

Age at Natural Menopause and the Risk of Epithelial Ovarian Cancer

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OBJECTIVE: To investigate the relationship between age at natural menopause and risk of developing epithelial ovarian cancer.

METHODS: Using data from six population-based, case-control studies conducted in the United States, age at natural menopause among 1411 women with epithelial ovarian cancer and 6380 control subjects were analyzed using survival analysis methods, including Kaplan-Meier and proportional hazards models. Subjects ranged from 20 to 81 years of age.

RESULTS: The median age at natural menopause was 50 years among cases compared with 51 years among controls, a difference of borderline statistical significance ($P = .06$). The hazard ratio for the relationship between case-control status and age at natural menopause was 1.09 (95% confidence interval 0.99, 1.20). Controlling for potential confounders including parity, oral contraceptive use, tubal ligation, smoking, and body mass index did not appreciably change this association. There was little evidence of an association between early age at natural menopause and early onset ovarian cancer (diagnosis age under 48 years).

CONCLUSION: We observed a weak association between ovarian cancer risk and age at natural menopause and, among women with early onset disease, there was little evidence to suggest that early menopause is related to ovarian cancer. Thus, there seems little need for increased surveillance or screening for ovarian cancer among women with early natural menopause. (Obstet Gynecol 2001;98:85-90. © 2001 by the American College of Obstetricians and Gynecologists.)

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It has been postulated that early menopause may be associated with an increased risk of developing ovarian cancer.¹ This idea was based on the gonadotropin hypothesis for ovarian cancer pathogenesis that predicts that the higher concentrations of FSH and LH that accompany ovarian senescence increase the risk of developing ovarian cancer. If gonadotropins act as tumor promoters, early age at natural menopause may be more directly linked to early onset ovarian cancer (eg, under age 45 or 50 years) than to later onset disease. In contrast, the "incessant ovulation" hypothesis proposes that ovarian cancer may arise from DNA damage that occurs from the ovulation-induced rupture and subsequent repair of epithelial tissue. Under this model, ovarian cancer risk would be expected to increase with a later age of menopause because older age at menopause would provide greater exposure to ovulatory cycles.²⁻⁴ However, ovarian cancer is most likely a heterogeneous disease with various underlying causes. It is also plausible that the "incessant ovulation" and the "gonadotropin" hypotheses may be interconnected and complementary rather than competing theories.

The epidemiologic literature concerning the relationship between age at natural menopause and ovarian cancer has been inconsistent.^{1,5-11} In this report, we examined the relationship between age at natural menopause and risk of developing epithelial ovarian cancer using data from six population-based, case-control studies conducted in the United States. A previous analysis of a portion of these data did not detect an association⁵ but was limited to women 55 years and older at diagnosis. By including women under age 55 in the current analysis, we are able to more fully evaluate the relationship between an early age at menopause and ovarian cancer and to specifically focus on early-onset disease.

MATERIALS AND METHODS

Data from 12 case-control studies of newly diagnosed epithelial ovarian cancer conducted during the period of 1956-1986 in the United States were combined for

Table 1. Sample Sizes and Median Ages of Studies

Study	Location	Years of diagnosis	Sample size		Median age (range)		
			Invasive ovarian cases	Controls	Cases	Controls	Overall
Casagrande et al ⁹	Los Angeles	1973–76	150	150	42 (25–49)	42 (25–49)	42 (25–49)
Cramer et al ¹⁰	Boston	1978–81	185	235	55 (20–78)	53 (20–79)	54 (20–79)
Nasca et al ¹³	New York	1977–80	314	708	56 (21–81)	56 (21–81)	56 (21–81)
Weiss et al ¹⁴	Seattle	1975–79	267	744	56 (20–74)	55 (21–79)	55 (20–79)
CASH ¹¹	8 SEER areas	1980–82	322	4220	48 (21–54)	45 (20–55)	45 (20–55)
Whittemore et al ⁵	San Francisco	1983–86	173	323*	53 (25–75)	47 (21–74)	48 (21–75)
Total			1411	6380			

CASH = Cancer and Steroid Hormone Study; SEER = surveillance, epidemiology, and end results.

Excludes women missing information on menopausal status.

* Hospital controls excluded from Whittemore et al study; all others were neighborhood or population controls.

analysis by the Collaborative Ovarian Cancer Group.¹² All data came from subjects using personal, structured interviews. Details of the process of identifying eligible studies, assembling the data, and assuring comparability of the variables have been described.¹² The present analysis was limited to women diagnosed with invasive ovarian cancer from the six population-based, case-control studies in the series (Table 1). We excluded the six studies with hospital-based control groups because some of the leading causes of morbidity and hospitalization in women (eg, heart disease, breast cancer) may be associated with age at natural menopause. The resulting sample consisted of 1431 women diagnosed with invasive epithelial ovarian cancer. We restricted our analyses to women with invasive tumors because there is some evidence suggesting that invasive epithelial ovarian cancer may be distinct from low malignant potential tumors. For example, tumors of low malignant potential have earlier age at diagnosis and better prognosis compared to invasive tumors.^{6–8} After excluding 20 cases and 40 controls who had a missing age at natural menopause, 1411 women diagnosed with invasive epithelial ovarian cancer and 6380 control subjects were included in the analysis.

Menopausal status was based on the “reference” age for cases and controls. The assignment of the reference date (and corresponding reference age) depended on the study and on the case-control status of the subject. For cases, five reports^{9–11,13,14} used diagnosis date and one¹⁵ used the year before diagnosis. For controls, four studies^{12,16–18} used interview date, one¹⁵ used the year before interview, and one⁹ used the date corresponding to the age of a matched case.

Menopausal status was determined by an algorithm reported by Whittemore et al.⁵ Regardless of reference age, a woman was classified as having had surgical menopause if the age at hysterectomy was the same age or within 1 year after the age at last menstrual period. A

woman was classified as premenopausal if her reference age was at most 55 years and her age at last menstrual period was at least that of her reference age. A woman was classified as natural menopausal if: 1) she had a hysterectomy at least 1 year after her age at last menstrual period; or 2) her reference age was greater than 55 and she had not had a hysterectomy by age 55; or 3) her reference age was less than 55, her age at last menstrual period was at least 1 year before her reference age, and she had not had a hysterectomy. Age at natural menopause was defined as age at last menstrual period for postmenopausal women who had either natural or surgical menopause. Women with unknown menopausal status were excluded from the analysis (23 ovarian cancer cases and 40 controls).

Subject characteristics available for all studies included age, race, ever married (yes, no), parity defined as the number of births of 20 or more weeks’ gestation (0, 1, 2–3, 4+), and ever use of oral contraceptives (OC) (yes, no). Additional variables that were available for some but not all of the studies included education (some college versus no college), tubal ligation (yes, no), family history of breast or ovarian cancer in a mother or sister (yes, no), infertility defined as having seen a doctor about problems getting pregnant (yes, no), body mass index (BMI) (kg/m²) as an adult, and smoking history (never smoked, current smoker, or ex-smoker).

The Kaplan-Meier method was used to estimate the age at natural menopause for ovarian cancer cases and controls. By using the Kaplan-Meier method and the proportional hazards model, we were able to study the occurrence and timing of natural menopause. In these analyses, women who were classified as premenopausal or surgically menopausal were censored at reference age/age at surgery, respectively. Stratified analyses were performed to examine possible effect modification by factors that may affect the risk of ovarian cancer (age, race, parity, family history, tubal ligation, OC use) or

factors that may affect age at natural menopause (smoking, BMI). The proportional hazards model was used to assess the association, estimated as the hazard ratio and 95% confidence intervals (CI), between case-control status and age at natural menopause. The hazard ratio is the ratio of the probability of experiencing natural menopause at a given time for an ovarian cancer case compared with a control. If the hazard ratio is greater than 1.0, cases are more likely than controls to have experienced earlier natural menopause, adjusting for the other variables in the model. Tests of interaction between case-control status and study site were conducted using proportional hazards analysis.

RESULTS

Subjects included in this analysis ranged from 20 to 81 years of age at diagnosis or interview with a median reference age of 47 years. Demographic and other characteristics of the study population, including the distribution of potential confounders, are shown in Table 2. Women with ovarian cancer were more likely to have known or suspected risk factors for ovarian cancer compared with control subjects. These factors included higher median age, a greater frequency of breast or ovarian cancers in a mother or sister, lower parity, higher median BMI, lower likelihood of using OC, and lower likelihood of having had a tubal ligation. Additionally, women with ovarian cancer were less likely to be premenopausal or to have had surgical menopause compared with control women.

Using the proportional hazards model, we tested the relationship between case-control status and age at natural menopause for each of the six case-control studies. Although the unadjusted hazard ratios differed between studies, with hazard ratios ranging from 0.85 to 1.36, tests for interaction for case-control status and studies were not statistically significant.

The cumulative distribution of age at natural menopause by case-control status is presented in Figure 1. Age at natural menopause was somewhat younger, and of borderline significance, among ovarian cancer cases compared with controls with a median age at natural menopause equal to 50 years among women with ovarian cancer compared with 51 years among controls (log rank = 3.60, $P = .06$, Table 3). No association was observed between age at natural menopause and early age at diagnosis when the analysis was limited to women whose age at diagnosis was less than 48 years (Table 3).

Stratified Kaplan-Meier analyses are shown in Table 3. These results indicate somewhat stronger associations between age at natural menopause and ovarian cancer risk in specific subgroups. For example, among parous

Table 2. Sociodemographics and Known Risk Factors

Variable*†	Ovarian cancer cases (n = 1411)	Controls (n = 6380)
Median age (y) (interquartile range)	51 (44–59)	47 (37–52)
Ever married (%)	90	95
White (%)	96	88
No college (%)	57	48
Ever pregnant (%)	81	89
Menopause status		
Premenopausal (%)	44	57
Post natural menopause (%)	45	29
Post surgical menopause (%)	11	14
Ever smoked (%)	54	54
OC use (%)	28	52
Tubal ligation (%)	7	14
Median BMI (kg/m ²) (interquartile range)	23 (21–25)	22 (20–25)
Family history of breast or ovarian cancer (%)	13	7

OC = oral contraceptive; BMI = body mass index.

* All characteristics and risk factors were significantly different between cases and controls ($P < .001$) except smoking status.

† Missing values (no. of cases, no. of controls): married ever (0, 3), race (2, 17), education (419, 899), pregnant (2, 5), smoking history (731, 1607), oral contraceptive use (12, 31), tubal ligation (584, 1493), BMI usual (510, 976), family history (607, 1586).

Cramer et al¹ did not include BMI.

Casagrande et al⁹ did not include education or smoking history.

Nasca et al¹³ did not include BMI, tubal ligations, family history, or smoking history.

Weiss et al¹⁴ did not include education, tubal ligations, family history, or smoking history.

women, the median age at natural menopause was 50 years for ovarian cases compared with 51 years for controls (log rank = 4.45, $P = .04$), but there was no difference between cases and controls in the distribution of age at natural menopause among nulliparous women. A similar pattern in the distribution of age at natural menopause was seen in the analyses stratified by family history of breast or ovarian cancer. The association between early menopause and ovarian cancer risk was seen among women with a family history (log rank = 3.82, $P = .05$). However, there was no evidence for effect modification of any of the factors in Table 3 when testing for interaction in a proportional hazards model ($P > .10$).

The hazard ratio for age at natural menopause, adjusting for study, was 1.09 (95% CI 0.99, 1.20) for ovarian cancer cases compared with controls. We performed additional multivariable analyses to adjust for potential confounders with risk factors for ovarian cancer or age at natural menopause. There was little change in the hazard ratio with further adjustment for marital status, parity, OC use, infertility, BMI, and education. Because data

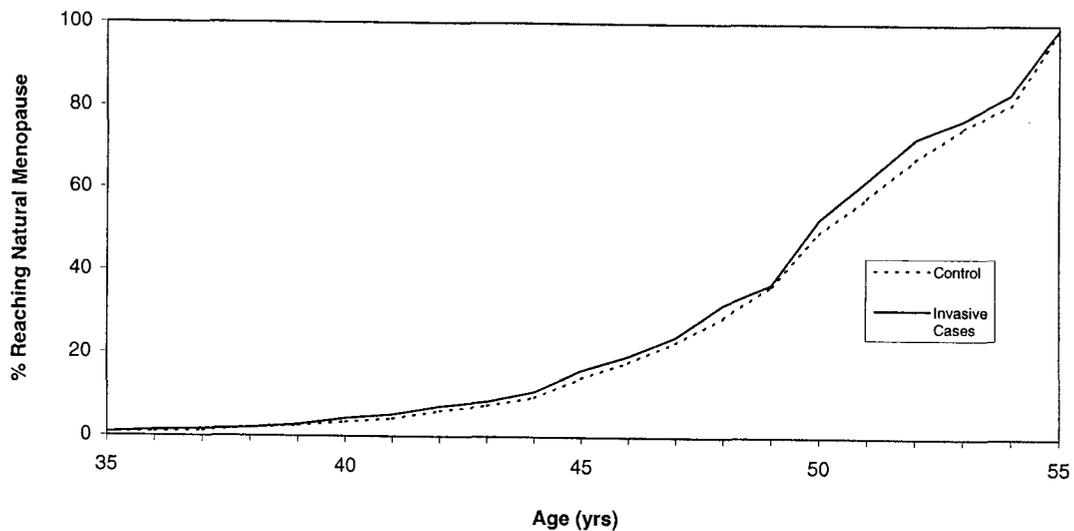


Figure 1. Cumulative distribution of age at natural menopause by ovarian cancer case-control status.

Schildkraut. Menopause and Ovarian Cancer. Obstet Gynecol 2001.

were not available from all six case-control studies for smoking, family history, and tubal ligation, evaluation of potential confounding by these factors was limited to a

subset of approximately 75% of the total sample. There was no evidence, in terms of a change in the hazard ratio, of confounding by these factors in these analyses.

Table 3. Age at Natural Menopause by Selected Risk Factors*

Strata	Number with natural menopause		Age at natural menopause by percentile				Log rank	P
	Cases	Controls	10th		50th (median)			
			Cases	Controls	Cases	Controls		
Invasive cases	633	1842	44	45	50	51	3.60	.06
Age at diagnosis/interview (y)								
<48 [†]	33	179	45	44	N/R	N/R	0.07	.79
≤55 [†]	242	1104	45	45	51	51	0.86	.35
>55	391	738	43	43	50	50	0.80	.37
Race								
White	615	1695	44	45	50	50	2.49	.11
Nonwhite	17	139	41	44	51	52	3.04	.08
Education								
Some college	165	626	46	45	51	51	0.51	.47
No college	318	837	43	44	50	50	3.29	.07
Parity								
Parous	507	1605	44	45	50	51	4.45	.04
Nulliparous	124	233	44	43	50	50	0.68	.41
Family history of breast or ovarian cancer								
Yes	45	97	44	45	51	52	3.82	.05
No	246	954	45	45	50	51	1.66	.20
Tubal ligation								
Yes	17	126	41	44	49	51	2.45	.12
No	287	954	44	45	50	51	2.85	.09
Smoking history								
Never smoked	130	441	45	45	50	51	3.17	.08
Ever smoked	166	630	44	44	50	50	2.68	.10
Ever used OCs								
Yes	88	503	44	45	51	51	1.67	.20
No	538	1324	44	45	50	50	1.56	.21

N/R = not reached; OC = oral contraceptive.

* Education, family history and tubal ligation information were only available in four of the six studies, and smoking information was only available in three of the six studies.

[†] Groups are not mutually exclusive.

DISCUSSION

The epidemiologic literature concerning the relationship between age at natural menopause and ovarian cancer has been inconsistent.^{1,5-12} Some studies report that women with ovarian cancer have a later age at natural menopause compared with controls,^{10,19} whereas others report either an earlier age of menopause^{16,20} or no difference in age at menopause among cases compared with controls.⁸⁻¹¹

The results of our combined analysis of data from six population-based, case-control studies suggest a weak association between early age at natural menopause and ovarian cancer risk, with a hazard ratio of 1.09. There was little evidence that early onset ovarian cancer (under age 48) was associated with early menopause. However, an association was seen within other subgroups of women, including parous women and women with a family history of breast or ovarian cancer.

Although this is a large study (1411 ovarian cancer cases), there was limited power to establish effect modification among subgroups in the analysis. There was also limited power to detect an association between age at natural menopause in women with early onset (under age 48) ovarian cancer because only 5% of subjects had experienced menopause by this age.

One explanation for not finding a stronger association between age at natural menopause is the possibility that ovarian cancer is a heterogeneous disease with several distinct etiologic pathways.^{6,21} Thus, if incessant ovulation and high gonadotropin levels each independently contribute to the risk of developing ovarian cancer, it is possible that an effect could be nullified by our inability to distinguish between cancers that arise through either of these two pathways.

A limitation of our analysis is that menopausal status and age at natural menopause were based on self-reported data. Recall error is possible, but previous studies have reported fairly high levels of accuracy or reliability for interview or questionnaire-based data on age at natural menopause^{17,18,22} and oophorectomy history.²³ Because it is not possible to use cessation of menses to determine age at ovarian senescence (menopause) among women with a surgical menopause (hysterectomy without bilateral oophorectomy), these women could not contribute to the analysis of age at menopause, and the resulting selection bias could have affected our results. However, the analytic methods we used allowed us to include these women in the analysis up to the time of their surgery. Age at natural menopause was truncated at 55 because of concerns about the accuracy of the data. This affected less than 1% of the total sample of cases and controls in our study. Alternatively, when we

used reported age of the last menstrual period as the age at natural menopause, the hazard ratio for the relationship between age at natural menopause and case-control status was 1.12 (95% CI 1.01, 1.23, $P = .02$). This is slightly higher than the hazard ratio calculated when age at natural menopause was truncated at 55 years. Thus, truncating age at natural menopause was a conservative approach for estimating the relationship with ovarian cancer.

Controlling for potential confounders in a proportional hazards model did not alter the relationship between age at natural menopause and ovarian cancer. We were able to control for the factors that have been most consistently reported to be associated with age at natural menopause: smoking²⁴⁻²⁶ and parity.^{25,27} Information on other potential confounders, such as irregularity of menstrual cycles before age 25, and family history of early menopause^{27,28} were not available in our data. Thus, although the possibility of residual confounding exists, the unmeasured factor would have to be strongly related to both age at natural menopause and ovarian cancer risk to have an effect on our results and the conclusions drawn.

Our analyses do not support that age at natural menopause is an important factor in predicting ovarian cancer risk. There was also no evidence that early menopause is related to ovarian cancer among women who had an early age at diagnosis of ovarian cancer. Therefore, there is no indication for increased surveillance among women with early menopause.

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