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Bone Loss Following Oophorectomy Among High-Risk Women: An NRG Oncology/Gynecologic Oncology Group study

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Abstract

OBJECTIVE—Women undergo premenopausal oophorectomy for a variety of reasons, including to reduce ovarian or breast cancer risk. However, surgically-induced menopause is associated with adverse sequelae, including accelerated bone loss, that have not been well characterized.

METHODS—The Gynecologic Oncology Group (GOG)-0215 randomized phase II trial of zoledronic acid was initiated to determine if post-oophorectomy bisphosphonate therapy could prevent this bone loss. The study was closed after slow accrual prevented evaluation of the primary study endpoint. We analyzed changes in bone mineral density (BMD) among the 80 women randomized to the observation arm of this study, as measured 3, 9 and 18 months post-enrollment.

RESULTS—The mean change in BMD from baseline to 18 months was -0.09 (95% Confidence Interval (CI) -0.12 – -0.07), -0.05 (95% CI -0.07 – -0.03), and -0.06 (95% CI -0.07 – -0.05) g/cm^2 across the lumbar spine, right hip, and left hip, respectively. This represents a BMD

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The following GOG member institutions participated in this protocol: Roswell Park Cancer Institute, Walter Reed National Military Medical Center, University of Minnesota Medical Center – Fairview, University of Colorado Cancer Center – Anschutz Cancer Pavilion, University of California at Los Angeles Health System, University of Cincinnati, University of North Carolina at Chapel Hill, University of California Medical Center at Irvine, The University of New Mexico Cancer Center, Ohio State University Comprehensive Cancer Center, Fox Chase Cancer Center, Women's Cancer Center of Nevada, University of Oklahoma Health Sciences Center, University of Virginia, Mayo Clinic, Case Western Reserve University, Yale University, Women & Infants Hospital, and Community Clinical Oncology Program.

decrease of –8.5% for the lumbar spine and –5.7% for both the right and left hips from baseline to 18 months' observation.

CONCLUSIONS—These results demonstrate that premenopausal women undergoing oophorectomy clearly experience bone loss, an adverse effect of oophorectomy, which requires attention and active management. BMD should be monitored post-oophorectomy, and treated per standard practice guidelines. Future studies will be required to determine if early treatment can mitigate fracture risk, and to test promising therapeutic interventions and novel prevention strategies, such as increased physical activity or alternative medications, in randomized trials.

Keywords

bone mineral density; oophorectomy; premenopausal

INTRODUCTION

Women undergo oophorectomy for a variety of reasons, including clinical indications such as increased risk of breast and ovarian cancer related to genetic mutations such as *BRCA 1/2* mutations or other conditions.^{1–4} Those women who are premenopausal at the time of oophorectomy experience immediate, surgically-induced, menopause and are at increased risk of bone loss associated with premature loss of estrogen, and thus increased risk of osteoporosis.^{1,5–7}

Osteoporosis is a disease characterized by low bone mineral density (BMD)^{8,9} and, worldwide, is responsible for more than nine million fractures each year and associated with increased mortality.^{8,10} The rate of bone loss among untreated post-menopausal women causes a doubling in the risk of fracture every 10 years, on average. In addition, age-related factors other than bone loss also contribute, causing fracture risk to double approximately every 5 years overall.¹¹ Thus, among women who experience surgically-induced menopause, post-oophorectomy, the risk is significantly increased for osteoporosis, fracture, as well as for subsequent morbidity and mortality.^{12,13} However, these studies were conducted among women who underwent natural menopause.^{11–13} There is limited evidence from longitudinal studies to describe the rate of decline in BMD among younger women following oophorectomy.

Few prospective studies have been conducted in a population of women at high risk for ovarian cancer who undergo premenopausal oophorectomy. However, studies demonstrate that, among women from the general population who experience surgically-induced menopause, the rate of bone loss was accelerated and the risk of osteoporosis was significantly higher.^{1,14–16} The use of hormonal therapy (HT) is a strategy that will help maintain bone density following menopause and there is data to show that HT in women experiencing premature menopause (up to mean age of menopause) can help prevent the devastating effects of estrogen deficiency (such as osteoporosis and cardiovascular disease (CVD)).¹⁷ If there are specific populations of concern, such as women with a history of estrogen receptor positive cancers, a consultation with a menopause expert should be considered to discuss the specific and individualized risk-benefit ratio.^{2,18} Thus, the current

study was designed to test one such strategy for the prevention of bone loss following oophorectomy.

Prompted by our experience with premenopausal oophorectomy among high-risk women in GOG-0199, the National Ovarian Cancer Prevention and Early Detection Trial,¹⁹ the Gynecologic Oncology Group (GOG) initiated protocol GOG-0215 to study the impact of an intravenous bisphosphonate (zoledronic acid) on bone loss in premenopausal women at high risk of ovarian cancer who elected to undergo risk reducing oophorectomy (RRO). The rationale for this study was based upon the knowledge that bisphosphonates are effective inhibitors of osteoclastic bone resorption,^{20,21} the recognition that compliance with long-term oral therapy is poor,^{22,23} and data from other studies of zoledronic acid that showed efficacy against risk of fracture in other non-cancer populations.²⁴ Unfortunately, GOG-0215 was closed prematurely due to slow accrual and follow-up. However, participants enrolled to the control arm of this study (observation only) provided important longitudinal data on post-ROO bone density that may serve to fill an important gap in current knowledge. Therefore, this exploratory study was conducted to measure the patterns and magnitude of bone loss following surgically-induced menopause. The results may be useful in the design of future trials and for the counseling of women considering prophylactic oophorectomy by providing additional knowledge about the rate of bone loss among women experiencing surgically-induced menopause during the first 18 months following surgery.

METHODS

Study Design

The GOG (now a component of NRG) is a National Cancer Institute's (NCI) cooperative cancer research group, which focuses on cancers of the gynecologic tract. GOG-0215 [NCT-00305695] was designed as a phase II trial, in which pre-menopausal women who were planning to undergo RRO were randomized to either observation or to receive three intravenous 4 mg doses of zoledronic acid at 3, 9, and 15 months post-surgery. Women at increased genetic risk of ovarian cancer were eligible for participation, but genetic-risk status was not a requirement and was not evaluated. It was hypothesized that the average decrease in BMD following oophorectomy in pre-menopausal women would be about 2% during the first year and about 1% per year thereafter.¹³ The study was conducted at 40 sites across the U.S. from November 2005 to April 2010. The GOG-0215 was approved by the respective Institutional Review Boards at each participating site prior to study activation at that study site.

Exclusion criteria

Eligible participants included premenopausal women who had already elected to undergo RRO or who had already undergone RRO (within 8 weeks). Eligible participants also were required to have normal renal function, a baseline BMD T-score of no less than -1.5 on both the lumbar spine and bilateral hip, and were required to have provided written informed consent prior to enrollment. Participants were ineligible if they had an existing fracture of the lumbar spine or bilateral hip, or a history of fracture of the hip or spine with or without trauma. Participants with a history of osteoporosis or other diseases that affect bone

metabolism (*e.g.*, Paget's disease, osteogenesis imperfecta), and participants with uncontrolled thyroid or parathyroid dysfunction, infections, type 2 diabetes, or any other uncontrolled cardiovascular, renal, hepatic or lung diseases and participants positive for HIV were also excluded from study participation. Prior bisphosphonate use, endocrine therapy, corticosteroid use, anabolic steroid or growth hormone use, systemic sodium fluoride, tibolone, HT, or any other agents known to affect bone (*e.g.*, calcitonin, mithramycin, selective estrogen receptor modulators, aromatase inhibitors) also resulted in the patient being ineligible for study entry. Due to the possible risks in the zoledronic acid treatment group, women were not eligible if they were pregnant, had active dental problems, or had either a recent or planned dental or jaw surgery, including tooth extraction or dental implants.

Treatment and BMD Measurement

For the purposes of the current analysis of GOG-0215, only those randomized to the observation arm were included. Participants were instructed to take 1200 mg of calcium supplements and a multi-vitamin tablet containing 400-800 IU of vitamin D once daily. Participants were required to undergo a DEXA BMD scan of L1-L4 and the bilateral hip at baseline and 3, 9, 15, and 18 months post-oophorectomy. Bone density was measured by T-score and Z-score at each follow up time point. While not used to formally measure osteopenia or osteoporosis, the Z-score data are an indication of bone loss relative to women of the same age. Traditionally, however, osteopenia is considered when bone density is $>0.648 \text{ g/cm}^2$ and 0.833 g/cm^2 ; while osteoporosis is defined as $\text{BMD} < 0.648 \text{ g/cm}^2$.²⁵ Participants were enrolled at 40 study sites, each of which used its own DEXA scan equipment and institutional imaging protocols for the study.

Statistical considerations

Participant characteristics and demographics at baseline were evaluated by means (observed range) and frequencies. The change in bone density was calculated for each patient from baseline to each follow up time point, and presented both in terms of g/m^2 and as a standardized z-score. The average change at each time point was evaluated. Due to a relatively small sample size and issues with study adherence, only trends in these data were evaluated. No statistical tests were employed to evaluate differences by anatomical location or time points.

RESULTS

The GOG-0215 study was activated for enrollment in November, 2005 and enrolled participants until it was closed to further accrual in April, 2010, having reached only approximately 70% of the planned accrual goals after more than four years of enrollment. A total 160 participants were enrolled, 80 of whom were randomized to observation only. The demographic characteristics of observation arm participants are presented in Table 1. The majority of women were between 40-49 years (60%), while 30% were between 30-39 years of age. Only a single participant (1.3%) was <30 years and 7 (8.8%) were over 50 years of age. The large majority of participants in the observation arm were White (90.0%) and non-

Hispanic (78.8%), while 8.7% and 12.5% reported African-American race and Hispanic ethnicity, respectively.

Protocol Adherence

Participant adherence to the study protocol for DEXA BMD scans is presented in Table 2. Fifty-three (66.2%) of 80 participants in the observation group completed all three DEXA scans. In comparison, only 48% of the treatment arm participants were adherent to bone density scans as required by the study protocol (data not shown). Of eligible observation arm participants, 78 (97.5%), 68 (85.0%), and 55 (68.8%) underwent a DEXA scan and provided bone density data available at the baseline, 9-month, and 18-month time points, respectively. However, as Table 2 also demonstrates, approximately one-third of participants, 27 (33.8%) missed at least one DEXA scan.

Bone mineral density (BMD)

The trends in BMD (mean and range) over time are presented in Table 3. Overall, we observed a trend of decreasing BMD over 18 months in the observation-only group at all body sites evaluated. For the lumbar spine, the mean baseline BMD was 1.18 g/cm² (range=0.82-1.59); by the 18 month visit, the mean BMD declined to 1.08 g/cm² (range=0.81-1.45). Measures from the right and left hips followed a similar declining pattern. The percent change in BMD after 18 months was -8.5% for the lumbar spine and -5.7% for both the right and left hip. Overall, the average mean changes over the study period were -0.09 (95% Confidence Interval (CI) = -0.12- -0.07), -0.05 (95% CI= -0.07- -0.03), and -0.06 (95% CI= -0.07- -0.05) g/cm² across the lumbar spine, right hip, and left hip, respectively. At all three measurement sites, the Z-scores demonstrated similar trends. The mean change in Z-score over the study period was -0.69 (95% CI -0.84- -0.54) g/cm² in the lumbar spine compared to -0.34 (95% CI= -0.48- -0.19) and -0.35 (95% CI= -0.44- -0.26) in the right and left hips, respectively.

DISCUSSION

The GOG-0215 phase II, randomized trial demonstrated bone loss in the lumbar spine and hips following risk-reducing oophorectomy. We observed a decrease in BMD at the lumbar spine and both hips (-8.5% and -5.7%, respectively) after 18 months. Correspondingly, we observed a mean decrease in BMD at the same sites from baseline to 18 months (-0.09, -0.05, and -0.06 g/cm² across the lumbar spine, left hip, and right hip, respectively). These losses occurred despite supplementation with 1200 mg of calcium and 400-800 IU vitamin D per day, which meet the current IOM recommendations for intake.²⁶ Parenthetically, it is worth noting that the data supporting the value of calcium/vitamin D supplements in mitigating the risk of osteoporosis-related fracture is much weaker than is commonly understood, evidence which underscores the need for more effective therapeutic options.^{27,28} Although this trial was stopped early due to slow accrual, our results from the control arm provide important evidence from a randomized clinical trial setting documenting the rapidity with which bone loss occurs immediately following oophorectomy. Additional randomized trials will be required to evaluate lifestyle and novel pharmacologic treatments for bone loss in this high-risk population of women.

Previous general population studies have shown that premature menopause due to oophorectomy is associated with an increased risk of osteoporosis,^{29,30} a disease characterized by low BMD, enhanced bone fragility, and increased susceptibility to fracture.^{9,31} Furthermore, additional studies have demonstrated that the rate of bone loss is accelerated in the first year post-oophorectomy.^{32,33} For example, Hashimoto *et al.* followed 244 women post-oophorectomy for more than ten years and reported that BMD loss was 10.7%, 5.7% and 1.1% in the first, second and subsequent years, respectively.³³ In a longitudinal study, Yoshida *et al.* compared bone density between healthy controls to women with post- surgically-induced menopause, and demonstrated that lumbar spine BMD decreased by 6.7% after one year post-op.¹⁶ However, a study by Svejme *et al.* demonstrated in a 34-year prospective study that on average women lost 2% BMD annually in the first 8 years following menopause then 1% beyond 8 years,¹³ and Aitken *et al.* reported up to 20% loss of BMD in the first 18 months following oophorectomy, accompanied by significantly increased osteoporosis risk within three to six years post-surgery.¹⁴

When planning the current study, it was estimated that the decrease in bone mineral density in pre-menopausal women would be approximately 2% during the first year following oophorectomy and about 1% per year thereafter. The results of GOG-0215 demonstrated that women lost almost 9% BMD from the lumbar spine and 6% in each hip. In a cross-sectional study of *BRCA* carriers, 71% of women who had undergone oophorectomy younger than 50 years of age were diagnosed by DEXA with either osteopenia (57%) or osteoporosis (14%), particularly in the absence of HT.³ Garcia et al. also recently reported that among 225 *BRCA1/2* carriers, followed for a median of 41 months post oophorectomy, nearly a third had normal DEXA scan results, while 55.6% showed osteopenia and 12.1% osteoporosis.⁵ Additional recent studies among *BRCA* carriers identified similar trends of lower BMD following oophorectomy.^{7,6} In contrast, a recent study by Fakkert et al. found that BMD was not significantly lower among premenopausal women (n=212) 5 years post-oophorectomy compared to general population data, though *BRCA* status was not considered.³⁴ In the current study, few participants fell below the threshold for osteopenia; however, *BRCA* status was unknown and significant study-related non-compliance may also have influenced these results.

The results of GOG-0215, similar to existing literature, demonstrate a rapid, short-term decline in BMD over time induced by early menopause and thus increased risk of osteoporosis. Strategies such as lifestyle interventions to increase physical activity^{1,35} or different medications such as zoledronic acid or denosumab^{36,37} should continue to be explored in large, long-term trials. It is estimated that 600,000 US women undergo hysterectomy per year for any reason, and that 50% of these procedures include removal of the ovaries, with a peak rate of concomitant oophorectomy occurring among women under age 54.³⁸ These women may also face the increased risk of osteoporosis and fracture associated with surgically-induced menopause, in combination with the normally occurring risk with increasing age and other established risk factors such as smoking, physical inactivity and overweight. Thus, it is critical to continue to study this growing population of high-risk women and evaluate alternative interventions to reduce the risk of bone disease.

The strengths of GOG-0215 include its randomized design and prospective follow-up of high risk participants. Furthermore, BMD was measured at multiple time points and three anatomical locations. Limitations include the challenges faced in both study recruitment and protocol compliance, which resulted in early study closure. In addition, the prospective follow-up was limited to only 18 months, as the original design of the study was intended to demonstrate a difference in the rate of bone loss between treated and untreated participants.

CONCLUSIONS

This study demonstrates a decline in bone mineral density, at three anatomical locations, among women who have undergone surgically-induced menopause following an oophorectomy. Future randomized studies in large populations with longitudinal measurement should be conducted to test alternative treatments for post-oophorectomy osteoporosis.

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Table 1

Demographics of enrolled participants enrolled to observation (n=80)

Demographic Characteristics	n (%)
Age category, n (%)	
<30 years	1 (1.3%)
30-39 years	24 (30.0%)
40-49 years	48 (60.0%)
>=50 years	7 (8.8%)
Ethnicity	
Hispanic or Latino	10 (12.5%)
Non-Hispanic	63 (78.8%)
Unknown/Not Specified	7 (8.8%)
Race	
African American	7 (8.7%)
White	72 (90.0%)
Unknown/Not specified	1 (1.3%)

Table 2

Adherence to DEXA scans of patients enrolled to observation by time point (n=80)

DEXA Scan Adherence	n (%)
No scans done	2 (2.5%)
Baseline scan only	8 (10%)
Baseline + 9 months scan	15 (18.8%)
Baseline + 18 months scan	2 (2.5%)
All scans done	53 (66.2%)

Table 3

Changes in bone mineral density in the observation group by time point

DEXA Location Lumbar Spine		
Time Point	N, Mean BMD g/cm ² (range) ^I	N, Mean z-score (range)
Baseline	n=78, 1.18 (0.82 to 1.59)	n=78, 0.31 (-3.30 to 3.20)
9 months	n=68, 1.10 (0.73 to 1.44)	n=68, -0.11 (-2.60 to 2.50)
18 months	n=52, 1.08 (0.81 to 1.45)	n=52, -0.22 (-2.10 to 2.10)
Mean change	n=52, -0.09 (-0.35 to 0.28)	n=52, -0.69 (-2.02 to 0.60)
(Baseline-18 months)	95% CI (-0.12,-0.07)	95% CI (-0.84,-0.54)
Right Hip		
Time Point	N, Mean BMD g/cm ² (range)	N, Mean z-score (range)
Baseline	n=77, 1.05 (0.79 to 1.31)	n=75, .53 (-1.90 to 2.70)
9 months	n=66, 1.02 (0.75 to 1.89)	n=69, 0.32 (-1.90 to 3.30)
18 months	n=53, 0.99 (0.78 to 1.37)	n=53, 0.24 (-2.30 to 3.70)
Mean change	n=51, -0.05 (-0.21 to 0.31)	n=51, -0.34 (-1.20 to 2.20)
(Baseline-18 months)	95% CI (-0.07,-0.03)	95% CI (-0.48,-0.19)
Left Hip		
Time Point	N, Mean BMD g/cm ² (range)	N, Mean z-score (range)
Baseline	n=78, 1.05 (0.79 to 1.35)	n=78, 0.53 (-1.50 to 3.70)
9 months	n=67, 1.01 (0.75 to 1.44)	n=67, 0.33 (-1.70 to 4.50)
18 months	n=54, 0.99 (0.80 to 1.28)	n=54, 0.24 (-1.90 to 3.20)
Mean change	n=54, -0.06 (-0.19 to 0.01)	n=54, -0.35 (-1.20, 0.80)
(Baseline-18 months)	95% CI (-0.07,-0.05)	95% CI (-0.44,-0.26)

^I A total of n=6 participants were missing a scan at one anatomical site (n=3 participants missing lumbar spine scans, n=2 missing right hip scans, and n=1 missing left hip scan).