



Original Contribution

Age at Natural Menopause and Cause-specific Mortality

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Several studies have suggested that a young age at menopause may be associated with increased risk of all-cause mortality. Few studies have examined the influence of age at menopause on specific causes of death other than coronary heart disease. Data from a prospective cohort study of US adults were used to examine the relation between age at natural menopause and all-cause and cause-specific mortality among women who never used hormone replacement therapy, who never smoked, and who experienced natural menopause between the ages of 40 and 54 years. After 20 years of follow-up between 1982 and 2002, 23,067 deaths had occurred among 68,154 women. Results from Cox proportional hazards models showed that all-cause mortality rates were higher among women who reported that menopause occurred at age 40–44 years compared with women who reported that menopause occurred at age 50–54 years (rate ratio (RR) = 1.04, 95% confidence interval (CI): 1.00, 1.08). This increased risk was largely due to higher mortality rates from coronary heart disease (RR = 1.09, 95% CI: 1.00, 1.18), respiratory disease (RR = 1.19, 95% CI: 1.02, 1.39), genitourinary disease (RR = 1.39, 95% CI: 1.07, 1.82), and external causes (RR = 1.56, 95% CI: 1.21, 2.02). These findings suggest that mortality from other diseases, as well as coronary heart disease, may contribute to the increased mortality associated with a younger age at menopause.

menopause; mortality; osteoporosis; prospective studies

Abbreviations: CI, confidence interval; CPS-II, Cancer Prevention Study II; ICD-9, *International Classification of Diseases*, Ninth Revision; ICD-10, *International Classification of Diseases*, Tenth Revision; RR, rate ratio.

Menopause is defined as the permanent cessation of menstruation due to loss of ovarian follicular function (1). As a result, production of estrogen by the ovaries declines steadily throughout the perimenopausal period; very low levels of circulating estrogen are observed in postmenopausal women (2). Estrogen has important effects on many different tissues and organs, including the cardiovascular system and bone (1), and postmenopausal status has been associated with increased risk of coronary heart disease, osteoporosis, and osteoporotic fracture (1–3). Therefore, it has been hypothesized that early natural menopause is associated with higher mortality rates.

There is epidemiologic evidence from five (4–8) of six (4–9) studies for a slightly higher mortality rate among women with a younger age at menopause. However, the in-

crease in mortality was statistically significant in only one study (8). The largest study, a prospective cohort of 19,731 Norwegian women followed for 37 years, found a higher risk of all-cause mortality associated with a younger age at menopause, but findings for cause-specific mortality were not reported (7).

Few studies have assessed which specific causes of death may be contributing to the increased mortality associated with earlier menopause. Four (6, 8–10) of five (5, 6, 8–10) studies reported an increased risk of death from coronary heart disease or cardiovascular disease with younger age at menopause, although none of these associations reached statistical significance. The Nurses' Health Study reported a statistically significant increased risk of coronary heart disease incidence with younger age at menopause (11).

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TABLE 1. Number and percentage of deaths by cause and by attained age, Cancer Prevention Study II baseline cohort women, 1982–2002

Cause of death	All deaths		Attained age, <75 years		Attained age, ≥75 years	
	No.	%	No.	%	No.	%
Cancer	5,404	23	2,445	45	2,959	17
Coronary heart disease	5,278	23	920	17	4,358	25
Other circulatory disease	3,386	15	545	10	2,841	16
Stroke	2,296	10	280	5	2,016	11
Respiratory disease	1,452	6	191	4	1,261	7
Digestive disease	698	3	168	3	530	3
External causes	518	2	161	3	357	2
Genitourinary disease	477	2	64	1	413	2
All other causes	3,558	15	669	12	2,889	16
Total	23,067		5,443		17,624	

Other than a positive correlation between age at menopause and risks of breast and endometrial cancer (12, 13), most studies have found no relation between specific cancers and age at menopause (12–16). To our knowledge, no studies have examined the association between age at menopause and any other specific causes of death. Importantly, most previous studies on this topic did not adequately account for a possible influence of cigarette smoking and hormone replacement therapy use.

We conducted an investigation in a large cohort of US women who experienced a natural menopause, had never smoked, and had never used hormone replacement therapy, to determine the relation between age at menopause and the risk of death from any cause and specific causes.

MATERIALS AND METHODS

Women in this study were selected from the 676,270 female participants in the Cancer Prevention Study II (CPS-II), a prospective mortality study of about 1.2 million US men and women, 30 or more years of age, begun by the American Cancer Society in 1982. The average age of study participants was 57 years. Participants were identified and were enrolled by more than 77,000 American Cancer Society volunteers in all 50 states, the District of Columbia, and Puerto Rico. Study subjects completed a confidential, self-administered questionnaire in 1982 that included personal identifiers, demographic characteristics, personal and family history of cancer and other diseases, reproductive history, and various behavioral, environmental, occupational, and dietary exposures. All aspects of the CPS-II are approved by the Emory University Institutional Review Board.

The vital status of study participants was determined from the month of enrollment through December 31, 2002, using two approaches. Volunteers made personal inquiries in September 1984, 1986, and 1988 to determine whether their enrollees were alive or dead and to record the date and place of all deaths (17). Automated linkage with the National Death Index was used to extend follow-up through Decem-

ber 31, 2002, and to identify deaths among 13,219 women (2 percent) lost to follow-up between 1982 and 1988 (17). At completion of mortality follow-up in December 2002, 184,718 women (27.3 percent) had died, 489,495 (72.4 percent) were still living, and 2,040 women (0.3 percent) were dropped from follow-up on September 1, 1988, because of insufficient data for National Death Index linkage. Death certificates including codes for multiple causes of death were obtained for 98.4 percent of all women known to have died.

Underlying causes of death were coded from the death certificates according to the *International Classification of Diseases*, Ninth Revision (ICD-9) (18) and Tenth Revision (ICD-10) (19). For cause-specific analyses, we grouped the observed deaths into nine main diagnostic categories: coronary heart disease (ICD-9 codes 410.0–414.9, ICD-10 codes I20.0–I25.9); stroke (ICD-9 codes 430.0–438.9, ICD-10 codes I60.0–I69.9); other circulatory diseases (ICD-9 codes 390.0–405.9, 415.0–429.9, and 440.0–459.9; ICD-10 codes I00.0–I19.9, I26.0–I59.9, and I70.0–I99.9); all cancer (ICD-9 codes 140.0–195.9 and 199.0–208.9, ICD-10 codes C00.0–C76.9 and C80.0–C97.9); respiratory diseases (ICD-9 codes 460.0–519.9, ICD-10 codes J00.0–J98.9); digestive diseases (ICD-9 codes 520.0–579.9, ICD-10 codes K00.0–K92.9); genitourinary diseases (ICD-9 codes 580.0–629.9, ICD-10 codes N00.0–N98.9); external causes (ICD-9 codes E80.0–E99.9, ICD-10 codes V01.0–Y89.9); and all other causes.

We excluded from the analysis 187,124 women who were not postmenopausal at baseline, 169,489 who may have experienced menopause as a consequence of ovarian surgery or hysterectomy, 49,042 who reported having had a surgery- or radiation-induced menopause, and 61,531 with a missing, invalid, or extreme (before age 40 or after 55 years) reported age at menopause. We further excluded 84,820 women who ever used hormone replacement therapy and 56,093 who ever smoked cigarettes. Cigarette smoking is the most important confounding factor in studies of age at menopause and mortality; smoking decreases a woman's age at menopause by an average of approximately 2 years (20, 21), and confounding by smoking remained after controlling for

smoking in a multivariate model in a study of age at menopause and coronary heart disease (11). After these exclusions, the analytical cohort consisted of 68,154 women who had experienced a natural menopause and who had not used tobacco or hormone replacement therapy.

Age at menopause was grouped into 5-year categories (40–44, 45–49, and 50–54 years) based on previous epidemiologic studies (4, 5, 8, 9, 11, 22, 23). We tested the linear trends by modeling the medians of the categories for age at menopause as continuous variables.

Cox proportional hazards models were used to compute rate ratios, adjusting for potential confounders. All Cox models were stratified on single year of age at enrollment, and multivariate models were further adjusted for partial year of age. This partial-year variable was created by subtracting a woman's exact age, calculated from her birthday and her date of interview, from her age rounded to the nearest year, and this variable was included as a continuous variable in our multivariate models. Multivariate models were further adjusted for race (White, Black, other), marital status (married, not married/missing), body mass index (weight (kg)/height (m)²) (<25, 25–<30, ≥30, missing), age (years) at menarche (<12, ≥12, missing), parity (no livebirths, any livebirths, missing), educational level (high school graduate or less, some college, college graduate or more, missing), alcohol consumption (none, former drinker, current ≤1 drink/day, 2–3 drinks/day, ≥4 drinks/day, missing), oral contraceptive use (ever, never, missing), and exercise (none, slight, moderate, heavy, missing). To examine potential effect modification, we modeled multiplicative interaction terms between age at menopause (in 5-year categories) and each covariate. We tested the significance of each interaction by use of the likelihood ratio test, except for the interaction with attained age that was assessed by the Wald χ^2 test.

RESULTS

The mean and median ages at menopause of the women included in our analytical cohort were 49 and 50 years, respectively. A total of 23,067 deaths were observed during the 20-year follow-up interval. Both cancer and coronary heart disease were the leading causes of death (23 percent), followed by stroke (10 percent) and other circulatory disease (15 percent). Each of the other causes of death that were examined in the cause-specific analyses contributed less than 10 percent to the total deaths (table 1). This distribution differed by attained age. Cancer was the most common cause of death among women younger than 75 years of age (45 percent); coronary heart disease was the main cause of death among older women (25 percent), followed by cancer (17 percent), stroke (11 percent), and other circulatory disease (16 percent) (table 1).

The age-adjusted percentage distribution of potential confounding factors varied by age at menopause (table 2). Women who experienced natural menopause at a young age were older at study entry and more likely to report a younger age at menarche, to be nulliparous, to be less educated, and to have never used oral contraceptives.

TABLE 2. Characteristics of the analytical cohort by age at natural menopause, Cancer Prevention Study II women, 1982–2002*,†

	Age at menopause		
	40–44 years	45–49 years	50–54 years
Birth year (%)			
<1920	56.7	44.6	43.2
1920–1924	16.6	18.1	24.1
1925–1929	12.4	20.0	28.2
1930–1934	9.2	16.4	4.5
1935–1939	4.9	1.0	0.0
≥1940	0.1	0.0	0.0
Race (%)			
White	92.6	93.7	92.0
Black	4.8	3.8	3.2
Other/missing	2.7	2.5	2.0
Marital status (%)			
Not married	33.7	31.6	29.4
Married	66.3	68.3	67.8
Body mass index (kg/m ²)			
Mean	25.1	25.0	25.2
Age at menarche (%)			
<12 years	15.2	13.9	13.3
≥12 years	82.0	83.4	81.2
Parity (%)			
No livebirths	16.9	14.1	11.9
Any livebirths	80.2	83.4	83.3
Education (%)			
≤High school	52.2	51.4	47.9
Some college	25.5	25.4	25.5
≥College graduate	20.8	21.7	22.6
Alcohol intake (%)			
None	21.6	22.1	21.2
Former drinker	0.7	0.7	0.6
Current drinker			
≤1 drink/day	9.9	11.1	11.6
2–3 drinks/day	2.0	2.4	2.3
≥4 drinks/day	0.7	0.7	0.8
Oral contraceptive use (%)			
Never	89.7	87.0	84.6
Ever	8.8	11.1	11.1
Exercise (%)			
None	3.0	2.8	2.5
Slight	20.8	21.6	20.5
Moderate	67.4	68.7	67.2
Heavy	6.8	5.3	5.3

* Percentages are standardized to the age distribution of the total female study population.

† Some columns may not add up to 100% because of missing values.

TABLE 3. Age at natural menopause and all-cause and cause-specific mortality, Cancer Prevention Study II women, 1982–2002

Cause of death	Age at menopause			<i>P</i> _{trend}
	40–44 years (<i>n</i> = 7,162)	45–49 years (<i>n</i> = 21,571)	50–54 years (<i>n</i> = 39,421)	
All causes				
No. of deaths	2,861	7,305	12,901	
Rate ratio (95% confidence interval)*	1.05 (1.01, 1.09)	1.02 (0.99, 1.05)	1.0 (referent)	0.02
Rate ratio (95% confidence interval)†	1.04 (1.00, 1.08)	1.02 (1.00, 1.05)	1.0 (referent)	0.04
Coronary heart disease				
No. of deaths	719	1,615	2,944	
Rate ratio (95% confidence interval)*	1.10 (1.01, 1.19)	0.97 (0.91, 1.03)	1.0 (referent)	0.18
Rate ratio (95% confidence interval)†	1.09 (1.00, 1.18)	0.98 (0.92, 1.04)	1.0 (referent)	0.20
Stroke				
No. of deaths	268	750	1,278	
Rate ratio (95% confidence interval)*	0.94 (0.82, 1.07)	1.04 (0.95, 1.14)	1.0 (referent)	0.67
Rate ratio (95% confidence interval)†	0.94 (0.82, 1.07)	1.04 (0.95, 1.14)	1.0 (referent)	0.69
Other circulatory disease				
No. of deaths	403	1,115	1,868	
Rate ratio (95% confidence interval)*	0.96 (0.86, 1.07)	1.06 (0.98, 1.14)	1.0 (referent)	0.94
Rate ratio (95% confidence interval)†	0.96 (0.86, 1.07)	1.07 (0.99, 1.15)	1.0 (referent)	0.88
All cancer				
No. of deaths	550	1,654	3,200	
Rate ratio (95% confidence interval)*	0.92 (0.84, 1.01)	0.98 (0.92, 1.04)	1.0 (referent)	0.09
Rate ratio (95% confidence interval)†	0.91 (0.83, 1.00)	0.98 (0.92, 1.04)	1.0 (referent)	0.06
Breast or ovarian cancer				
No. of deaths	125	506	1,010	
Rate ratio (95% confidence interval)*	0.69 (0.57, 0.83)	0.93 (0.83, 1.04)	1.0 (referent)	0.0002
Rate ratio (95% confidence interval)†	0.68 (0.56, 0.82)	0.93 (0.83, 1.03)	1.0 (referent)	0.0001
Colorectal cancer				
No. of deaths	94	256	470	
Rate ratio (95% confidence interval)*	1.03 (0.82, 1.29)	1.02 (0.88, 1.19)	1.0 (referent)	0.76
Rate ratio (95% confidence interval)†	1.00 (0.80, 1.25)	1.02 (0.87, 1.19)	1.0 (referent)	0.94
Lung cancer				
No. of deaths	36	94	191	
Rate ratio (95% confidence interval)*	1.00 (0.70, 1.44)	0.94 (0.74, 1.21)	1.0 (referent)	0.84
Rate ratio (95% confidence interval)†	0.97 (0.67, 1.40)	0.91 (0.71, 1.18)	1.0 (referent)	0.65
Other cancer				
No. of deaths	295	798	1,529	
Rate ratio (95% confidence interval)*	1.03 (0.91, 1.17)	1.00 (0.91, 1.09)	1.0 (referent)	0.76
Rate ratio (95% confidence interval)†	1.03 (0.91, 1.17)	1.00 (0.92, 1.09)	1.0 (referent)	0.73

Table continues

Women who reported that menopause had occurred when they were between 40 and 44 years of age had a 4 percent higher risk of all-cause mortality compared with women whose menopause had occurred when they were between 50 and 54 years of age (table 3). To further explore potential confounding by age due to differential misclassification of age at menopause, we ran the models using age as the time axis, but the results were unchanged (data not shown). In

analyses by specific cause of death, younger age at menopause (40–44 years) was associated with higher mortality due to heart disease (rate ratio (RR) = 1.09), respiratory disease (RR = 1.19), genitourinary disease (RR = 1.39), and external causes (RR = 1.56), all of which were statistically significant (table 3). However, the trend for increasing mortality with decreasing age at menopause was not significant for heart disease mortality.

TABLE 3. Continued

Cause of death	Age at menopause			<i>P</i> _{trend}
	40–44 years (<i>n</i> = 7,162)	45–49 years (<i>n</i> = 21,571)	50–54 years (<i>n</i> = 39,421)	
Respiratory disease				
No. of deaths	214	450	788	
Rate ratio (95% confidence interval)*	1.21 (1.04, 1.41)	1.02 (0.91, 1.14)	1.0 (referent)	0.03
Rate ratio (95% confidence interval)†	1.19 (1.02, 1.39)	1.01 (0.90, 1.14)	1.0 (referent)	0.06
Pneumonia and influenza				
No. of deaths	118	250	400	
Rate ratio (95% confidence interval)*	1.25 (1.02, 1.54)	1.09 (0.93, 1.27)	1.0 (referent)	0.03
Rate ratio (95% confidence interval)†	1.23 (1.00, 1.52)	1.08 (0.92, 1.27)	1.0 (referent)	0.05
Inhalation pneumonia				
No. of deaths	22	28	59	
Rate ratio (95% confidence interval)*	1.64 (1.00, 2.68)	0.83 (0.53, 1.31)	1.0 (referent)	0.19
Rate ratio (95% confidence interval)†	1.51 (0.91, 2.48)	0.82 (0.52, 1.29)	1.0 (referent)	0.31
Other respiratory disease				
No. of deaths	74	172	329	
Rate ratio (95% confidence interval)*	1.08 (0.84, 1.40)	0.96 (0.80, 1.16)	1.0 (referent)	0.75
Rate ratio (95% confidence interval)†	1.08 (0.83, 1.39)	0.96 (0.80, 1.16)	1.0 (referent)	0.80
Digestive disease				
No. of deaths	95	219	384	
Rate ratio (95% confidence interval)*	1.19 (0.94, 1.49)	1.02 (0.86, 1.21)	1.0 (referent)	0.21
Rate ratio (95% confidence interval)†	1.19 (0.95, 1.50)	1.03 (0.87, 1.22)	1.0 (referent)	0.17
Genitourinary disease				
No. of deaths	72	167	238	
Rate ratio (95% confidence interval)*	1.38 (1.06, 1.80)	1.26 (1.04, 1.54)	1.0 (referent)	0.005
Rate ratio (95% confidence interval)†	1.39 (1.07, 1.82)	1.27 (1.04, 1.55)	1.0 (referent)	0.004
External causes				
No. of deaths	82	179	257	
Rate ratio (95% confidence interval)*	1.59 (1.23, 2.04)	1.27 (1.04, 1.54)	1.0 (referent)	0.0001
Rate ratio (95% confidence interval)†	1.56 (1.21, 2.02)	1.27 (1.04, 1.54)	1.0 (referent)	0.0002
Falls				
No. of deaths	29	44	80	
Rate ratio (95% confidence interval)*	1.63 (1.06, 2.50)	0.98 (0.68, 1.42)	1.0 (referent)	0.07
Rate ratio (95% confidence interval)†	1.62 (1.05, 2.49)	0.99 (0.68, 1.44)	1.0 (referent)	0.08
Motor vehicle accidents				
No. of deaths	11	45	52	
Rate ratio (95% confidence interval)*	1.17 (0.61, 2.27)	1.59 (1.05, 2.40)	1.0 (referent)	0.17
Rate ratio (95% confidence interval)†	1.16 (0.60, 2.24)	1.59 (1.05, 2.40)	1.0 (referent)	0.18
Other external causes				
No. of deaths	42	90	125	
Rate ratio (95% confidence interval)*	1.71 (1.20, 2.43)	1.32 (1.00, 1.75)	1.0 (referent)	0.002
Rate ratio (95% confidence interval)†	1.68 (1.17, 2.39)	1.32 (1.00, 1.74)	1.0 (referent)	0.003
All other causes				
No. of deaths	458	1,156	1,944	
Rate ratio (95% confidence interval)*	1.11 (1.00, 1.23)	1.08 (1.00, 1.16)	1.0 (referent)	0.02
Rate ratio (95% confidence interval)†	1.08 (0.97, 1.19)	1.07 (1.00, 1.15)	1.0 (referent)	0.06

* Adjusted for age.

† Adjusted for age, race, marital status, body mass index, age at menarche, parity, education, alcohol consumption, oral contraceptive use, and exercise.

TABLE 4. Age at natural menopause and all-cause and cause-specific mortality by attained age, Cancer Prevention Study II women, 1982–2002

Cause of death	Attained age, <75 years			Attained age, ≥75 years		
	40–44 years	45–49 years	50–54 years	40–44 years	45–49 years	50–54 years
All causes						
No. of deaths	476	1,710	3,257	2,385	5,595	9,644
Rate ratio (95% confidence interval)*	0.95 (0.86, 1.04)	0.95 (0.89, 1.00)	1.0 (referent)	1.10 (1.05, 1.15)	1.04 (1.01, 1.08)	1.0 (referent)
Rate ratio (95% confidence interval)†	0.90 (0.82, 0.99)	0.94 (0.89, 1.00)	1.0 (referent)	1.07 (1.03, 1.12)	1.03 (0.99, 1.06)	1.0 (referent)
P_{trend}		0.007			0.002	
$P_{\text{interaction}}$	0.001‡	0.01§				
Coronary heart disease						
No. of deaths	95	279	546	624	1,336	2,398
Rate ratio (95% confidence interval)*	1.13 (0.91, 1.40)	0.93 (0.80, 1.07)	1.0 (referent)	1.15 (1.06, 1.26)	1.00 (0.94, 1.07)	1.0 (referent)
Rate ratio (95% confidence interval)†	1.05 (0.85, 1.31)	0.92 (0.80, 1.07)	1.0 (referent)	1.11 (1.02, 1.22)	0.98 (0.91, 1.05)	1.0 (referent)
P_{trend}		0.83			0.10	
$P_{\text{interaction}}$	0.64‡	0.48§				
Stroke						
No. of deaths	24	86	170	244	664	1,108
Rate ratio (95% confidence interval)*	0.92 (0.60, 1.41)	0.91 (0.70, 1.17)	1.0 (referent)	0.97 (0.85, 1.12)	1.07 (0.97, 1.18)	1.0 (referent)
Rate ratio (95% confidence interval)†	0.89 (0.58, 1.37)	0.91 (0.70, 1.19)	1.0 (referent)	0.95 (0.83, 1.09)	1.05 (0.95, 1.16)	1.0 (referent)
P_{trend}		0.45			0.89	
$P_{\text{interaction}}$	0.78‡	0.33§				
Other circulatory disease						
No. of deaths	52	173	320	351	942	1,548
Rate ratio (95% confidence interval)*	1.05 (0.79, 1.41)	0.98 (0.82, 1.18)	1.0 (referent)	1.00 (0.89, 1.12)	1.09 (1.00, 1.18)	1.0 (referent)
Rate ratio (95% confidence interval)†	0.99 (0.74, 1.33)	0.97 (0.81, 1.17)	1.0 (referent)	0.96 (0.86, 1.08)	1.06 (0.98, 1.15)	1.0 (referent)
P_{trend}		0.84			0.92	
$P_{\text{interaction}}$	0.88‡	0.41§				
Cancer						
No. of deaths	187	758	1,500	363	896	1,700
Rate ratio (95% confidence interval)*	0.81 (0.69, 0.94)	0.91 (0.84, 1.00)	1.0 (referent)	0.99 (0.88, 1.11)	0.98 (0.90, 1.06)	1.0 (referent)
Rate ratio (95% confidence interval)†	0.79 (0.67, 0.91)	0.91 (0.84, 1.00)	1.0 (referent)	0.98 (0.88, 1.10)	0.97 (0.89, 1.05)	1.0 (referent)
P_{trend}		0.0006			0.56	
$P_{\text{interaction}}$	0.02‡	0.32§				

Table continues

Infectious pneumonia, influenza, and inhalation pneumonia were specific causes contributing to the elevated risk of death due to respiratory disease (table 3). All other causes included in the respiratory disease mortality group were not associated with age at menopause (table 3). Among external causes, death from falls was significantly associated with a younger age at menopause (RR = 1.62). No significant association was seen with motor vehicle accidents (table 3).

There was not sufficient power to look at other components of external causes of mortality separately, but collectively, the remaining deaths due to external causes were also significantly associated with a younger age at menopause (table 3).

Cancer was the only cause of death for which mortality rates were lower among women with a younger age at menopause. This association was solely due to breast and ovarian cancer deaths (table 3).

TABLE 4. Continued

Cause of death	Attained age, <75 years			Attained age, ≥75 years		
	40–44 years	45–49 years	50–54 years	40–44 years	45–49 years	50–54 years
Respiratory disease						
No. of deaths	23	59	109	191	391	679
Rate ratio (95% confidence interval)*	1.36 (0.87, 2.14)	0.96 (0.70, 1.32)	1.0 (referent)	1.24 (1.05, 1.45)	1.03 (0.91, 1.16)	1.0 (referent)
Rate ratio (95% confidence interval)†	1.26 (0.80, 1.97)	0.95 (0.69, 1.30)	1.0 (referent)	1.20 (1.02, 1.41)	1.00 (0.88, 1.13)	1.0 (referent)
P_{trend}		0.56			0.08	
$P_{\text{interaction}}$	0.85‡	0.76§				
Digestive disease						
No. of deaths	13	55	100	82	164	284
Rate ratio (95% confidence interval)*	0.85 (0.48, 1.51)	0.99 (0.71, 1.37)	1.0 (referent)	1.30 (1.01, 1.66)	1.04 (0.86, 1.27)	1.0 (referent)
Rate ratio (95% confidence interval)†	0.78 (0.44, 1.39)	0.97 (0.70, 1.35)	1.0 (referent)	1.29 (1.01, 1.65)	1.03 (0.85, 1.25)	1.0 (referent)
P_{trend}		0.46			0.08	
$P_{\text{interaction}}$	0.10‡	0.51§				
Genitourinary disease						
No. of deaths	9	23	32	63	144	206
Rate ratio (95% confidence interval)*	1.84 (0.88, 3.85)	1.27 (0.74, 2.17)	1.0 (referent)	1.35 (1.02, 1.79)	1.25 (1.01, 1.54)	1.0 (referent)
Rate ratio (95% confidence interval)†	1.71 (0.81, 3.60)	1.26 (0.74, 2.16)	1.0 (referent)	1.32 (0.99, 1.75)	1.22 (0.99, 1.51)	1.0 (referent)
P_{trend}		0.14			0.02	
$P_{\text{interaction}}$	0.94‡	0.33§				
External causes						
No. of deaths	17	66	78	65	113	179
Rate ratio (95% confidence interval)*	1.39 (0.83, 2.36)	1.50 (1.08, 2.09)	1.0 (referent)	1.63 (1.23, 2.17)	1.14 (0.90, 1.45)	1.0 (referent)
Rate ratio (95% confidence interval)†	1.35 (0.80, 2.28)	1.49 (1.07, 2.07)	1.0 (referent)	1.60 (1.20, 2.12)	1.13 (0.89, 1.43)	1.0 (referent)
P_{trend}		0.05			0.003	
$P_{\text{interaction}}$	0.58‡	0.18§				
All other causes						
No. of deaths	56	211	402	402	945	1,542
Rate ratio (95% confidence interval)*	0.90 (0.68, 1.19)	0.92 (0.78, 1.09)	1.0 (referent)	1.15 (1.03, 1.28)	1.09 (1.01, 1.19)	1.0 (referent)
Rate ratio (95% confidence interval)†	0.82 (0.62, 1.09)	0.91 (0.77, 1.07)	1.0 (referent)	1.12 (1.01, 1.25)	1.08 (0.99, 1.17)	1.0 (referent)
P_{trend}		0.11			0.02	
$P_{\text{interaction}}$	0.04‡	0.07§				

* Adjusted for age.

† Adjusted for age, race, marital status, body mass index, age at menarche, parity, education, alcohol consumption, oral contraceptive use, and exercise.

‡ Wald's chi-square test: $H_0 = \beta_{\text{attained age} < 75, \text{ age at menopause } 40-44} = \beta_{\text{attained age} \geq 75, \text{ age at menopause } 40-44} = 0$.§ Wald's chi-square test: $H_0 = \beta_{\text{attained age} < 75, \text{ age at menopause } 45-49} = \beta_{\text{attained age} \geq 75, \text{ age at menopause } 45-49} = 0$.

Stratified analyses by attained age showed that the increased risk of all-cause mortality with a younger age at menopause was limited to women aged 75 years or older (table 4), because of a strong decreased risk of cancer mortality associated with a younger age at menopause among

women younger than 75 years of age. There was no interaction between attained age and any other specific cause of death (table 4). We found no effect modification with any of the following factors: body mass index, alcohol intake, level of education, parity, or exercise.

DISCUSSION

Results from this very large prospective study on age at menopause and mortality suggest that early age at natural menopause is associated with higher overall mortality rates in older, never smoking women who have not been exposed to exogenous hormones. This study also indicates that causes other than coronary heart disease mortality, such as respiratory and genitourinary diseases, and external causes are contributing to this association.

Our results for all-cause and coronary heart disease mortality are consistent with those of most previous studies on these topics (4–8), and the magnitude of the association is very similar to those reported by the largest previous prospective studies on age at menopause and all-cause mortality (7) and coronary heart disease mortality (10). Although the magnitude of the increased risk of coronary heart disease mortality observed in our cohort is modest, it contributes to the overall increase in mortality because 23 percent of the observed deaths were due to coronary heart disease. One of the strengths of our study is the ability to assess the association between specific causes of death in relation to age at menopause.

The association between age at menopause and mortality was limited to older women, contrary to what has been reported in a previous study conducted in Norway (7). Differences by age in the overall association between age at menopause and mortality may be due to a different distribution of causes of death in younger versus older women. The most common cause of death among women younger than 75 years of age in our study was cancer, and cancer was the only specific cause of death for which there was a significant interaction by attained age.

Several biologic mechanisms would support the observed association between younger age at menopause and risk of death from coronary heart disease, respiratory and genitourinary disease, and external causes. First, estrogen receptors are found in most tissues including vascular endothelial cells, smooth muscle cells, myocardial cells, bone, bladder, urethra, and ovary (2, 24), indicating that all of these tissues may be affected by a decrease in estrogen like that observed in postmenopausal women. Second, estrogen may play a role in the maintenance of immune function; it has been shown that women who underwent surgically induced menopause developed impaired immune function that returned once they were given estrogen replacement therapy (25). Finally, the observed increases in mortality from respiratory and genitourinary diseases and external causes could also be mediated by osteoporosis. Low estrogen levels are associated with a decrease in bone density and osteoporosis, which often leads to fractures (1). Common complications of osteoporotic fracture include pneumonia and urinary tract infections (26–29). Little work has been done to determine the specific causes of death that contribute to excess mortality following osteoporotic fracture, but a few studies of postfracture mortality have indicated that pneumonia, cardiovascular diseases, and renal diseases, including urinary tract infections, have been among the causes of death observed postfracture (30–35). One study, in particular, indicated that the rate ratio of observed to expected pneumonia deaths

among women during the first year after hip fracture was 7.46 (95 percent confidence interval (CI): 6.51, 8.55) and remained high during the second year after hip fracture (RR = 4.00, 95 percent CI: 3.46, 4.62) (35). Similarly, this study found that the rate ratio of observed to expected renal disease deaths during the second year after hip fracture was 9.36 (95 percent CI: 7.17, 12.22) (35).

Our questionnaire did not include questions about bone density, osteoporosis, or history of fracture, so we are limited in our ability to explore this hypothesis. However, a subset of the women in the CPS-II cohort were recruited into the CPS-II Nutrition Cohort in 1992, and these women were given a follow-up survey in 1997 (36) that included a question on whether a physician had ever diagnosed them with osteoporosis. Among the 8,226 women who completed the 1997 questionnaire, the age-adjusted prevalence of osteoporosis was higher in women who experienced menopause at a younger age (27 percent for menopause at ages 40–44 compared with 20 percent for menopause at ages 50–54 years). This is consistent with the hypothesis that the increased mortality associated with a younger age at menopause in our cohort could be partly mediated by osteoporosis.

Strengths of this study include the prospective design and the large sample size, which allowed us to restrict our cohort to women who had never smoked and who had never taken hormone replacement therapy. Additionally, we were able to look at specific causes of death rather than just overall mortality. We were limited, however, by the fact that age at menopause was self-reported and was collected retrospectively, likely resulting in some misclassification of age at menopause. Although misclassification of reported age at menopause may be differential, as suggested by Rockhill et al. (37), with older women falsely reporting a younger age at menopause, we believe that our results are not significantly biased, because we controlled tightly for age and have fit our models using age as the time axis, as well as using calendar time as the time axis. In both models, the results were identical. Finally, although we did have a large sample size, statistical power was still somewhat limited when the specific causes of death were examined.

In summary, results from this study and other studies suggest that a younger age at menopause is associated with a small increase in all-cause mortality and that mortality from coronary heart disease and other causes, such as respiratory disease, genitourinary disease, and external causes, may contribute to the increased mortality.

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