States who were aged 45 years or older and free of cardiovascular disease, cancer, or other major illnesses were randomly assigned to receive aspirin, 100 mg every other day; vitamin E, 600 IU every other day; both agents; or placebo. Information on baseline variables was collected by using mailed questionnaires. Follow-up questionnaires that asked participants about study outcomes and other information were sent every 6 months during the first year and every 12 months thereafter. Self-reported PAD was systematically confirmed by both participant interview and medical record review.

For our study, we excluded 15 participants with confirmed PAD before study entry and 36 participants with missing baseline information on smoking. Thus, our final study population comprised 39 825 women. Of these, 28 314 (71.1%) provided baseline blood samples from which measurements of high-sensitivity C-reactive protein (hsCRP) and soluble intercellular adhesion molecule-1 (sICAM-1) were available for analysis (18). All participants gave written informed consent. The study was approved by the institutional review board of Brigham and Women's Hospital, Boston, Massachusetts, and was monitored by an external data and safety monitoring board.

Definition of Smoking Status

On the baseline questionnaire, participants answered the question, "Have you smoked 100 cigarettes or more in your lifetime?" Possible responses were "no," "yes, currently smoke," or "yes, smoked in past but quit." Current smokers were queried about the average number of cigarettes they smoked per day at study entry (none, 1 to 4, 5 to 14, 15 to 24, 25 to 35, 36 to 44, or ≥ 45 cigarettes/d). Participants answered the same questionnaire again at months 12, 24, 48, 72, and 96; at the end of the randomized portion of the study; and 3 more times during the observational follow-up study. On the basis of their answers, women were classified as never-smokers, former smokers, current smokers who smoked fewer than 15 cigarettes per day, or current smokers who smoked 15 or more cigarettes per day. Participants were asked how many total years they had smoked (< 5 , 5 to 9, 10 to 19, 20 to 29, 30 to 39, 40 to 49, or ≥ 50 years) and the number of cigarettes they had smoked per day across 8 age categories, ranging from younger than 15 years to 70 years or older. Pack-years of cigarette smoking were calculated by multiplying the midpoint of the "total number of years smoked" category by the average number of cigarettes smoked per day on the baseline questionnaire. For women who reported being former smokers at enrollment, we calculated the number of years since smoking cessation by subtracting the midpoint of the age category when they reported quitting smoking from their age at enrollment.

Laboratory Analyses

Blood samples were stored in liquid nitrogen (-150 to -180 °C) until analysis. All blood analyses were performed in a core laboratory certified by the Centers for Disease Control and Prevention–National Heart, Lung, and Blood Institute Lipid Standardization Program. High-density lipoprotein cholesterol was ascertained with direct measurement assays (Roche Diagnostics, Indianapolis, Indiana). Plasma levels of hsCRP were measured with a validated immunoturbidimetric method (Denka Seiken, Niigata, Japan). The interassay coefficients of variation, using 2 levels of control materials, ranged from 1.07% to 5.20%. Levels of sICAM-1 were measured by using a quantitative, sandwich enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota) with a reproducibility of 8.89% and 6.39% at concentrations of 171.8 and 289.1 $\mu\text{g/L}$, respectively.

Outcome Ascertainment

Participants were surveyed annually for multiple health outcomes, including symptomatic PAD events (defined as intermittent claudication or peripheral artery surgery, including catheter-based interventions). Cases were confirmed by telephone interview with a cardiovascular physician who was blinded to the participants' smoking status. The presence of vascular claudication was established by using the Edinburgh Claudication Questionnaire, a modified version of the World Health Organization–

Rose questionnaire on intermittent claudication, which was validated in a community outpatient setting with 92% sensitivity and 99% specificity for physician-diagnosed intermittent claudication (19). We also obtained medical records to assess the concordance of reported symptoms with diagnostic testing, when available. Reports of peripheral artery surgery or peripheral angioplasty were confirmed after review of operative notes or procedural reports, respectively. Each case was reviewed and validated on the basis of response to the claudication questionnaire and medical record documentation of diagnostic procedures or vascular intervention. Of 695 self-reported PAD events that occurred as of 23 November 2007, 178 were confirmed by using these methods. Among self-reported events designated as non-PAD outcomes during case validation, venous disease, lower-extremity arthritis, lumbar disk disease, and peripheral neuropathy were the main causes of non-ischemic leg pain. Only confirmed events were considered in our analysis.

Statistical Analysis

Baseline characteristics were age-adjusted by using direct standardization for categorical variables and general linear models for continuous variables and were compared according to smoking status at study entry (never, former, <15 cigarettes/d, or ≥ 15 cigarettes/d) by using 3-*df* tests of general linear models for continuous variables and Mantel-Haenszel chi-square tests for categorical variables. Individual person-years of follow-up were calculated from the date of return of the baseline questionnaire to the date of incident PAD, loss to follow-up, death, or 23 November 2007, whichever came first. We then constructed a series of multivariate Cox proportional hazards models to estimate HRs and 95% CIs for incident PAD according to baseline smoking status, adjusted for age; history of hypertension, diabetes, or hypercholesterolemia; body mass index; alcohol consumption; and physical activity. We also constructed time-varying Cox proportional hazards models in which a participant's baseline smoking status was updated with information provided on subsequent questionnaires. We then assessed the dose-response relationship between lifelong smoking exposure and incident PAD by using pack-years of smoking (0, <10, 10 to 29, or ≥ 30 pack-years), with adjustment for the same variables. Because previous studies (20) described an earlier age of menopause in smokers than in nonsmokers, we performed an analysis stratified by postmenopausal status. Effect modification due to menopausal status or random treatment assignments was assessed by using multiplicative interaction terms and likelihood ratio tests. The incidence of PAD over time across categories of pack-years was estimated by using Kaplan-Meier survival curves, and the results were compared by using the log-rank test.

We evaluated the effect of smoking cessation by comparing the HRs and 95% CIs for symptomatic PAD among women who stopped smoking fewer than 10, 10 to

20, or more than 20 years ago with that of current smokers. The 241 smokers (1.7%) who did not report when they quit smoking were excluded from these analyses.

To gain further insight into the relationship between smoking and incident PAD and to identify variables that could mediate such an association, we constructed another series of Cox proportional hazards models for the 28 314 women with available blood samples. On the basis of our previous findings, we focused on hsCRP and sICAM-1 for these analyses (21, 22). Biomarker levels were log-transformed to normalize the variable distribution and better meet the assumption of linearity in risk.

Tests for linear trend were performed by using integer scores across categories. The proportional hazards assumption was examined by including a time-by-smoking interaction term in the model (23). No violation of this assumption was detected. We used a complete-case analysis in multivariate models, with no imputation for missing data. No exposure of interest had more than 2.1% missing data (Table 1). In the primary analyses presented in Tables 2 and 3, no multivariate model excluded more than 865 participants (2.2%) because of missing data. All analyses were performed by using SAS, version 9.1 (SAS Institute, Cary, North Carolina). A 2-tailed *P* value less than 0.05 indicated statistical significance.

Role of the Funding Source

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RESULTS

At study entry, 20 336 women (51.1%) were never-smokers, 14 263 (35.8%) were former smokers, 1967 (4.9%) smoked fewer than 15 cigarettes per day, and 3259 (8.2%) smoked 15 or more cigarettes per day. Table 1 shows age-adjusted baseline characteristics by smoking status. Current smokers were younger, had a lower body mass index, exercised less frequently, had less education, and consumed more alcohol than never-smokers. Among women with available blood samples, current smokers had higher levels of total cholesterol, hsCRP, and sICAM-1 and lower levels of high-density lipoprotein cholesterol (Table 1).

During a median follow-up of 12.7 years (interquartile range, 12.4 to 13.8 years), 178 symptomatic PAD events occurred. Age-adjusted incidence rates revealed a strong risk gradient for incident PAD across the 4 smoking categories (Table 2). Women who never smoked had a very low incidence of symptomatic PAD (0.12 events per 1000 person-years of follow-up), whereas the risk was more than 10-fold higher among women who smoked 15 or more cigarettes per day at study entry (1.63 events per 1000

Table 1. Age-Adjusted Baseline Characteristics of the Study Population, by Smoking Status

Characteristic	Never-Smokers	Former Smokers	Current Smokers		P Value*	Participants With Missing Data, n (%)
			<15 cigarettes/d	≥15 cigarettes/d		
All women (n = 39 825)*						
Participants, n	20 336	14 263	1967	3259		
Mean age (95% CI), y	54.5 (54.4–54.6)	55.0 (54.9–55.1)	54.1 (53.8–54.4)	53.8 (53.6–54.0)	<0.001	0 (0)
History of hypertension, %	26.4	25.5	23.2	25.5	0.021	9 (0.02)
History of diabetes, %	2.9	2.9	2.7	3.4	0.193	0 (0)
Mean body mass index (95% CI), kg/m ²	26.1 (26.0–26.2)	26.2 (26.1–26.2)	25.3 (25.1–25.6)	25.5 (25.3–25.7)	<0.001	818 (2.1)
Exercise frequency, %					<0.001	20 (0.05)
Rarely or never	37.2	35.1	44.9	55.1		
<1 time/wk	19.9	19.1	21.2	22.2		
1–3 times/wk	32.1	33.3	27.7	18.9		
>3 times/wk	10.8	12.6	6.2	3.8		
Highest education level, %					<0.001	670 (1.7)
Less than bachelor's degree	54.4	56.0	69.0	74.1		
Bachelor's degree	24.0	23.7	18.8	16.5		
Master's degree or doctorate	21.6	20.3	12.2	9.4		
Alcohol consumption, %					<0.001	10 (0.03)
Rarely or never	53.2	34.2	40.3	45.1		
1–3 drinks/mo	13.1	13.4	12.5	13.1		
1–6 drinks/wk	27.7	38.0	33.0	26.3		
≥1 drink/d	6.0	14.4	14.2	15.6		
History of hypercholesterolemia, %	29.2	29.4	28.8	31.0	0.022	16 (0.04)
Postmenopausal, %	52.9	54.6	58.9	59.7	<0.001	71 (0.2)
Hormone replacement therapy, %	41.8	43.2	36.9	37.7	<0.001	78 (0.2)
Randomly assigned to receive aspirin, %	50.0	50.2	49.1	49.1	0.48	0 (0)
Randomly assigned to receive vitamin E, %	49.9	50.4	49.6	49.4	0.77	0 (0)
Subcohort with available blood samples (n = 28 314)						
Participants, n	14 631	10 389	1255	2039		
Mean total cholesterol level (95% CI)					<0.001	404 (1.4)
mmol/L	5.51 (5.48–5.53)	5.52 (5.49–5.55)	5.64 (5.57–5.70)	5.72 (5.66–5.77)		
mg/dL	212.6 (211.5–213.6)	213.1 (212.0–214.3)	217.6 (215.1–220.1)	220.6 (218.6–222.7)		
Mean low-density lipoprotein cholesterol level (95% CI)					<0.001	403 (1.4)
mmol/L	3.21 (3.19–3.23)	3.17 (3.15–3.20)	3.30 (3.25–3.36)	3.38 (3.33–3.43)		
mg/dL	123.9 (123.0–124.8)	122.5 (121.6–123.5)	127.6 (125.4–129.7)	130.5 (128.7–132.3)		
Mean high-density lipoprotein cholesterol level (95% CI)					<0.001	404 (1.4)
mmol/L	1.34 (1.34–1.35)	1.37 (1.36–1.38)	1.28 (1.26–1.30)	1.22 (1.20–1.23)		
mg/dL	51.9 (51.5–52.3)	53.0 (52.6–53.4)	49.4 (48.6–50.2)	46.9 (46.3–47.5)		
Mean high-sensitivity C-reactive protein level (95% CI)					<0.001	403 (1.4)
nmol/L	18.7 (18.2–19.3)	19.1 (18.4–19.7)	18.7 (17.4–20.0)	24.8 (23.4–26.3)		
mg/L	1.97 (1.91–2.03)	2.00 (1.94–2.07)	1.96 (1.83–2.11)	2.60 (2.5–2.8)		
Mean soluble intercellular adhesion molecule-1 level (95% CI), μg/L	345.9 (344.0–347.8)	348.5 (346.5–350.6)	397.0 (392.1–402.0)	457.0 (452.3–461.7)	<0.001	551 (1.9)

* Calculated from 3-*df* tests of general linear models for continuous variables and Mantel–Haenszel chi-square tests for categorical variables.

person-years of follow-up), which corresponded to a 16.5-fold increased relative hazard for PAD in age-adjusted Cox regression models. Former smokers had a 3-fold increased risk for PAD compared with never-smokers. Multivariate adjustment for traditional risk factors, menopausal status, or the use of hormone replacement therapy had little effect on these findings. Neither menopausal status nor hormone replacement therapy was associated with incident PAD in these models (data not shown). Finally, separate analyses for women with only intermittent claudication or those

undergoing invasive procedures yielded consistent results (**Appendix Table**, available at www.annals.org).

Using time-varying covariates to update smoking status during follow-up further strengthened the association between active smoking and PAD, such that smoking fewer than 15 cigarettes per day was associated with an almost 12-fold increased risk for symptomatic PAD and smoking 15 or more cigarettes per day was associated with a more than 20-fold increased risk (**Table 2**). Similar results were obtained when participants with a diagnosis of

Table 2. Risk for Incident Peripheral Artery Disease, by Smoking Status

Variable	Never-Smokers	Former Smokers	Current Smokers		P for Trend*
			<15 cigarettes/d	≥15 cigarettes/d	
All women (n = 39 825)					
Participants, n	20 336	14 263	1967	3259	
Events/person-years of follow-up	30/260 855	63/182 532	22/24 440	63/39 502	
Age-adjusted incidence rate†	0.12	0.34	0.95	1.63	
Hazard ratios (95% CI)					
Baseline examination					
Age-adjusted model (n = 39 825)	1.0 (reference)	2.95 (1.91–4.55)	8.76 (5.05–15.21)	16.51 (10.66–25.57)	<0.001
Multivariate model 1 (n = 39 803)‡	1.0 (reference)	2.96 (1.92–4.58)	9.26 (5.33–16.09)	16.53 (10.66–25.62)	<0.001
Multivariate model 2 (n = 38 960)§	1.0 (reference)	3.14 (2.01–4.90)	8.93 (5.02–15.89)	16.95 (10.77–26.67)	<0.001
Smoking status updated during follow-up					
Age-adjusted model (n = 39 825)	1.0 (reference)	2.97 (1.94–4.55)	11.28 (6.62–19.21)	20.99 (13.29–33.15)	<0.001
Multivariate model 1 (n = 39 803)‡	1.0 (reference)	2.98 (1.95–4.56)	11.89 (6.97–20.28)	21.19 (13.40–33.50)	<0.001
Multivariate model 2 (n = 38 960)§	1.0 (reference)	3.16 (2.04–4.89)	11.94 (6.90–20.65)	21.08 (13.10–33.91)	<0.001
Subcohort with available blood samples (n = 28 314)					
Participants, n	14 631	10 389	1255	2039	
Events/person-years of follow-up	21/188 625	43/133 470	14/15 742	39/24 878	
Age-adjusted incidence rate†	0.11	0.32	1.02	1.57	
Hazard ratios (95% CI)					
Age-adjusted model (n = 28 314)	1.0 (reference)	2.85 (1.69–4.80)	8.98 (4.56–17.68)	16.45 (9.65–28.05)	<0.001
Multivariate model 1 (n = 27 347)	1.0 (reference)	2.89 (1.70–4.91)	7.12 (3.46–14.63)	13.46 (7.38–23.42)	<0.001
Multivariate model 2 (n = 27 159) ¶	1.0 (reference)	2.83 (1.64–4.86)	5.58 (2.61–11.93)	9.52 (5.17–17.53)	<0.001

* Across categories of cigarette smoking.

† Per 1000 person-years of observation.

‡ Additionally adjusted for history of hypertension, diabetes, or hypercholesterolemia.

§ Additionally adjusted for body mass index, alcohol consumption, and physical activity.

|| Additionally adjusted for history of hypertension or diabetes, body mass index, alcohol consumption, physical activity, and measured total and high-density lipoprotein cholesterol levels.

¶ Additionally adjusted for high-sensitivity C-reactive protein and soluble intercellular adhesion molecule-1 levels.

cardiovascular disease before PAD were censored (data not shown). However, in analyses that examined differences according to baseline menopausal status, the risk for symptomatic PAD in smokers seemed to be stronger among premenopausal than among postmenopausal women. Compared with women who never smoked, the HRs among premenopausal women were 1.98 (CI, 0.78 to 5.04) for former smokers, 8.57 (CI, 2.79 to 26.36) for those who smoked fewer than 15 cigarettes per day, and 26.73 (CI, 12.0 to 59.54) for those who smoked 15 or more cigarettes per day; the respective HRs among postmenopausal women were 3.50 (CI, 2.10 to 5.86), 9.04

(CI, 4.61 to 17.37), and 12.82 (CI, 7.29 to 22.55) (P for interaction = 0.024). No statistically significant evidence for an interaction between smoking and either aspirin or vitamin E therapy was observed (P for interaction = 0.186 and 0.40, respectively).

The relationship between smoking status and risk for symptomatic PAD in the subcohort of 28 314 women who provided a blood sample was similar to that observed in the entire cohort (Table 2). The risk estimates for each smoking category were slightly attenuated when baseline total and high-density lipoprotein cholesterol levels were added to the regression models. Adding hsCRP and sICAM-1

Table 3. Risk for Incident Peripheral Artery Disease, by Pack-Years of Smoking

Variable	Pack-Years of Smoking				P for Trend*
	None	<10	10 to <30	≥30	
Events/person-years of follow-up	30/260 855	28/110 538	67/94 648	49/33 887	
Age-adjusted incidence rate†	0.12	0.28	0.72	1.33	
Hazard ratios (95% CI)					
Age-adjusted model (n = 39 227)	1.0 (reference)	2.30 (1.38–3.86)	6.43 (4.18–9.89)	11.06 (7.01–17.43)	<0.001
Multivariate model 1 (n = 39 803)‡	1.0 (reference)	2.33 (1.39–3.90)	6.54 (4.25–10.06)	10.76 (6.82–16.97)	<0.001
Multivariate model 2 (n = 38 960)§	1.0 (reference)	2.52 (1.49–4.25)	6.75 (4.33–10.52)	11.09 (6.94–17.72)	<0.001

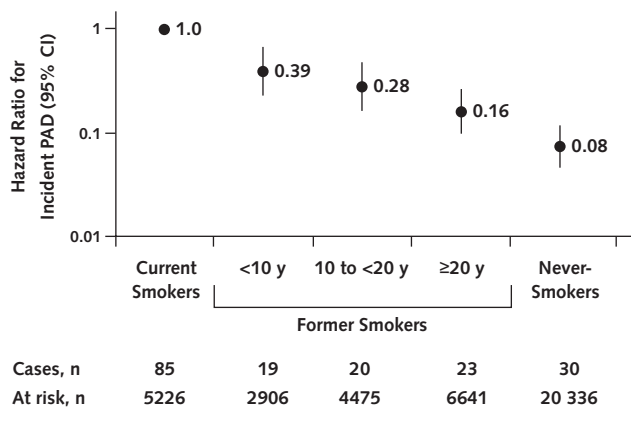
* Across categories of cigarette exposure.

† Per 1000 person-years of observation.

‡ Additionally adjusted for history of hypertension, diabetes, or hypercholesterolemia.

§ Additionally adjusted for body mass index, alcohol consumption, and physical activity.

Figure. Hazard ratio for incident PAD.



Hazard ratios are adjusted for age, hypertension, diabetes, hypercholesterolemia, body mass index, alcohol consumption, and physical activity. Current smokers are the reference group. PAD = peripheral artery disease.

levels to the multivariate models attenuated risk estimates for current smoking more substantially; however, smoking fewer than 15 cigarettes per day was still associated with a more than 5-fold increased risk for symptomatic PAD during follow-up (HR, 5.58 [CI, 2.61 to 11.93]), and smoking 15 or more cigarettes per day was associated with an almost 10-fold increased risk (HR, 9.52 [CI, 5.17 to 17.53]). In contrast, including hsCRP or sICAM-1 levels did not appreciably affect the increased risk among former smokers (Table 2).

Lifelong smoking exposure, defined by pack-years of smoking, had a strong dose-response relationship with risk for symptomatic PAD (Table 3 and Appendix Figure, available at www.annals.org). In age-adjusted models, HRs among women whose lifetime exposure was fewer than 10, 10 to 29, or 30 or more pack-years were 2.30 (CI, 1.38 to 3.86), 6.43 (CI, 4.18 to 9.89), and 11.06 (CI, 7.01 to 17.43), respectively, compared with women who never smoked (*P* for linear trend < 0.001). Multivariate adjustment did not attenuate this relationship. Again, censoring participants with a diagnosis of cardiovascular disease before PAD did not appreciably change our results (data not shown).

Among former smokers, 2906 quit smoking within 10 years before study entry, 4475 quit between 10 and 20 years earlier, and 6641 quit more than 20 years earlier. Smoking cessation markedly decreased the risk for PAD compared with active smoking, and longer smoking abstinence was associated with an additional reduction of this risk (Figure). Fully adjusted HRs for smoking abstinence of fewer than 10, 10 to 20, or more than 20 years and for lifelong nonsmoking were 0.39 (CI, 0.24 to 0.66), 0.28 (CI, 0.17 to 0.46), 0.16 (CI, 0.10 to 0.26), and 0.08 (CI, 0.05 to 0.12), respectively (*P* for linear trend < 0.001) (Figure).

DISCUSSION

Our large-scale prospective study, conducted among initially healthy women, yielded at least 2 major findings. First, smoking is a potent risk factor for symptomatic PAD, even after accounting for several established risk factors and markers of subclinical inflammation. In addition, smoking cessation is associated with a substantial reduction in the risk for PAD, thus highlighting the importance of aggressive efforts to promote smoking cessation.

Although previous prospective studies having consistently shown an increased risk for PAD among smokers, few analyses assessed smoking as a main exposure variable and the strength of the relationship varied widely across reports, with relative risks of current smoking that ranged from 1.6 to 10.2 (8–14). Our data indicate one of the strongest associations for current smoking reported thus far, which may be due to our focus on symptomatic as opposed to subclinical disease (9) and our evaluation in an exclusively female, relatively young, and otherwise low-risk population. Even in this relatively homogeneous group, the risk for PAD associated with smoking is higher among younger, premenopausal women. Similarly, a previous study (24) reported that current smoking confers a higher relative risk for myocardial infarction among younger and relatively low-risk persons (odds ratio for nonfatal myocardial infarction, 3.53 [CI, 3.23 to 3.86] in younger persons vs. 2.55 [CI, 2.35 to 2.76] in older persons; *P* for interaction < 0.001). Whether the strength of this association is also influenced by sex should be assessed in other mixed-sex cohorts.

We also demonstrate a strong dose-response relationship between lifelong smoking exposure and subsequent PAD, which confirms previous studies (10, 13) that suggested such an association. Although our data show no particular threshold below which smoking does not confer an increased risk, women who indicated at least 10 pack-years of smoking exposure had a particularly steep risk increase.

Our finding that smoking cessation is associated with a dramatic reduction in incident PAD is also important. Previous investigations in this context have focused on total cardiovascular morbidity and mortality. For example, in the Nurses' Health Study (7), the risk for vascular death among women who stopped smoking gradually decreased as duration of smoking abstinence increased, reaching the relative risk of never-smokers after approximately 20 years. Although we also found a gradual decrease in risk with an increased duration of smoking abstinence, even women who quit smoking more than 20 years before inclusion in our study had a higher risk for symptomatic PAD than women who had never smoked. This residual risk may relate to long-term adverse effects of smoking on the peripheral vasculature. For patients and their physicians, our findings suggest that long-term smoking cessation substantially reduces the risk for symptomatic PAD, whereas the

residual risk even among former smokers who abstain for at least 20 years underscores the importance of primary efforts for smoking prevention.

There was no strong confounding of the adverse effects of smoking by any of the traditional risk factor variables included in the multivariable models. Adding hsCRP and sICAM-1 as markers of subclinical inflammation somewhat attenuated the coefficients for actively smoking women (Table 2), which suggests that these factors may in part mediate the adverse effects of smoking. However, the increased risk associated with smoking remains largely unexplained even after multivariate adjustment, which is consistent with one of the few previous studies on this issue (13).

The strengths of our study include its prospective design; large sample size; long-term follow-up with many confirmed end points; and homogeneous study sample, which may have reduced confounding. However, our study also has potential limitations. First, we included mainly white women, and our findings may not be generalizable to other groups. Second, because our study is observational, unmeasurable or residual confounding may be present. Third, the use of symptomatic PAD as the a priori primary end point excludes subclinical disease, which may have otherwise been detected by abnormal pulse examination or ankle-brachial index (25). However, we believe our data to be not only relevant from a mechanistic perspective but also of clinical importance, because claudication and revascularization of an ischemic limb are the principal clinical manifestations of PAD. Of note, events included in this analysis were confirmed by a validated claudication questionnaire, cardiovascular physician interview, and medical record review. Our focus on symptomatic disease and the characteristics of our study population may also have reduced the likelihood of end point misclassification. Our participants were health professionals and therefore were less likely to encounter barriers to medical care, which may otherwise have led to misdiagnosis or underdiagnosis among all smoking exposure groups. Whether women with PAD are more likely to have atypical leg symptoms or more often be asymptomatic is controversial (26, 27), especially because some studies suggest that a lower (less stringent) ankle-brachial index cutoff for PAD diagnosis is more appropriate in women (28, 29). Regardless, if smoking is even modestly associated with PAD, misclassification of women with atypical PAD symptoms as noncases would, if anything, tend to bias our results toward the null by including relatively more smokers in the non-PAD group. Finally, we did not consider exposure to second-hand smoke, which has been shown to be an important risk factor for PAD in women (30).

In conclusion, our large prospective study emphasizes the importance of smoking as a risk factor for symptomatic PAD. Although this association seems partly mediated by inflammation, most of the excess risk conferred by smoking remains unexplained. Although smoking cessation dra-

matically reduces the risk for PAD, an increased disease risk remains even after long-term smoking cessation, which demonstrates the importance of both prevention of smoking initiation and efforts to promote long-term abstinence.

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Appendix Table. Risk for Incident Peripheral Artery Disease, by Smoking Status and Symptomatic Event

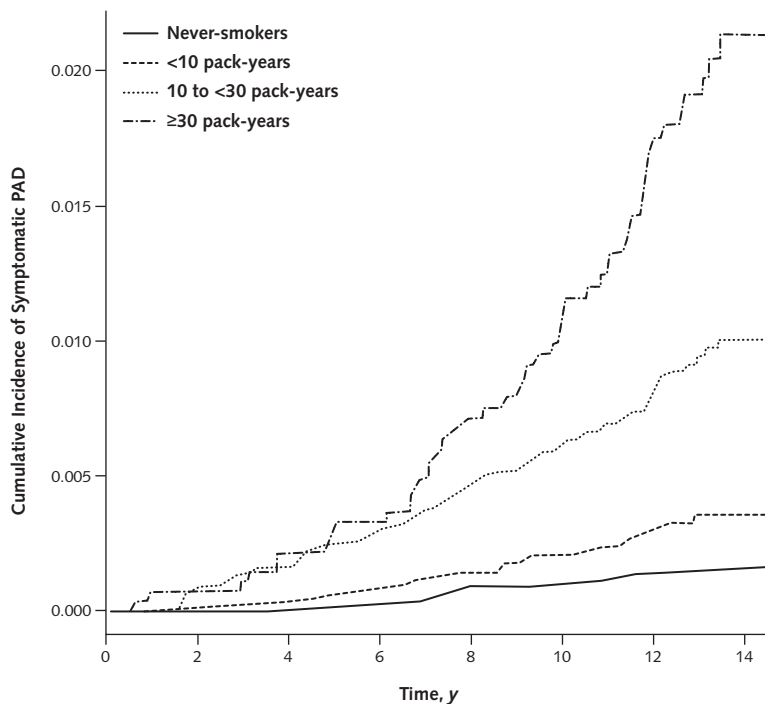
Event	Hazard Ratio (95% CI)				P for Trend*
	Never-Smokers (n = 20 336)	Former Smokers (n = 14 263)	Current Smokers		
			<15 cigarettes/d (n = 1967)	≥15 cigarettes/d (n = 3259)	
Claudication only (85 events)					
Age-adjusted model (n = 39 825)	1.0 (reference)	2.12 (1.25–3.93)	3.83 (1.53–9.61)	12.72 (7.12–22.71)	<0.001
Multivariate model 1 (n = 39 803)†	1.0 (reference)	2.22 (1.25–3.94)	4.03 (1.61–10.13)	12.59 (7.05–22.51)	<0.001
Multivariate model 2 (n = 38 960)‡	1.0 (reference)	2.32 (1.30–4.16)	3.45 (1.28–9.33)	12.37 (6.81–22.47)	<0.001
Peripheral artery revascularization (93 events)					
Age-adjusted model (n = 39 825)	1.0 (reference)	4.21 (2.13–8.34)	17.14 (7.95–36.99)	23.07 (11.62–45.79)	<0.001
Multivariate model 1 (n = 39 803)†	1.0 (reference)	4.25 (2.15–8.42)	18.24 (8.45–39.41)	23.34 (11.75–46.36)	<0.001
Multivariate model 2 (n = 38 960)‡	1.0 (reference)	4.70 (2.30–9.62)	19.25 (8.57–43.25)	25.64 (12.44–52.87)	<0.001

* Across categories of cigarette smoking.

† Additionally adjusted for history of hypertension, diabetes, or hypercholesterolemia.

‡ Additionally adjusted for body mass index, alcohol consumption, and physical activity.

Appendix Figure. Cumulative incidence of PAD, by pack-years of smoking.



Patients at risk, <i>n</i>	0	2	4	6	8	10	12	14
Never-smokers	20 305	20 224	20 110	19 934	19 570	17 992	9366	1037
<10 pack-years	8597	8557	8502	8409	8252	7636	4036	480
10 to <30 pack-years	7464	7407	7329	7223	7043	6438	6410	433
≥30 pack-years	2777	2731	2672	2597	2480	2216	1141	131

PAD = peripheral artery disease.