



Bone loss in women with BRCA1 and BRCA2 mutations

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HIGHLIGHTS

- Women with BRCA mutations who undergo oophorectomy have a high risk of bone loss.
- BMI, race, SERM use and age are all factors affecting bone loss in women with BRCA mutations.
- Higher BMI is protective of bone loss in women with BRCA mutations and oophorectomy.

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ABSTRACT

Objective. Estimate the prevalence and identify risk factors for bone loss in women with BRCA mutations.

Methods. Women, age 40 and older, with BRCA mutations identified from the Breast Cancer Surveillance database at Kaiser Permanente Northern California were invited to participate and undergo a dual-energy x-ray absorptiometry scan to assess for bone loss (osteopenia or osteoporosis). Multivariable logistic regression analysis was performed to assess clinical factors associated with bone loss.

Results. Of the 238 women in the final cohort, 20 women had intact ovaries (median age 54.5 years) and 218 had undergone risk reducing salpingo-oophorectomy (RRSO) (median age 57). The prevalence of bone loss was 55% in the no RRSO group and 72.5% in the RRSO group ($P = 0.10$). In multivariable analysis, only higher body mass index (OR 0.6 per 5 kg/m², 95% CI: 0.4–0.7) and nonwhite race compared to white (OR 0.5, 95% CI: 0.2–0.9) were protective for bone loss while older age (OR 1.5 per 10 years, 95% CI: 1.1–2.1) and selective estrogen receptor modulator use (3.1, 95% CI: 1.2–10.1) were associated with increased odds of bone loss. Among women with RRSO, bone loss was more frequent in women who had postmenopausal ($n = 106$) compared to women who had premenopausal RRSO ($n = 112$), (82.1% and 63.4% respectively, $P = 0.002$). In multivariable analysis, only BMI was protective of bone loss (OR 0.5, 95% CI: 0.4–0.7) but neither age nor menopausal status at RRSO were associated with bone loss.

Conclusion. Bone loss is common in women with BRCA mutations who undergo RRSO.

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1. Introduction

Women carriers of BRCA1 or BRCA2 mutations who utilize chemoprevention, surveillance, and surgical risk reduction strategies are expected to avoid cancer and prolong their life expectancy [1,2]. National guidelines for mutation carriers including the National Comprehensive Cancer Network (NCCN) and American College of Obstetrics and Gynecology (ACOG) guidelines recommend women with BRCA1

mutations undergo risk reducing salpingo-oophorectomy (RRSO) between ages 35 and 40, and women with BRCA2 mutations undergo RRSO by age 45 [3,4]. These women will experience premature surgical menopause, and many will not be eligible for estrogen replacement therapy due to a personal history of breast cancer. Given there is an expanding cohort of women, living many years beyond surgical menopause; the later health outcomes of early estrogen deprivation have become a greater concern [5,6]. Due to the risk of negative health outcomes such as bone loss, heart disease, and menopausal symptoms, young mutation carriers may choose to delay RRSO beyond the recommended age [7]. It is therefore important to understand the extent of post-RRSO health consequences in order to properly counsel these women.

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In a previous study, we identified women with BRCA mutations who had a dual-energy X-ray absorptiometry (DXA) scan in their medical record after RRSO in Kaiser Permanente Northern California (KPNC) [8]. In that study, Garcia et al. found that 68% of these women had bone loss; 56% were diagnosed with osteopenia and 12% with osteoporosis. This high rate of bone loss in BRCA mutation carriers undergoing RRSO is concerning, but interpretation is limited by selection bias given that <50% of women who had undergone RRSO had a subsequent DXA scan. Other studies showing significant bone loss in this group of women also suffer the same selection bias [9,10]. Regardless of oophorectomy status, women with BRCA mutations have many other risk factors for bone loss. For example, a history of breast cancer will likely be associated with exposure to cancer therapeutics, early non-surgical menopause, and use of aromatase inhibitors or Tamoxifen, which all play a role in bone loss [11]. In the current study, we seek to clarify risk for bone loss associated with RRSO in women with BRCA mutations relative to effects of menopause and the many other risk factors common to women with BRCA mutations. Specifically, we want to assess the independent impact of RRSO, menopause, age and cancer treatment on bone loss to more accurately counsel these women who may delay RRSO based on the concern for health impact. We hypothesized that bone loss would be greatest in women with BRCA mutations who underwent RRSO before menopause.

2. Methods

The primary objectives of this study were to describe the prevalence of bone loss and risk factors associated with bone loss in women with BRCA1 or BRCA2 mutations and assess differences by RRSO status and timing of RRSO relative to menopause. This study was performed in Kaiser Permanente Northern California (KPNC), an integrated health care system in which women with BRCA mutations are prospectively entered into a regional database. Women were eligible if they were age 40 and older with BRCA1 or BRCA2 deleterious mutation documented in the medical record and had current KPNC membership. Exclusion criteria included pregnancy, a diagnosis of ovarian cancer, and contact for another open study for ovarian cancer surveillance in BRCA mutation carriers who had ovaries. The Kaiser Foundation Research Institute's Institutional Review Board approved this study.

Potentially eligible women were contacted for enrollment from December 2015 – November 2016 in two ways: (1) Flyers were distributed in the Genetics Department and through Breast and Gynecologic Care providers who participate in the Hereditary Cancer Risk Program. These providers notified study personnel of women interested in the study and (2) Women in the regional BRCA database who met inclusion criteria were contacted via a mailed letter followed by phone contact by research personnel. Written informed consent was obtained from eligible women who agreed to participate. Enrolled women completed a questionnaire which included information on demographics, height, weight, fractures, and clinical factors related to bone loss including alcohol, smoking, exercise, menopausal status, breast and gynecology surgery including RRSO, cancer and cancer treatments, use of calcium, vitamin D, bisphosphonates, selective estrogen receptor modulators (SERM), aromatase inhibitors, hormonal contraception, and hormone replacement therapy (HRT). History of bone loss and age at diagnosis were also reported on the questionnaire. Data on DXA bone densitometry imaging studies, FRAX scores and BMI (kg/m^2) were obtained from the electronic health record.

The primary study outcome was bone loss, which was defined as presence of osteopenia or osteoporosis on the most recent DXA scan prior to study enrollment. Women who did not have a DXA scan within 3 years prior to enrollment were asked to have a DXA scan performed. For women with RRSO, the DXA had to have been performed after the RRSO. Osteoporosis was defined based on the World Health Organization standard of a T-score ≤ -2.5 , osteopenia as a T-score of between -2.5 and -1.0 , and normal if the T-score was ≥ -1.0 . DXA scans

were categorized and in the same order: osteoporosis (T score of less than or equal to minus 2.5) osteopenia (T score -1.0 to -2.5) and normal (T score greater than -1.0) [12].

We estimated we would have 80% power to detect a 28.5 percentage point difference in the proportion of women with bone loss comparing women with and without RRSO using a two-sided continuity corrected Chi square test, if we enrolled 180 women and 30 who did not have an RRSO, assuming 20% of women without RRSO would have evidence of bone loss. Statistical analysis was performed using SAS software, Version 9.3 (SAS Institute Inc., Cary, NC, USA). We compared study groups using Kruskal Wallis test for non-normally distributed continuous variables and Chi square or Fischer's exact tests for categorical variables. A p-value < 0.05 was considered significant. A multivariable logistic regression analysis was performed to assess clinical factors associated with bone loss using factors identified in the bivariate analysis, which predicted bone loss and which were considered by the study team to be clinically relevant and along the causal path. The first model included the full cohort and factors identified in the bivariate analysis which were then used in the multivariable analysis including RRSO status, age at DXA scan, BMI, a binary race variable (white/non-white) and Tamoxifen/SERM use. A second model evaluated predictors of bone loss only in women with RRSO in bivariate analysis and factors including menopausal status at RRSO, age at DXA scan, BMI, race, and Tamoxifen/SERM use were then used in a multivariable analysis.

3. Results

Recruitment letters were sent to 485 women, who were either identified from the regional BRCA database or recruited directly from the Hereditary Cancer Risk Center in KP San Francisco. Of these, 433 had undergone a prior RRSO, 223 of whom consented to participate. Because of a competing ovarian cancer screening trial, only 52 women without RRSO were identified for recruitment and a smaller number of these women ($n = 21$) consented to participate. Of those who had undergone RRSO, 218 of 223 consented women, completed the questionnaire and of those who had not undergone RRSO, 20 of 21 consented women completed the questionnaire. Altogether, there were 244 women who enrolled and completed a questionnaire between December 2015 and November 2016; of whom, 238 completed a DXA scan and made up the final cohort (218 RRSO and 20 with no RRSO). Of this study cohort, 78% (186/238) did not have a DXA performed within 3 years of enrollment in the study and the DXA was ordered at the time of enrollment. Of the 52 women who had a prior DXA within 3 years prior to enrollment, the median interval was 11 months before enrollment. One woman who had not had an RRSO had a prior DXA, 18 women (16.1% of those with RRSO before menopause) and 33 (31.1% of those with RRSO after menopause) had a DXA before study entry.

Demographic and clinical risk factors for bone loss for the full study cohort by RRSO status are shown in Table 1. The difference between median age at index (DXA) in women without RRSO (54.5 years, interquartile range 44–60) and women with RRSO (57 years, interquartile range 50–65) ($P = 0.15$) was not statistically significant. The time from menopause to index (DXA) was 7.5 years in women without RRSO and 9 years in women with RRSO ($P = 0.63$). Women without RRSO were more likely to be non-white (45.0% white) compared to women with RRSO (71.6% white, $P = 0.01$), and less likely to use HRT (0 versus 18.6% current users; $P = 0.07$). Women with RRSO had a longer time from gene test to study enrollment and were statistically more likely to have a hysterectomy, to be menopausal, and to have had cancers other than breast cancer than those who did not have RRSO.

Overall 71% of women in the study cohort had measured bone loss (Table 1). While there was a larger proportion of women with RRSO (72.5%) with bone loss compared to women without RRSO (55%), the difference was not statistically significant ($P = 0.10$). Similarly, women without RRSO were less likely to self-report a history of bone

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