Bone Fractures and Incident Epithelial Ovarian Cancer in a Prospective Cohort Study

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Abstract

Objective: Osteoporosis and osteoporotic fractures are hypothesized to reflect circulating hormone levels in older women and have been inversely associated with breast and endometrial cancers. However, associations between fractures and ovarian cancer, another hormonal cancer, have not been examined. Therefore, we conducted a prospective study among women in the Breast Cancer Detection Demonstration Project Follow-up Study.

Methods: Fractures after age 45 were assessed using two questionnaires from 1987 to 1995. Relative risks (RRs) and 95% confidence intervals (CIs) were estimated by Cox proportional hazards models, adjusting for potential confounders. Fracture location was used to further evaluate the fractures most likely to be osteoporotic.

Results: Among 36,115 women with up to 11 years of follow-up (average follow-up was 8.3 years), there were 151 cases of incident ovarian cancer. Fractures were reported by 19% ($n = 6,919$) of women. Ovarian cancer risk was not associated with any (RR = 1.13, 95% CI 0.74-1.71) or likely osteoporotic (RR = 1.05, 95% CI 0.65-1.69) fractures. Among never users of postmenopausal hormones, the association between any fracture and ovarian cancer (RR = 1.21, 95% CI 0.55-2.65, $n = 50$ cases) also was statistically nonsignificant.

Conclusions: Data from this large, prospective study do not support an association between fractures and ovarian cancer risk.

Introduction

OVARIAN CANCER, like breast and endometrial cancers, is considered a hormonally mediated cancer. Although endogenous hormone levels and certain hormone-related risk factors, such as body mass index (BMI), have been less consistently associated with ovarian cancer than with the other female reproductive cancers,¹⁻⁶ factors related to exogenous hormones, particularly use of oral contraceptives and postmenopausal hormones, are consistently associated with ovarian cancer.⁷⁻¹⁰

Fracture risk may reflect lifetime hormone levels. Age-related declines in bone mass and bone mineral density (BMD), resulting in part from age-related declines in endogenous estrogen levels, increase the probability of osteoporosis and related fractures among older women.^{11,12} Early life events related to hormone levels, such as age at menarche and length of the reproductive cycle, also have been associated with BMD and fracture risk among older women.^{13,14} In addition, postmenopausal hormone use has been associated with increased BMD and decreased fracture risk.^{15,16} Thus, fractures may represent biological markers of risk for hormonally mediated cancers.

Because fracture incidence is inversely associated with hormone levels,^{15,17} women with a history of fractures might be at reduced risk of ovarian cancer. Few data on the potential association between fractures and ovarian cancer have been published. One population-based linkage study found a nonsignificantly reduced risk of ovarian cancer in women with osteoporosis (SIR = 0.79, 95% CI 0.60-1.01, $n = 61$ cases¹⁸), but the absence of other risk factor information raises questions about the validity of that finding. Therefore, we investigated the potential association between fractures and ovarian cancer risk in a prospective study of primarily postmenopausal women.

Materials and Methods

The Breast Cancer Detection Demonstration Project Follow-up Study

From 1973 to 1980, approximately 280,000 women aged 35-74 from 27 U.S. cities enrolled in the Breast Cancer Detection Demonstration Project (BCDDP), a mammography study conducted by the American Cancer Society (ACS) and

National Cancer Institute (NCI).^{19,20} In 1979, the NCI invited 64,182 women to participate in a follow-up study: all women who were diagnosed with breast cancer ($n=4,275$), underwent breast surgery but were not diagnosed with cancer ($n=25,114$), or were referred for but did not undergo surgical consultation ($n=9,628$) plus a sample of women neither diagnosed nor suspected of having breast cancer ($n=25,165$). Of the women invited, 61,431 (96%) enrolled in the follow-up study. The BCDDP Follow-up Cohort Study was approved by the Institutional Review Board at the NCI, and written informed consent was obtained from all participants.

The follow-up study was conducted in four phases. The first phase (1979–1986) consisted of a baseline telephone interview followed by up to six (usually four) annual telephone interviews. Information was collected on basic demographic and lifestyle factors, including age at menarche and use of oral contraceptives. Three self-administered questionnaires were subsequently mailed to collect more detailed demographic, lifestyle, and health information during the following time periods: 1987–1989 (phase 2), 1993–1995 (phase 3), and 1995–1998 (phase 4). Certain data, such as menopausal status, gynecological surgeries, and postmenopausal hormone use were updated in each questionnaire. Overall response to the mailed questionnaires was 85% for phase 2, 74% for phase 3, and 71% for phase 4.¹⁹

Fractures

In phase 2 (1987–1989), women were first asked if they had ever been diagnosed with a fracture after age 45 and, if they had, for the date of their first diagnosis. Fracture location was asked as an open-ended question; multiple fractures could be reported. We reviewed fracture site responses and coded them as wrist; arm or elbow; ankle; leg or knee; rib(s); hip or pelvis; vertebrae or spine; shoulder or collarbone; head, neck, or face; hand or fingers; foot or toes; or other/unknown. Fracture information was updated on the phase 3 (1993–1995) questionnaire.

Study population

The current analysis excluded women who reported a bilateral oophorectomy ($n=14,053$), who were diagnosed with breast ($n=3,961$) or ovarian ($n=226$) cancer, or who died ($n=2,227$) before study baseline, which was defined as the phase 2 questionnaire for this analysis. Women who reported radiation as the reason for menopause ($n=295$) or never menstruating ($n=8$) also were excluded, as were participants without any information on fractures ($n=4,543$) or who developed nonepithelial ovarian cancer ($n=3$). The final study population included 36,115 women who accrued 290,192 person-years during follow-up.

Ovarian cancer

Ovarian cancer was first assessed on the phase 2 questionnaire, when women were asked if they had ever been diagnosed with ovarian cancer. Subsequently, on the phase 3 and phase 4 questionnaires, women were asked about ovarian cancer diagnoses since their last report. Self-reported ovarian cancer diagnoses were confirmed through medical record abstraction. Additionally, ovarian cancers were identified through linkage to cancer registries in 19 states (using par-

ticipants' last known addresses); most state registries provided data through at least 1997, although a few provided coverage only through 1995. Cases also were identified through linkage to the National Death Index through 1997.¹⁹

Of the 36,115 women in the study, 151 developed ovarian cancer. Ovarian cancers were identified from medical records ($n=58$), state cancer registry data ($n=54$ cases), death certificates ($n=30$), and self-report ($n=9$) for women whose medical records were not available. The date of diagnosis was defined hierarchically using medical records, state cancer registry data, self-report, and death certificates. Histological type was available from medical records and cancer registries for 69 ovarian tumors; 60% were serous, 32% were endometrioid, 4% were mucinous, and 4% were clear-cell.

Statistical analysis

Follow-up began with the phase 2 questionnaire, and women were censored at the earliest of ovarian cancer diagnosis ($n=151$), bilateral oophorectomy ($n=1,594$), death ($n=2,713$), or the end of follow-up ($n=31,657$), as described previously.¹⁹ If women were missing information on fractures in phase 2 but subsequently reported fracture information in phase 3, their follow-up began with their phase 3 questionnaire.

Multivariable Cox proportional hazards regression models for time-varying covariates (also called extended Cox models) were used to estimate relative risks (RRs) and 95% confidence intervals (CIs), stratifying on follow-up time and adjusting for age, BMI, parity, oral contraceptive use, menopausal status/postmenopausal hormone use, cigarette smoking, physical activity, osteoporosis, and a family history of ovarian cancer (time-varying covariates were age, BMI, use of postmenopausal hormones, and osteoporosis). Additionally, we considered age at menarche, age at menopause, hysterectomy, calcium intake, lactose intake, vitamin D supplements, and race as potential confounders, but they were not included in the final models because they did not affect risk estimates. Adding each covariate changed the RR estimates by <10% for any fracture or likely osteoporotic fractures; in most cases, the RR changed by $<\pm 0.01$.

Fractures were classified in two ways. First, we examined any report of fracture after age 45 (yes vs. no). Fracture reports were considered to be cumulative, such that a woman who reported a fracture in phase 2 was considered to have a history of fracture in phase 3 as well. However, for women who reported not having a fracture, information was not carried forward; if these women did not respond to the subsequent fracture question, they were coded as missing for subsequent person-years. Second, although most fractures in this older population of women can be assumed to be osteoporotic, in secondary analyses we classified fractures of the ankle, head/neck/face, and hand/fingers as likely to be traumatic (not osteoporotic) and fractures at other specified sites as likely to be osteoporotic.^{21–23} If multiple fractures were reported, any report of a fracture at a site considered likely to be osteoporotic resulted in the fracture history being coded as likely osteoporotic.

In sensitivity analyses, we used a diagnosis of osteoporosis, in addition to fracture location, to classify fractures as likely osteoporotic vs. likely traumatic. We also examined associations between ovarian cancer risk and a diagnosis of either

fracture or osteoporosis, as well as osteoporosis by itself. Because associations between fracture and ovarian cancer risk might be most apparent in sedentary women,²² we also restricted our study population to women reporting less than the median physical activity level in the cohort. Finally, we examined associations in postmenopausal women stratified by never vs. ever use of postmenopausal hormones.

Results

The mean age at study baseline was 62 years, and mean follow-up time was 8.3 years. Most study participants (90%) were Caucasian. Of the 36,115 women in the study population, 6,919 (19%) reported having a fracture. Among women who provided information on individual fractures, most reported only one fracture (71%), but 22% reported two fractures and 7% reported three or more fractures. Characteristics were generally similar for women who reported a fracture and those who did not (Table 1). Women reporting a fracture were slightly older than women who did not report a fracture, more likely to have been diagnosed with osteoporosis (21% vs. 7%) and used postmenopausal hormones (49% vs. 45%), and less likely to have used oral contraceptives (25% vs. 33%). As expected, women with fractures classified as osteoporotic were more likely than women with fractures classified as traumatic to have a diagnosis of osteoporosis (22% vs. 14%).

The age-adjusted and multivariable results were similar. Ever reporting a fracture was not associated with ovarian cancer risk (RR = 1.13, 95% CI 0.74-1.71) (Table 2), with 77% power to detect an RR of 0.50.^{24,25} There was no trend across total number of fractures ($p = 0.12$), although power was limited because almost all cases occurred among women with zero, one, or two fractures. Fractures classified as likely to be osteoporotic (RR = 1.05, 95% CI 0.65-1.69) were not associated with ovarian cancer (Table 2). Fractures at sites likely to be traumatic were associated with an increased risk of ovarian

cancer (RR = 2.23, 95% CI 1.08-4.58), but this was based on only eight ovarian cancers among women with traumatic fractures. When fracture type was classified using both fracture location and information on osteoporosis diagnoses, results were similar to models incorporating only fracture location; no overall association was observed (data not shown). Additionally, when only osteoporosis was examined in multivariable models (not adjusting for fractures), associations remained null (RR = 0.93, 95% CI 0.55-1.59).

Among postmenopausal women, no association between fractures and ovarian cancer risk was observed among never users of postmenopausal hormones (RR = 1.21 ever vs. never fracture, 95% CI 0.55-2.65, $n = 8$ ovarian cancers among women with fractures), (Table 3) or ever users of postmenopausal hormones (RR = 1.00, 95% CI 0.55-1.82). In additional sensitivity analyses, fractures were not associated with ovarian cancer risk among women with relatively low physical activity levels or BMI <25 kg/m² (data not shown).

Discussion

In this prospective study of older women, we did not observe any overall association between a history of fractures after age 45 and ovarian cancer risk. Results were consistent when fractures were restricted to those likely to be osteoporotic and, therefore, more likely related to hormone levels and among postmenopausal women who reported never using postmenopausal hormones. We had detailed information on fractures, including fracture location, as well as data on numerous potential confounders, and exposure and covariate information were updated during the study period. We also had approximately 80% power to detect an RR of 0.50. Therefore, our study likely rules out a strong inverse association between fractures and ovarian cancer risk.

The use of fractures as a proxy for hormone levels is supported by findings from studies on breast and endometrial

TABLE 1. CHARACTERISTICS OF 36,115 BREAST CANCER DETECTION DEMONSTRATION PROJECT FOLLOW-UP STUDY PARTICIPANTS BY FRACTURE STATUS AND SITE

Characteristic	Fracture		Fracture type by site	
	No	Yes	Likely osteoporotic	Likely traumatic
Persons	29,196	6,919	4,407	855
Age at baseline, years, mean (SD)	61.2 (8.1)	64.6 (8.3)	65.5 (8.5)	63.2 (7.7)
Age at menarche, years, mean (SD)	12.8 (1.4)	12.9 (1.4)	12.9 (1.4)	12.8 (1.4)
Age at natural menopause, years, mean (SD)	50.0 (4.0)	49.6 (4.2)	49.5 (4.2)	50.0 (4.0)
BMI ^a at baseline (kg/m ²), mean (SD)	24.7 (4.3)	24.6 (4.1)	24.5 (4.1)	25.5 (4.4)
Person-years	244,128	46,064	33,369	6,583
Menopausal status, %				
Premenopausal	25.8	25.6	25.8	25.3
Postmenopausal	73.1	72.9	72.9	72.4
Ever use of postmenopausal hormones, ^b %	44.9	49.2	49.2	46.2
Ever use of oral contraceptives, %	32.9	24.8	23.5	28.9
Parous women, %	87.7	85.7	85.7	85.5
Mean No. of children (among parous)	2.9	2.8	2.8	2.9
Ever cigarette smoking, %	43.2	42.2	41.3	43.8
Hysterectomy, %	26.6	27.0	27.1	27.3
Diagnosis of osteoporosis, %	6.8	21.1	21.8	14.2
Family history of ovarian cancer, %	4.4	4.8	4.7	5.0

^aBMI, body mass index.

^bAmong postmenopausal women.

TABLE 2. AGE-ADJUSTED AND MULTIVARIABLE^a RELATIVE RISKS FOR EPITHELIAL OVARIAN CANCER RISK AND REPORT OF FRACTURE AFTER AGE 45

	Cases	Person-years	Age-adjusted RR (95% CI)	Multivariable ^a RR (95% CI)
Fracture				
No	121	244,128	Referent	Referent
Yes	30	46,064	1.19 (0.79-1.79)	1.13 (0.74-1.71)
Likely osteoporotic ^b fracture				
No	121	244,128	Referent	Referent
Yes	21	33,369	1.12 (0.70-1.79)	1.05 (0.65-1.69)

^aAdjusted for age (continuous), body mass index (continuous), parity (continuous), oral contraceptive use (ever/never), menopausal status and postmenopausal hormone use (premenopausal, postmenopausal/nonhormone user, postmenopausal/ever hormone user, unknown menopausal status), cigarette smoking (ever/never), physical activity (quintiles, missing category), osteoporosis (ever/never), and family history of ovarian cancer (yes, no, missing).

^bLikely osteoporotic fractures, as classified based on fracture site (i.e., excluding fractures of the ankle, head/neck/face, and hand/fingers).

cancers that have observed decreased risks of cancer among women with a fracture history, consistent with the hypothesis that fractures reflect lower lifetime hormone levels.^{22,26} In one study, strong inverse associations between fractures and breast and endometrial cancers reflected the expected sensitivity of those tumors to circulating estrogen levels, based on both tumors' associations with postmenopausal hormone use.²² Our null associations may reflect the weaker associations between ovarian cancer and endogenous hormone levels and hormone-related characteristics, such as BMI, compared with breast and endometrial cancers.¹⁻⁶

In contrast to our generally null point estimates, one large population-based linkage study in Denmark observed a nonsignificant reduction in ovarian cancer risk among women with osteoporosis.¹⁸ The inverse association in that study may have been due to inclusion of women with hysterectomy or bilateral oophorectomy, both of which have been associated with an increased risk of fracture.^{27,28} Hysterectomy has been associated with a decreased risk of ovarian cancer⁷; therefore, inclusion of women with a hysterectomy or bilateral oophorectomy or both could create the appearance of an inverse relationship between fractures and ovarian cancer. In our study, we censored women at bilateral oophorectomy and considered hysterectomy as a potential confounder.

Our conclusions are based on multiple approaches to the potentially complex relationships among fracture history after age 45, other related health factors, and ovarian cancer. Associations were consistent using different exposure classifications and among different subgroups of women. Adjust-

ment for numerous potential confounders, including calcium and lactose intake, did not change risk estimates. Analyses restricted to women with less than the median physical activity level, in whom the association with fractures might be most apparent,²² also produced null associations, as did stratification according to use of postmenopausal hormones (which reduces fracture risk¹⁵ but increases ovarian cancer risk^{7-10,19}).

Although many fractures among older women are likely to be osteoporotic, we attempted to identify and exclude fractures that were likely to be traumatic and, therefore, less likely than osteoporotic fractures to be associated with hormone levels. There is some disagreement about which exact fracture sites are associated with osteoporosis,^{21,29} so we employed numerous approaches to classifying fractures as likely osteoporotic vs. traumatic (e.g., using different groupings of fracture sites, information on osteoporosis diagnoses). Results were unchanged after each approach. The association between ovarian cancer and traumatic fractures might reflect statistical chance because there were only eight ovarian cancers among women with traumatic fractures.

Our study has several limitations. The use of fracture as a proxy for hormone levels, particularly endogenous hormone levels, is consistent with the risk factors for fractures and is further supported by research on fractures and other cancers. However, we had limited ability to definitively identify osteoporotic fractures. We restricted fractures to those occurring after age 45 to increase the likelihood that reported fractures were osteoporotic, but there was probably still residual

TABLE 3. AGE-ADJUSTED AND MULTIVARIABLE^a RELATIVE RISKS FOR EPITHELIAL OVARIAN CANCER RISK AND REPORT OF FRACTURE AMONG POSTMENOPAUSAL WOMEN BY HORMONE USE

	Cases	Person-years	Age-adjusted RR (95% CI)	Multivariable ^a RR (95% CI)
Never users of postmenopausal hormones				
Fracture				
No	42	95,912	Referent	Referent
Yes	8	16,534	1.20 (0.55-2.61)	1.21 (0.55-2.65)
Users of postmenopausal hormones				
Fracture				
No	57	80,148	Referent	Referent
Yes	15	16,536	1.08 (0.60-1.93)	1.00 (0.55-1.82)

^aAdjusted for age (continuous), body mass index (continuous), parity (continuous), oral contraceptive use (ever/never), cigarette smoking (ever/never), physical activity (quintiles, missing category), osteoporosis (ever/never), and family history of ovarian cancer (yes, no, missing).

misclassification. Women without fractures were less likely to be diagnosed with osteoporosis than women with fractures, but osteoporosis diagnoses were higher among women with both likely osteoporotic and likely traumatic fractures. It is unclear whether this reflects underdiagnosis of osteoporosis among women without fractures or misclassification of the fracture sites. We also did not examine associations by tumor subtype because of low statistical power for those analyses. However, given the null overall associations we observed, strong inverse associations with one histological subtype, such as endometrioid tumors, would have to be offset by strong positive associations with another histological subtype, such as mucinous tumors.

Conclusions

Our results do not support an overall association between fractures and reduced risk of ovarian cancer. Other studies are needed to determine if fractures are associated with specific ovarian subtypes. Understanding the relationship between fractures and ovarian cancer risk might facilitate useful comparisons with breast and endometrial cancers and improve the understanding of hormone-related risk factors across the female reproductive cancers.

Acknowledgments

This research was supported by the Intramural Research Program of the National Cancer Institute, NIH. K.N.D. was supported in part by the Sallie Rosen Kaplan Fellowship for Women Scientists in Cancer Research, National Cancer Institute, NIH.

We thank Susan Englehart, Catherine Ann Grundmayer, and the members of the BCDDP Staff at Westat Inc., Rockville, MD and Leslie Carroll, Franklin Demuth, and Jennifer Boyd-Morin, of IMS Inc., Silver Spring, MD, for computer support. We acknowledge the California Department of Health Services, Cancer Surveillance Section; Florida Cancer Data System, under contract to the Florida Department of Health; Maryland Cancer Registry, Maryland Department of Health and Mental Hygiene; Michigan Cancer Surveillance Program within the Division of Vital Records and Health Statistics, Michigan Department of Community Health; Pennsylvania Department of Health; Tennessee Cancer Registry; Texas Department of Health; and the states of Arizona, Georgia, Hawaii, Idaho, Iowa, New Jersey, New York, North Carolina, Ohio, Oregon, and Rhode Island for providing data from their cancer registries for use in these analyses. The views expressed in this article are solely those of the authors and do not necessarily reflect the opinions of any state agency listed.

Disclosure Statement

The authors have no conflicts of interest to report.

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