

Factors Associated with Age at Natural Menopause in a Multiethnic Sample of Midlife Women

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An unprecedented number of women will experience menopause in the next decade. Although the timing of menopause affects long-term disease risk, little is known about factors that affect this timing. In the present 1995–1997 cross-sectional study, the Study of Women's Health Across the Nation, the relation of demographic and lifestyle factors to age at natural menopause was examined in seven US centers and five racial/ethnic groups. All characteristics were self-reported by women aged 40–55 years ($n = 14,620$). Cox proportional hazards models were used to estimate the probability of menopause by age. Overall, median age at natural menopause was 51.4 years, after adjustment for smoking, education, marital status, history of heart disease, parity, race/ethnicity, employment, and prior use of oral contraceptives. Current smoking, lower educational attainment, being separated/widowed/divorced, nonemployment, and history of heart disease were all independently associated with earlier natural menopause, while parity, prior use of oral contraceptives, and Japanese race/ethnicity were associated with later age at natural menopause. This sample is one of the largest and most diverse ever studied, and comprehensive statistical methods were used to assess factors associated with age at natural menopause. Thus, this study provides important insights into this determinant of long-term disease risk in women. *Am J Epidemiol* 2001;153:865–74.

age of onset; ethnic groups; life style; menopause; proportional hazards models; risk factors; smoking

Over the next decade, approximately 40 million women will experience menopause (1). Age at the natural final menstrual period may be an important risk indicator for subsequent morbidity and mortality. The risks of cardiovascular disease (2–4) and osteoporosis (5) tend to be higher for women with an earlier menopause, but women who experience an earlier menopause are protected against breast cancer (6). One possible explanation for these effects is the duration of exposure to high circulating estrogen levels, which could produce distinct outcomes based on the relation between estrogen and the particular disease.

Age at natural menopause has also been related to all-cause mortality. In one US population-based study, women who experienced nonsurgical menopause prior to age 40 years had a 50 percent higher mortality rate than those reporting menopause at age 50 years or older (4). Women whose nonsurgical menopause occurred between ages 40 and 50 years had no increased mortality compared with those whose menopause occurred at an older age. Another community-based cohort study reported a 95 percent increase in all-cause mortality associated with nonsurgical menopause occurring before age 40 years compared with menopause at age 50 years or older (2). However, women aged 40–49 years at menopause were also at a 35 percent higher risk of mortality compared with women aged 50 years or older at natural menopause. Several complex causes may underlie the observed relation between earlier age at menopause and mortality, including genetic factors, behavioral and environmental exposures, hormonal mechanisms, and health-related factors. Understanding the associations of these factors with age at natural menopause may help to elucidate the mechanisms underlying the relation of age at menopause to morbidity and mortality.

Most estimates of age at natural menopause are based on samples of Caucasian women in western societies, although one international study of 18,997 women from 11 countries found the median age at natural menopause to be 50 years (range, 49–52 years) (7). A few studies of non-Caucasian women, conducted primarily outside the United States, have reported younger ages at menopause than those for Caucasian women. The better-designed studies suggest that

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Abbreviations: BMI, body mass index; SWAN, Study of Women's Health Across the Nation.

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Africans (8, 9), African Americans (10, 11), and Hispanics of Mexican descent (12) have an earlier age at menopause than Caucasian women do, while Japanese (13) and Malaysian (14) women report a median age at menopause similar to that for women of European descent.

The most consistent finding regarding behavioral factors has been that for smokers, menopause occurs 1–2 years earlier than for nonsmokers (10, 15–19). With varying consistency, studies have found that an earlier natural menopause is also associated with less education (20, 21), low social class (15, 22), nulliparity or having fewer children (21, 23, 24), never having used oral contraceptives (21, 22, 25), and low relative weight (18, 26). Being on a weight reduction diet has also been associated with earlier menopause (10). Most of these factors may affect the hypothalamic-pituitary-gonadal axis and its regulation of gonadotropins and sex steroid hormones.

Many prior studies have not had sufficiently large sample sizes to provide stable estimates of age at menopause (10, 27), did not control statistically for confounding variables, or used inappropriate statistical techniques. In the present study, we analyzed data from a large, multicenter study (Study of Women's Health Across the Nation (SWAN)) of a multiracial/multiethnic sample of women to examine the independent association of a number of factors with age at natural menopause by using multivariate survival statistical techniques to adjust simultaneously for the effects of multiple factors.

MATERIALS AND METHODS

Study participants

The design and sampling strategy of SWAN have been described in detail elsewhere (28). Briefly, the study is being conducted at seven US sites, each of which has recruited a sample of Caucasian women and women of one racial/ethnic minority. The study sites are located in Boston, Massachusetts; Chicago, Illinois; the Detroit, Michigan, area; Pittsburgh, Pennsylvania; Los Angeles, California; Newark, New Jersey; and the Oakland, California, area. Five racial/ethnic groups were recruited: African American (Boston, Chicago, Detroit, Pittsburgh), Caucasian (all sites), Chinese (Oakland), Hispanic (Newark), and Japanese (Los Angeles).

A two-stage recruitment process was used. First, during 1995–1997, a cross-sectional survey was conducted, by telephone at most sites and in person for about half of the women at two sites (with African Americans as their minority sample), to assess eligibility for enrollment into a cohort study and to collect health, reproductive, demographic, and lifestyle data. Eligibility criteria for the cross-sectional survey were as follows: age 40–55 years, self-designated as one of the targeted racial/ethnic groups for the site, residence near one of the seven clinic sites, speaker of English or one of the other selected languages (Spanish, Japanese, Cantonese), and able to give verbal consent. Community-based sampling from established lists of populations at five sites and random digit dialing, combined with a “snowball” approach at two sites (28) (those with the Hispanic and

Japanese minority samples), were used. In the snowball technique, women first identified by using a list-based or random-digit-dialing technique were asked for the names and contact information of other women who met the eligibility criteria; these women in turn were contacted, were screened for eligibility, and were asked for the names of other appropriate women. This process continued until a sufficient number of eligible women was identified. In the second stage of the study, a longitudinal cohort was recruited from those women screened and found eligible in the cross-sectional survey. A total of 16,065 women participated in the cross-sectional survey, 3,150 of whom enrolled in the cohort study.

Data collection

Assessment of the outcome (age at menopause). Natural menopause was defined according to the World Health Organization (29) as at least 12 consecutive months of amenorrhea not due to surgery or other obvious cause, such as extreme weight loss. Women who reported that they had had a hysterectomy or oophorectomy (unilateral vs. bilateral was not specified, since in pretests women could not distinguish between the two) were asked the year of surgery; age at surgery was computed by subtracting birth year from the year of surgery. Women not reporting such surgery were asked whether they had menstruated in the past 12 months. Among those with 12 or more months of amenorrhea, women whose periods had not stopped because of surgery, medical treatment, pregnancy, breastfeeding, or severe weight loss were defined as naturally postmenopausal (29). These women were asked in what year their last menstrual period had occurred; their year of birth was subtracted from this year to obtain age at menopause. Menopausal status was defined as *surgical amenorrhea* if menses had stopped as a result of hysterectomy and/or oophorectomy, *naturally postmenopausal* if menses had stopped for at least 12 months without surgery, *late perimenopause* if menses had occurred in the past 12 months but not in the last 3 months, *early perimenopause* if menses had occurred in the past 3 months but had become less predictable, and *premenopause* if menses had occurred in the past 3 months with no decreased predictability.

Independent variables. All independent variables of interest were obtained by self-report during the interview. Included were demographic factors (age, race/ethnicity, educational attainment, employment, marital status, number of children, and ability to pay for basics, i.e., food, shelter, clothing, and heat), lifestyle factors (smoking, physical activity), and health-related factors (height and weight (converted to body mass index (BMI): weight in kilograms/height in meters²), ever having been told by a health care provider that she had heart disease, cancer, hypertension, or diabetes).

Primary race/ethnicity was self-defined as Black or African American, non-Hispanic Caucasian, Chinese or Chinese American, Japanese or Japanese American, or Hispanic (Central American, Cuban or Cuban American, Dominican, Mexican or Mexican American, Puerto Rican, South American, Spanish, or other Hispanic). Respondents

could also specify “other,” “mixed,” or no primary ethnic affiliation. Since most extant literature regarding age at menopause is based on non-Hispanic Caucasians, they were used as the reference group.

Cigarette smoking was categorized as never, former, or current smoker and number of cigarettes *currently* smoked per day, based on modified American Thoracic Society questions (30). Physical activity was assessed with one global question about activity level relative to other women of the respondent’s age (31).

Data analyses

Approach. Menstrual status groups were compared with respect to key demographic, lifestyle, and health characteristics by using chi-square statistics. We performed bivariate Kaplan-Meier survival analyses (32) and Cox proportional hazards regression analyses (33) to evaluate the relation of categorical and of continuous variables, respectively, to age at menopause. Variables found in bivariate analyses to be related ($p < 0.15$), or suggested by previous literature to be related, to age at natural menopause were included in the multivariate Cox proportional hazards analyses.

Exclusions. Women whose menstrual periods had stopped because of medication, radiotherapy, pregnancy or lactation, or extreme weight change ($n = 311$) were excluded from the present analyses. Also excluded were women whose data on current menstrual status ($n = 109$) or whose information on any covariate ($n = 1,141$) was missing. Women who identified their primary race/ethnicity as “mixed” or “other” ($n = 1,694$) constituted a heterogeneous group whose results could not be interpreted clearly and were thus excluded. The remaining sample size used in this analysis was 14,620.

Cox proportional hazards modeling. Cox proportional hazards models were estimated to assess associations of age at natural menopause with independent variables. Women not currently using reproductive hormones who were not surgically or naturally menopausal were censored at their current age.

Women who had had a hysterectomy and/or oophorectomy ($n = 3,069$) were censored at their age at surgery, since surgery masks the age at which a woman would become menopausal in the absence of this surgery (34). (We did not have information on whether oophorectomy was unilateral or bilateral.) We also conducted analyses by excluding these women; the result was that overall age at menopause was reduced by 0.4 years and all point estimates changed less than 10 percent (data not shown). Including these women and censoring them assumes that, given their covariate information, the distribution of their “true” age at natural menopause (which cannot be observed) is the same as that for naturally menopausal women. Their inclusion is important because they are not a random subsample of middle-aged women (35–40); excluding them could lead to biased results. They also constitute a nonnegligible proportion of the population (41, 42), and their data may be informative regarding the timing of natural menopause.

Women who had used hormones, including oral contraceptives, in the past 3 months (“current users,” $n = 1,151$) were initially considered in two ways, first by excluding them (10) and then by leaving them in the analysis and censoring at the age computed by subtracting the total number of years of hormone use from their current age. The results of these two approaches did not differ, but the latter approach provided a slightly better model fit; thus, its results are presented in this paper. Data on women whose menopause preceded hormone use were included as menopausal events.

Continuous variables (e.g., parity, BMI) were initially maintained in multivariable models as continuous variables. For ease of interpretation, this paper reports hazard ratios by categories of these variables. For categorical variables, a conceptually logical referent level was selected for comparison. All other levels of ordinal (e.g., educational level) variables were coded as dummy variables, rather than assuming rankings in the models.

Dummy indicator variables for field site were included in the multivariable models (43). For each of the three racial/ethnic groups studied at a single site only (Chinese, Hispanic, and Japanese), the coefficients reflect a direct comparison with the Caucasians at the same site only. Interactions between site and race/ethnicity for these three groups could not be estimated given the study design. Four sites interviewed African Americans and Caucasians, enabling us to examine interactions between race/ethnicity and site for these two racial/ethnic groups, that is, whether the racial/ethnic difference in age at menopause varied across these four sites. We also examined interaction terms for smoking with race/ethnicity, BMI, history of use of oral contraceptives, parity, education, employment, marital status, site, or history of heart disease. Goodness of fit of the multivariate Cox models was assessed by using the link test (44, 45).

RESULTS

Unadjusted demographic, lifestyle, and health characteristics

The majority of women (57.7 percent) were still menstruating. A much greater proportion of African Americans than all other racial/ethnic groups were surgically amenorrheic, the highest proportion of women currently using hormones were Caucasian, and the highest proportions of premenopausal women were among Chinese and Japanese women (table 1). Higher educational level was associated with being premenopausal and with current hormone use, while women with lower educational attainment were more likely to have surgical amenorrhea. Women who had no difficulty paying for basics, were employed, were nonsmokers, or reported being more physically active than other women of their age were more likely to be premenopausal or to be using hormones. Women who were single or married (or living as married) were more likely to be premenopausal and less likely to be surgically amenorrheic, while widowed women were more likely to be post- or surgically menopausal. Women with lower BMI were more likely to be pre-

TABLE 1. Demographic, lifestyle, and health characteristics of the study population, by menstrual status, Study of Women's Health Across the Nation, United States, 1995–1997*

Characteristic	Premenopausal (<i>n</i> = 4,514, 30.0%)		Early and late perimenopausal (<i>n</i> = 4,173, 27.7%)		Postmenopausal (<i>n</i> = 2,247, 14.3%)		Surgical amenorrhea (<i>n</i> = 3,069, 20.2%)		Current hormone use (<i>n</i> = 1,151, 7.6%)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Race/ethnicity										
African American	1,030	24.4	1,187	28.1	535	12.7	1,322	31.3	143	3.4
Caucasian	2,183	29.0	2,122	28.2	1,104	14.7	1,305	17.4	806	10.7
Japanese	370	44.7	213	25.8	90	10.9	82	9.9	72	8.7
Chinese	294	46.3	177	27.9	74	11.7	37	5.8	53	8.3
Hispanic	637	34.3	474	25.6	344	18.5	323	17.4	77	4.2
Educational attainment										
<12 years	385	25.7	421	28.1	292	19.5	348	23.2	53	3.5
High school/GED† certificate	1,237	25.9	1,346	28.2	789	16.5	1,100	23.0	307	6.4
Some college	1,149	29.4	1,094	28.0	477	12.2	883	22.6	308	7.9
College graduate	891	36.0	692	27.9	299	12.1	364	14.7	231	9.3
Graduate/professional school	852	35.7	620	26.0	290	12.1	374	15.7	252	10.6
Difficulty paying for basics										
Very difficult	433	25.1	537	31.1	280	16.2	401	23.2	75	4.3
Somewhat difficult	1,495	30.7	1,388	28.5	712	14.6	992	20.3	288	5.9
Not at all difficult	2,565	30.5	2,235	26.6	1,144	13.6	1,667	19.8	787	9.4
Employment										
No	991	27.2	990	27.2	638	17.5	836	23.0	187	5.1
Yes	3,521	30.9	3,180	27.9	1,509	13.2	2,233	19.6	964	8.5
Marital status										
Never married	621	32.9	554	29.4	259	13.7	330	17.5	122	6.5
Married/living as married	2,994	31.5	2,644	27.8	1,230	13.0	1,821	19.2	806	9.1
Separated	214	29.3	220	30.1	97	13.3	169	23.2	30	4.1
Widowed	97	17.4	127	22.7	161	28.8	149	26.7	25	4.5
Divorced	582	24.7	618	26.2	394	16.7	595	25.2	168	7.1
Livebirths										
None	778	32.6	648	27.2	336	14.1	378	15.8	245	9.5
Any	3,732	29.5	3,519	27.8	1,811	14.3	2,689	21.2	906	7.2
Physical activity‡										
Much less	182	21.2	260	30.2	132	15.3	232	27.0	54	6.3
Somewhat less	582	26.4	676	30.7	318	14.4	484	22.0	142	6.4
Some	1,765	30.4	1,639	28.2	803	13.8	1,176	20.2	427	7.3
Somewhat more	1,146	32.0	939	26.2	507	14.2	668	18.7	321	9.0
Much more	675	31.3	566	26.3	318	14.7	419	19.4	178	8.3

Table continues

menopausal, but women with higher BMI were more likely to be surgically amenorrheic. Women who had never used oral contraceptives were more likely than ever users to be postmenopausal. A greater proportion of women who had high blood pressure, diabetes, or heart disease were post- or surgically menopausal than women without these conditions, although these data were difficult to interpret because of the cross-sectional design of this portion of the study.

Multivariate associations of risk factors with age at natural menopause

The overall multiply adjusted median age at natural menopause was 51.4 years. Current smoking, lower educational attainment, not being married, not being employed, and having a history of heart disease were all significantly,

independently associated with earlier natural menopause, while ever using oral contraceptives, being parous, and Japanese race/ethnicity were significantly, independently associated with later age at natural menopause after adjustment for site and each variable for all other important variables (table 2, figures 1–3). Hispanics had a significantly earlier menopause than Caucasians did (hazard ratio = 1.16, 95 percent confidence interval: 1.01, 1.34) when site was not included in the multivariate model. The effect of prior use of oral contraceptives was also examined by duration of use, and parity was examined by number of children; neither estimate changed (data not shown).

Initial multivariate Cox proportional hazards models showed no significant associations, after adjustment for other variables, of age at menopause with self-reported physical activity, history of cancer (including breast cancer),

TABLE 1. Continued

Characteristic	Premenopausal (n = 4,514, 30.0%)		Early and late perimenopausal (n = 4,173, 27.7%)		Postmenopausal (n = 2,247, 14.3%)		Surgical amenorrhea (n = 3,069, 20.2%)		Current hormone use (n = 1,151, 7.6%)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Smoking										
Never	2,418	33.9	2,120	27.2	1,005	12.9	1,443	18.5	594	7.6
Former	895	26.9	1,009	27.0	527	14.1	843	22.6	353	9.4
Current (no. of cigarettes/day)										
<10	230	28.8	269	31.6	128	15.0	165	19.4	45	5.3
10–19	262	24.9	301	26.7	198	17.6	280	24.8	68	6.0
≥20	251	19.5	430	31.5	280	20.5	310	22.7	80	5.9
Body mass index (kg/m ²)										
<19	298	32.2	291	31.5	132	14.3	151	16.3	53	5.7
19 to 26.9	2,678	33.0	2,152	22.5	1,114	14.1	1,374	16.9	763	19.4
27 to 31.9	849	26.3	903	27.9	487	15.1	790	24.4	203	6.3
≥32	689	24.7	827	29.7	387	13.9	754	27.0	132	4.7
Use of oral contraceptives										
No	1,353	31.3	1,217	28.2	787	18.2	798	18.5	165	3.8
Yes (no. of years)										
<1	662	29.5	661	29.4	271	12.1	496	22.1	155	7.9
1 to <3	814	31.6	701	27.2	495	13.6	529	20.6	180	7.0
3 to <5	732	32.8	592	20.5	266	11.9	453	20.3	187	8.4
≥5	929	25.8	975	27.1	462	12.8	777	21.6	460	12.8
History of high blood pressure										
No	3,702	32.7	3,219	28.4	1,547	13.7	1,963	17.3	895	7.9
Yes	807	21.7	951	25.6	599	16.1	1,104	29.7	255	6.9
History of diabetes										
No	4,318	30.7	3,923	27.9	1,963	13.9	2,769	19.7	1,101	7.8
Yes	194	20.0	246	25.4	182	18.8	297	30.7	50	5.2
History of heart disease										
No	4,460	30.5	4,084	27.9	2,057	14.1	2,881	19.7	1,137	7.8
Yes	49	11.5	88	20.7	90	21.1	185	43.4	14	3.3

* All chi-square statistics had *p* values of <0.001.

† GED, general educational development.

‡ Level relative to other women of the respondent's age.

high blood pressure or diabetes, BMI, self-assessed health status, limitation of activities because of health, or difficulty paying for basics. Thus, these variables were excluded from the final multivariate models. Age at menopause did not increase with duration of prior use of oral contraceptives. Clinic site was retained in the model, although not significantly associated with the outcome. Interaction terms for smoking with other risk factors were not statistically significant, nor were interactions between site and African-American race/ethnicity (data not shown).

DISCUSSION

In the present study, the overall median age at natural menopause was found to be 51.4 years after adjustment for multiple factors, which is comparable to previous reports in other US studies (10, 19, 21, 27, 34, 46–48). However, our study demonstrated that Japanese women have a later natural menopause than Caucasian, African-American, Hispanic, or Chinese women do. Our results also confirm those from previous studies showing that current smoking,

lower educational attainment, and nonemployment were related to earlier age at natural menopause and that prior use of oral contraceptives and parity were associated with later age at menopause, as previously reported by some (49, 50).

Race/ethnicity

Unlike our study, prior studies have reported that age at menopause for Japanese women was similar to that for Caucasian women (51, 52). One study of 2,221 Japanese women reported a median age at menopause of 50.4 years (13). Another study of 400 Malaysian women reported a similar median age at menopause of 50.7 years (14). However, a study of 2,354 Thai women aged 45–59 years, sampled from Bangkok health centers in lower-middle socioeconomic status areas, reported a median age at menopause of 49.5 years (53). Filipino Malay women were reported to be an average age of 47–48 years at menopause (54), although the methods used in both of these latter studies may have biased their results toward lower estimates.

TABLE 2. Adjusted hazard ratios (and 95% confidence intervals) and median ages at natural menopause for demographic, lifestyle, and health characteristics of the study population, Study of Women's Health Across the Nation, United States, 1995–1997

Characteristic	Adjusted* hazard ratio	95% confidence interval	Median age at meno- pause (years)
Smoking			
Never†	1.00		51.4
Former	1.04	0.92, 1.17	51.7
Current (no. of cigarettes/day)			
<10	1.17	0.97, 1.42	51.1
10–19	1.70	1.44, 2.00	50.2
≥20	1.63	1.40, 1.89	50.8
Use of oral contraceptives			
Never†	1.00		51.0
Ever	0.84	0.76, 0.93	51.6
Livebirths			
None†	1.00		51.2
Any	0.80	0.70, 0.93	51.3
Educational attainment			
≤High school	1.48	1.26, 1.73	51.0
Some college	1.29	1.10, 1.51	51.5
College graduate	1.15	0.96, 1.38	51.5
Graduate/professional school†	1.00		51.7
Marital status			
Never married	1.16	0.99, 1.36	51.0
Married/living as married†	1.00		51.7
Separated/widowed/divorced	1.27	1.14, 1.41	51.0
Race/ethnicity			
African American	1.02	0.88, 1.16	51.4
Caucasian†	1.00		51.4
Japanese	0.74	0.55, 1.00	51.8
Chinese	1.16	0.83, 1.62	51.5
Hispanic	0.94	0.79, 1.12	51.0
Employment			
No	1.20	1.08, 1.33	51.1
Yes†	1.00		51.4
History of heart disease			
No†	1.00		51.4
Yes	1.36	1.08, 1.71	50.0

* Also adjusted for site.

† Referent category.

Several studies have reported that Latina women experience natural menopause about 2 years earlier than Caucasian women, but we found no difference after adjustment for covariates. For Mexican women, median ages at menopause have been reported to be 48.2 years (12) and 47 years (22), although the latter study was based on only currently menopausal women and was thus likely to underestimate median menopausal age. Peruvian and Mayan women, despite their high parity, have also been reported to experience menopause earlier, ranging from age 45 to 47 years (49, 55).

Two previous studies also suggested that African-American women experience menopause 6–12 months earlier than Caucasians, with a median age of 49.3 years for African Americans in both studies (10, 11), in contrast to our study showing no difference between African Americans and Caucasians, possibly because of the age group of our sample or greater censoring of African Americans because of more surgical menopause. Studies in South Africa (8) and Ghana (9) also reported an earlier age at menopause for African compared with Caucasian women, but a small Nigerian study reported the average age at menopause to be 52.8 years (56).

Smoking

The results of the present study add to a growing body of literature showing that current, but not former, smoking is associated with earlier age at natural menopause after adjustment for confounding factors. Women who smoke stop menstruating 1–2 years earlier than comparable nonsmokers (10, 15, 19, 20, 46–48, 50, 57–59) and may have a shorter perimenopause (27). Some studies have reported that heavy smokers have an earlier menopause than light smokers (15, 18, 60, 61). However, we observed no dose-response effect of smoking, consistent with at least one other study (19). Previous studies have shown that former smokers have no or only a slightly earlier age at menopause than never smokers (18, 19, 62), suggesting that the effect of smoking may not be permanent, a finding inconsistent with a toxic effect leading to atrophy of ovarian follicles. Polycyclic aromatic hydrocarbons in cigarette smoke are toxic to ovarian follicles (63, 64) and could result in their loss and thus in earlier menopause in smokers. Greater prevalence of hysterectomy among premenopausal smokers than nonsmokers (60, 65) does not account for the earlier menopause in smokers (66).

Socioeconomic status

We found that lower educational attainment and nonemployment were significantly, independently associated with earlier age at menopause, although difficulty paying for basics was not. Several previous studies indicate that lower educational attainment and/or socioeconomic status, often determined by occupational status of the woman or her husband, is associated with earlier age at menopause (15, 20, 21, 50), although the findings are not wholly consistent (10). Social and physical stress are also associated with amenorrhea and reproductive dysfunction (67, 68), and low socioeconomic status or low educational level may be markers for elevated stress.

Marital status and parity

In our study, separated/divorced/widowed women had an earlier menopause than women who were married or were living as married. For parous women, age at natural menopause occurred significantly later than for nulliparous women, concurring with the results of most previous work

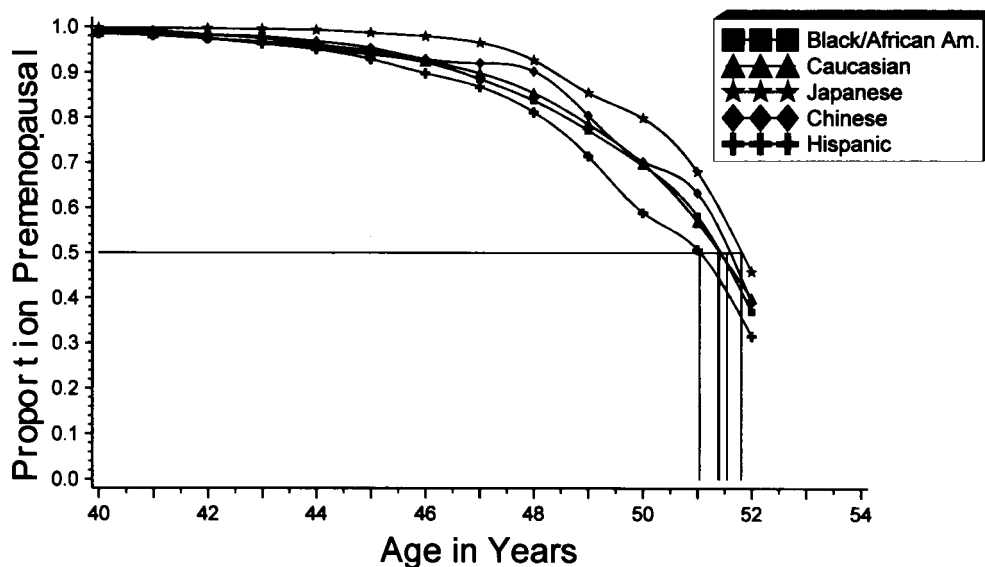


FIGURE 1. Adjusted proportional hazards of age at menopause, by race/ethnicity, for women in the Study of Women's Health Across the Nation, United States, 1995–1997. Values were adjusted for site, smoking, use of oral contraceptives, parity, education, marital status, employment, and heart disease; p value for Japanese compared with Caucasian women = 0.0476. Am., American.

(10, 15, 21, 23–25, 27, 50, 69). We observed a trend of increasing age at menopause with increasing number of live-births, but the trend was not strongly monotonic, unlike that in some previous reports (24). Since onset of menopause is theorized to be related to the rate of loss of oocytes and thus to the occurrence of ovulatory cycles (21, 23, 70), the proposed mechanism by which parity and use of oral contraceptives may result in later age at natural menopause is by

reducing ovulatory cycles earlier in life and thus preserving oocytes longer, resulting in later menopause.

Oral contraceptive use

We found that prior use of oral contraceptives was associated with earlier age at natural menopause, although no relation with increasing duration of use was observed. This

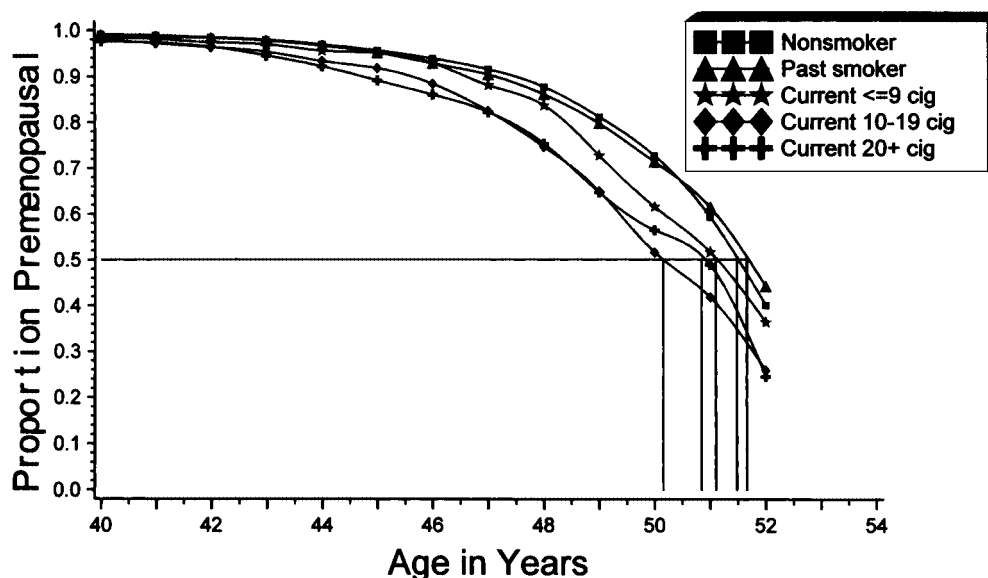


FIGURE 2. Adjusted proportional hazards of age at menopause, by smoking, for women in the Study of Women's Health Across the Nation, United States, 1995–1997. Values were adjusted for site, use of oral contraceptives, parity, education, marital status, race/ethnicity, employment, and heart disease; p value for currently smoking 16–19 and ≥ 20 cigarettes (cig)/day compared with never smoking = <0.0001 .

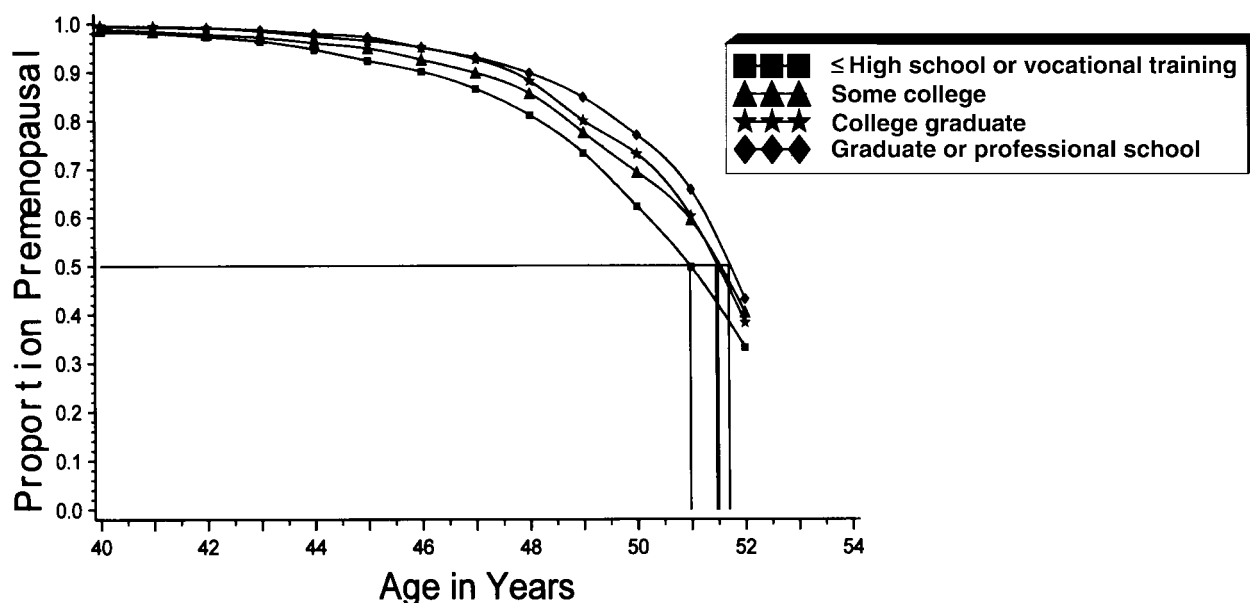


FIGURE 3. Adjusted proportional hazards of age at menopause, by educational attainment, for women in the Study of Women's Health Across the Nation, United States, 1995–1997. Values were adjusted for site, smoking, use of oral contraceptives, parity, marital status, race/ethnicity, employment, and heart disease; p value for \leq high school/vocational school compared with graduate = <0.0001 and p value for some college compared with graduate = 0.0022.

finding is consistent with those of some prior prospective studies (49, 50) but inconsistent with other results (10, 24) that either did not use survival analyses or did not control for the effects of covariates.

Body mass

In the present study, BMI and physical activity were not related to age at natural menopause. Although some studies have observed that women with lower BMI had an earlier natural menopause (18, 26, 69), other work has not confirmed this finding (10). In primates and humans, caloric restriction and nutritional deficiencies are associated with amenorrhea (71–73). The production of estrone in adipose tissue, which is greater in more-obese women, may result in higher levels of circulating estrogens that may contribute to longer reproductive functioning. Obesity, however, has also been associated with inadequate ovarian function (74).

Heart disease

We found that women who had heart disease were significantly younger at natural menopause, consistent with prior reports showing a protective effect of later age at natural menopause on heart disease morbidity and mortality (34, 75). However, given the cross-sectional nature of our data, we are uncertain whether natural menopause preceded a diagnosis of heart disease. When we did not include this variable in the multivariate model, none of the findings changed more than 10 percent. Interestingly, 45 percent of the women reporting heart disease had had a hysterectomy and/or oophorectomy, thus resulting in a high proportion of

censored women with this condition. Recent work (76) shows an estrogen receptor polymorphism to be associated with earlier menopause and with surgical menopause. Unlike some (77, 78) but not all (79) studies, age at natural menopause was not related to diabetes or to hypertension in our study.

Strengths and limitations

Our use of multivariate survival analyses (which included and censored women who were still menstruating, had surgical amenorrhea, or were currently using female hormones) enabled systematic examination of the relation of a number of independent variables to age at natural menopause. However, because of the limited time available for the cross-sectional interview, data were not collected on important details such as ages at which reproductive hormones were used and on other potentially important factors such as age at menarche, age at maternal or sibling menopause, history of long or short or irregular menstrual cycles, diet (such as consumption of fat, cholesterol, meat, and phytoestrogens), and alcohol and caffeine consumption (10, 21, 24, 50, 80, 81). All of these factors will be studied prospectively in the SWAN cohort, with results available within the next few years. In addition, in the cross-sectional portion of SWAN, we had recalled data on only the year of the final menstrual period and lacked knowledge regarding timing of the factors examined relative to the final period. Furthermore, we had information on only the year of the final menstrual period (surgical or natural); thus, our estimates of age may have been inaccurate by up to 1 year, either older or younger, a source of variability that will be reduced in the cohort por-

tion of SWAN. A final limitation is the varied sampling methods used by the study sites, necessitated by difficulties in achieving the needed sample size of minority populations, making use of formal estimation procedures inappropriate. Thus, the present confidence intervals should be interpreted with caution.

Nonetheless, the present study is one of the largest, is comprised of one of the most diverse study populations, and has been analyzed by using the most comprehensive statistical methods. Thus, the findings regarding the relations with race/ethnicity, current smoking, parity, use of oral contraceptives, educational attainment, and unemployment, and the lack of association with BMI, are likely to be robust and suggest that multifactorial host (possibly genetic) and environmental factors are involved in a likely complex mechanism to determine onset of menopause.

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