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Bone mineral density and fractures after risk-reducing salpingo-oophorectomy in women at increased risk for breast and ovarian cancer

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\textbf{Abstract}  \textbf{Aim:} Risk-reducing salpingo-oophorectomy (RRSO) reduces ovarian cancer risk in \textit{BRCA} mutation carriers. RRSO is assumed to decrease bone mineral density (BMD) and increase fracture risk more than natural menopause. We aimed to compare BMD and fracture incidence after premenopausal RRSO to general population data and identify risk factors for low BMD and fractures after RRSO.

\textbf{Methods:} In 212 women with RRSO at premenopausal age, BMD was measured by dual energy X-ray absorptiometry. Fractures and risk factors were assessed by self-administered questionnaire. Fracture incidence after RRSO was compared to general practitioner data by using standardised incidence ratios (SIRs). Risk factors for low standardised BMD-scores and fractures were identified by regression analyses.
Results: Median age at RRSO was 42 years (range 35–65) and duration of follow-up 5 years (2–8). Standardised lumbar spine (Z = 0.01, p = 0.870) and femoral neck BMD (Z = 0.15, p = 0.019) were not lower than population BMD. Higher age at time of RRSO and use of hormonal replacement therapy were associated with higher, and current smoking with lower standardised BMD-scores. Sixteen women reported 22 fractures. Fracture incidence was not higher than expected from the general population (all fractures: 25–44 years: SIR 2.12 [95% confidence interval (CI) 0.85–4.37]; 45–64 years: SIR 1.65 [95% CI 0.92–2.72]).

Conclusion: Five years after RRSO, BMD and fracture incidence were not different than expected from the general population. Based on these data it appears safe not to intensively screen for osteoporosis within five years after RRSO, although prospective research on the long-term effects of RRSO on bone is warranted.

1. Introduction

Breast and ovarian cancer risk is elevated in women with a family history of breast cancer (hereditary breast ovarian cancer, HBOC), especially in women carrying a germ line mutation in the BRCA1 and BRCA2 genes [1,2]. These women often opt for risk-reducing salpingo-oophorectomy (RRSO) to reduce ovarian cancer risk, as ovarian cancer screening is not effective [3]. RRSO reduces ovarian cancer risk by up to 96% [4]. RRSO is advised in BRCA1 and BRCA2 mutation carriers at the age of 35–40 years and 40–45 years, respectively [5]. The median age at RRSO, which leads to acute oestrogen deprivation, is about 10 years earlier than natural menopause [6].

When ovarian oestrogen production declines during natural menopause, bone mineral density (BMD) decrease accelerates and fracture incidence increases [7]. Reports on the effect of early and surgical menopause on BMD and fracture incidence are inconclusive. Several studies suggested that BMD was lower and fracture incidence higher after early natural and surgical menopause, than after natural menopause at normal age [8,9]. Others found a transient effect on fracture incidence or no effect at all [10,11]. Several studies reported a high risk of osteoporosis after RRSO; however, these studies were all prone to bias, due to retrospective study designs, selected study populations and in some cases lack of a control group [12–15].

This study aimed to compare BMD and fracture incidence after RRSO before menopausal age in an unselected consecutive series of BRCA1/2 mutation carriers and women with a family history of breast and ovarian cancer, to what can be expected from the general female population. The secondary aim was to identify risk factors for low BMD and fracture incidence after RRSO.

2. Patients and methods

2.1. Study population and protocol

Since 1994 all women visiting the family cancer clinic at the University Medical Center Groningen are registered in a prospective database [16]. Between February 2011 and May 2012, all BRCA1/2 mutation carriers and women with a positive family history of breast and ovarian cancer with RRSO at the age of ≤52 were invited to attend osteoporosis and fracture screening if they were ≥ two years after RRSO. Women in whom ovarian cancer was detected at RRSO were excluded. Of the 254 invited women, 212 attended and gave written informed consent for the study (Fig. 1).

Women were evaluated by a researcher, under supervision of a medical doctor, according to a standard protocol which included measurement of height, weight, a self-administered questionnaire, collection of blood samples and BMD measurement. The institutional ethics review board considered this study extended standard care.

2.2. BMD measurement

BMD of the lumbar spine (LS; anterior-posterior projection at L1–L4) and femoral neck (FN) were measured by dual energy X-ray absorptiometry (DXA) using a Hologic Discovery A densitometer (Hologic Inc., Bedford, MA). Vertebral fracture assessment (VFA) was performed with the same DXA machine, as previously described [17].

Abbreviations: RRSO is risk-reducing salpingo-oophorectomy.
2.3. Questionnaire

The questionnaire aimed at identifying history of bone fractures and risk factors for osteoporosis and low BMD. It was based on the clinical questionnaire used at the fracture and osteoporosis outpatient clinic at our centre [18]. The questionnaire was sent to the patients before their osteoporosis and fracture screening visit. During the visit, missing or inconsistent answers were discussed by the researcher and the patient and corrected by the researcher if appropriate.

2.4. Laboratory assessments

A non-fasting blood sample was collected between 9:00 a.m. and 4:30 p.m. Calcium and albumin were measured by colorimetric assay (Roche Modular P, Mannheim, Germany; inter-assay coefficient of variation (IA-CV) < 2.0% and < 1.8%; lower detection limit 0.05 mmol/L and 10 g/L for calcium and albumin, respectively). Calcium was corrected for albumin levels with the following formula: Corrected calcium (mmol/L) = measured total calcium (mmol/L) + 0.02 (41 – serum albumin [g/L]). Serum 25(OH)D3 was measured by isotope dilution–online solid phase extraction liquid chromatography–tandem mass spectrometry [19]. Method specifications were: level of quantification 4.0 nmol/L; IA-CV <14.1%; recovery 93–98%; linearity \( r^2 = 0.9972 \). Accuracy was secured by the use of reference material from the National Institute of Standards & Technology (Gaithersburg, MD).

2.5. Study end-points

Results of BMD measurement were expressed as BMD in g/cm² and standardised by using Z- and T-scores. Z-scores present the number of standard deviations (SD) from the mean bone mineral density in woman of the same age [20,21]. T-scores present the number of SDs from the mean peak BMD as reached in women between 20 and 30 years of age [20,21]. According to the World Health Organisation definition, ‘osteoporosis’ is defined as a T-score of \( \leq -2.5 \); ‘osteopenia’ as a T-score between \(-2.5\) and \(-1.0\); and ‘normal’ as a T-score \( \geq -1.0 \).

Fracture incidence after RRSO was evaluated by questionnaire. Fractures that were impossible based on clinical data were excluded. Aetiology of fractures was assessed to determine if they were fragility fractures, i.e. caused by low energy trauma. Low energy trauma was defined as a fall from standing position or a height of one metre or less [18].

To identify the prevalence of occult vertebral fractures, VFA data were used. Vertebral-shape deformities were classified using the Genant classification (grade 0: no deformities; grade 1: mild deformity, 20–25% height decrease; grade 2: moderate deformity, 25–40% height decrease; and grade 3: severe deformity, >40% height decrease) [22]. In patients with a relative height reduction of any vertebra of \( \geq 20\% \) on VFA and no known previous vertebral fracture at that site, an X-ray of the thoracic and lumbar spine was made for further evaluation. According to the Dutch guidelines, a vertebral fracture was defined as a height reduction of \( \geq 25\% \) on lateral X-ray of the spine or of \( \geq 40\% \) on VFA scans [23].

2.6. Reference population

The standard Hologic reference databases for Caucasian women were used to calculate Z- and T-scores [20,21]. For femoral neck references, data were retrieved from NHANES III [20]. For lumbar spine, data were retrieved from a Hologic study on BMD in healthy American women [21].

Age-specific fracture incidence in Dutch women was obtained from a national survey on disease incidence in four general practices [24].

2.7. Statistical analysis

Analyses were conducted using IBM SPSS Statistics version 20 (IBM Corporation, Armonk, NY, United States of America (USA)). \( p\)-Values <0.05 were considered significant. Descriptive statistics were used to present patient characteristics using mean ± SD for parametric, median (range) for non-parametric and number (%) for dichotomous data.

To compare BMD in the study population to the reference population, mean BMD Z-scores for the total group were compared to the mean Z-score in a healthy reference population (i.e. \( Z = 0 \), \( SD = 1 \)) by using unpaired one-sample t-test.

Fracture incidence after RRSO was compared to age-specific fracture incidence in the Dutch female population by using standardised incidence ratios (SIRs). SIRs were calculated for first and all incident fractures after RRSO.

Multiple imputation was applied to impute missing values for: BMD LS Z-score \( (N = 1) \), long term use of glucocorticosteroids (i.e. 7.5 mg prednisolone or equivalent \( \geq 3 \) months; \( N = 1 \)), corrected serum calcium \( (N = 2) \) and serum 25(OH)D3 \( (N = 1) \), using all variables included in the regression models. Ten imputed datasets were used in the regression analyses and results were combined according to Rubin’s rules [25].

Factors associated with BMD LS and FN Z-score were identified using linear univariate regression analyses. Factors individually characterising the women who developed incident fractures after RRSO were identified using univariate logistic regression analysis. For the univariate analysis we selected factors from the questionnaire associated with breast cancer and clinical risk.
factors associated with fracture risk in the FRAX-tool [18,26]. Multivariate regression analyses were performed with conditional stepwise backward inclusion of those variables with a p-value < 0.250 in univariate analysis. Multivariate analyses were corrected for ever use of anti-osteoporotic drugs (AOD) and calcium and vitamin D3 supplementation. Because fracture incidence was measured retrospectively, while questionnaire items and BMD were measured cross-sectionally, we analysed risk factors that we assumed to be constant for a longer period of time, such as ever smoking, but not current smoking.

3. Results

3.1. Study population

In a total of 212 women, median age at RRSO was 42 years (range 30–52) and median current age was 49 years (36–65; Table 1). Follow-up time from RRSO to screening was 5 years (2–25). Of the 18 (9%) women who reported the use of anti-osteoporotic drugs after RRSO, eight were using these drugs at the time of screening. Indications for AOD use are described in Table 1.

Table 1

| Demographics and main clinical features of the study population (N = 212). |
|-----------------|-----------------|-----------------|
| Basic characteristics | M M | M M |
| Age in years | 49 (36-65) | 0 | Ever use calcium supplement | 63 (30) | 0 |
| Age at RRSO in years | 42 (30-52) | 0 | Current use | 46 (22) | 0 |
| Follow-up in years | 5 (2-25) | 0 | Ever use vitamin D3 supplement | 61 (29) | 0 |
| BMI in kg/m² | 26 (18-54) | 0 | Current use | 49 (23) | 0 |
| Menopausal status before RRSO | 0 | Smoking – current | 41 (19) | 0 |
| Premenopausal | 177 (84) | Alcohol consumption in units/week | 2 (0-35) | 0 |
| Regularly menstruating | 94 (44) | ≤7 units/week | 174 (82) | 0 |
| Irregularly menstruating | 29 (14) | >7 units/week | 38 (18) | 0 |
| OCP use | 54 (26) | Long-term use GCSa | 8 (4) | 1 |
| Postmenopausal | 27 (13) | History of breast cancer | 80 (38) | 0 |
| Natural | 11 (5) | Chemotherapy | 60 (28) | 0 |
| Chemotherapy induced | 16 (8) | Ever use AI | 11 (5) | 0 |
| Unknown: Hysterectomy | 8 (4) | Ever use tamoxifen | 17 (8) | 0 |
| Fracture before RRSO | 64 (30) | Mutation status | 0 | 0 |
| Parent with hip fracture | 5 (2) | | |
| Ever use AOD | 18 (9) | 0 | BRCA1 | 121 (57) | 0 |
| Current use | 8 (4) | 0 | BRCA2 | 60 (28) | 0 |
| Indication AOD | 0 | 0 | | |
| AI use | 3 (1) | Ever use HT | 100 (47) | 0 |
| GCS use | 2 (1) | Current use HT | 51 (24) | 0 |
| Prevention | 3 (1) | Lab | |
| Osteoporosis | 3 (1) | Corrected serum calcium in mmol/Lb | 2.3 (2.0–2.5) | 2 |
| Osteopaenia | 5 (2) | Serum 25(OH)D3 in nmol/L | 64 (16–151) | 1 |
| Fracture after RRSO | 2 (1) | |

Values are median (range) and No. (%); M is missing. RRSO is risk-reducing salpingo-oophorectomy, BMI is body mass index, AI is aromatase inhibitor, HBOC is hereditary breast ovarian cancer, HT is hormonal replacement therapy, GCS is glucocorticosteroid, AOD is anti-osteoporotic drugs.

a Use of prednisone 7.5 mg or equivalent ≥3 months or ≥3 oral prednisolone courses per years.
b Calcium was corrected for albumin levels with the following formula: Corrected calcium (mmol/L) = measured total Calcium (mmol/L) + 0.02 (41 / serum albumin [g/L]).

3.2. Bone mineral density

BMD LS and FN Z-scores were not lower than Z = 0 (mean Z score 0.01 ± 1.09, p = 0.870 and mean Z-score 0.15 ± 0.93, p = 0.019, respectively; Table 2). Of all patients 6% (n = 13) had osteoporosis according to T-score, 12 of the lumbar spine and one of the femoral neck. Mean Z-scores for women with osteoporosis were −1.8 ± 0.44 and −0.08 ± 0.55 for lumbar spine and femoral neck respectively. Osteoporosis incidence was 9.2/1000 women-years.

In the multivariate linear regression model, older age at RRSO, higher BMI and current hormonal replacement therapy (HT) use were positively associated with BMD LS Z-score, while no covariates were significantly negatively associated (Table 3). For BMD FN Z-score, longer duration of follow-up, higher BMI and ever use of HT were positively associated, while current smoking was negatively associated (Table 3).

3.3. Incident fractures

Seventeen (8%) women reported 23 fractures after RRSO. One fracture was excluded, as clinical data described a cartilage defect, but not a bone defect. Of
the remaining 22 fractures in 16 women, 19 were consid-
ered fragility fractures (Table 2). Median follow-up to
first fracture after RRSO was 5 years (1–15). Fracture
incidence after RRSO was comparable to fracture inci-
dence in the GP reference population (Table 4). In the
multivariate analysis, alcohol consumption was posi-
tively associated with the occurrence of fractures after
RRSO (Table 5).

3.4. VFA outcomes

On VFA, 12 (6%) women had 13 relative vertebral
height reductions of $\geq 20\%$. The affected vertebrae were:
Th6, Th7 ($N = 2$), Th11 ($N = 2$), Th12 ($N = 3$), L1 ($N = 3$), L2 and L3. In five women, these vertebral
deforrmities were diagnosed before study entry and were
considered known vertebral fractures. Of the other seven
women, four had a minimal deformity and three a mod-
erate deformity according to the Genant classification
on VFA. None of these seven women had height reduc-
tions of $>25\%$ on X-ray, so none of the deformations
detected with VFA fulfilled the Dutch definition of a
vertebral fracture on X-ray [23].

3.5. Secondary causes of osteoporosis

Several women reported co-morbid diseases that may
have contributed to a higher fracture risk according to
the QFracture algorithm, either in medical history or
at the time of study participation [27]. Of all women,
37% ($n = 79$) reported one or more co-morbid diseases,
of the women with fractures this was 41% ($n = 7$,
$p = 0.728$; table on co-morbid diseases Supplementary
Online).

4. Discussion

In an unselected consecutive series of 212 women
with RRSO at age $\leq 52$, after a median follow-up of
5 years, BMD was not lower (BMD LS $Z$-score: 0.01,
$p = 0.870$ and BMD FN $Z$-score: 0.15, $p = 0.019$) and
fracture incidence was not higher (all fractures: 25–
44 years: SIR 2.12 [95% confidence interval (CI) 0.85–
4.37]; 45–64 years: SIR 1.65 [95% CI 0.92–2.72]) than
what can be expected from an age-matched reference
population. These findings are in contrast to the common hypoth-
oses that after RRSO BMD decreases and fracture inci-
dence rises faster than after natural menopause. However, these are in line with the results of previous
studies that failed to find an effect of early and surgical
menopause on bone mineral density and fractures
[11,28], and studies that found an effect of early or sur-
gical menopause only in the first years after the proce-
dure, which suggests that the effect of RRSO might
eventually be overruled by chronological age [10,29].

However, an effect of RRSO on BMD or fracture
risk in this study population cannot be completely
excluded because of several reasons. Firstly, a large proportion of women had used bone protective medication, such as HT (47%), tamoxifen (8%) and AOD (9%). This might have attenuated the effect of RRSO on both BMD and fracture incidence. HT use was associated with higher BMD LS and FN Z-scores in multivariate analysis, which confirms the known protective effect of HT on BMD [30]. Secondly, a positive relation between age at RRSO and BMD Z-score was shown, which might indicate that BMD is lower in women who have RRSO at younger age. Thirdly, it is known that fracture incidence is relatively low at young age and increases significantly with older age [10]. A long-term effect of RRSO on fracture risk at older age needs to be further investigated in a prospective longitudinal study. Lastly, changes in bone characteristics might increase fracture risk independently of actual BMD, such as structural changes in bone architecture and changes in bone loss rate. BMD measurement by DXA might not be sensitive enough to evaluate bone architecture and detect structural changes in bone after RRSO. It is possible that these changes are visible on more advanced techniques like quantitative computed tomography, which measures cortical and trabecular BMD separately or on DXA using trabecular bone score software [31,32]. Also, a higher rate of bone loss has been shown to be associated with fracture risk independent of actual BMD and a higher rate of bone loss in surgical menopause compared to natural menopause has been reported by others [33,34]. As BMD was measured cross-sectionally in this study, BMD before and after RRSO could not be compared in the same woman to calculate bone loss rates. Bone turnover marker measurement might be useful to estimate bone loss rate after RRSO [35].

In addition, this study has several limitations. Questionnaires were used to assess fracture incidence and risk factors, which might have induced a risk of selective reporting. Fracture incidence was not systematically confirmed with hospital data. We considered a question-
naire a reliable tool to measure fracture incidence. Clinical confirmation was available for 16/22 fractures, which might be considered a limitation.

Fracture incidence in the control population was assessed through general practitioner (GP) reports, which might have resulted in underreporting of the actual fracture risk, as some fractures are directly seen at the emergency department. However, as almost all Dutch citizens are registered with a GP who records all their diagnoses, and because GPs function as the gatekeepers for specialized medical care, one can assume that GPs have the most complete file on the incidence of health problems in the general population. Moreover, within this study, GPs are trained for adequately registering health problems and quality of the registration was monitored [24]. This was further supported by the finding that fracture incidence before RRSO was comparable to fracture incidence in the reference population (Supplementary table online).

To our knowledge, this study is the largest study on the effects of RRSO at premenopausal age on bone mineral density and fracture incidence. Participation rate was as high as 83%. Also, we are the first to measure BMD after RRSO in an unselected consecutive

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Comparison of fracture incidence observed after RRSO to fracture incidence expected after RRSO from general practitioner data using standardised incidence ratios (SIRs).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>No. of women</td>
</tr>
<tr>
<td>First incident fractures</td>
<td></td>
</tr>
<tr>
<td>25–44</td>
<td>139</td>
</tr>
<tr>
<td>45–64</td>
<td>158</td>
</tr>
<tr>
<td>65–74</td>
<td>1</td>
</tr>
<tr>
<td>All incident fractures</td>
<td></td>
</tr>
<tr>
<td>25–44</td>
<td>139</td>
</tr>
<tr>
<td>45–64</td>
<td>160</td>
</tr>
<tr>
<td>65–74</td>
<td>2</td>
</tr>
</tbody>
</table>

RRSO is risk-reducing salpingo-oophorectomy; No. is number; FI is fracture incidence/1000 women-years; Exp. is expected number of fractures; Obs. is observed number of fractures; SIR is standardised incidence ratio; CI is confidence interval.

* No. of women attributing to calculation of total no. of women-years per age group.

† van de Lisdonk et al. [24].

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Uni- and multivariate logistic regression analyses on women who reported fractures after RRSO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysis</td>
<td>Multivariate analysisa</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.0</td>
</tr>
<tr>
<td>Age at RRSO (per year)</td>
<td>1.0</td>
</tr>
<tr>
<td>Duration of follow-up (per year)</td>
<td>1.1</td>
</tr>
<tr>
<td>BMI (per kg/m²)</td>
<td>1.0</td>
</tr>
<tr>
<td>Postmenopausal before RRSO</td>
<td>0.4</td>
</tr>
<tr>
<td>Fracture before RRSO</td>
<td>1.1</td>
</tr>
<tr>
<td>Parent with hip fracture</td>
<td>-</td>
</tr>
<tr>
<td>Ever smoking</td>
<td>0.5</td>
</tr>
<tr>
<td>Alcohol (per unit/week)</td>
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</tr>
<tr>
<td>Alcohol &gt;7 units/week</td>
<td>3.1</td>
</tr>
<tr>
<td>Long-term use GCSb</td>
<td>1.7</td>
</tr>
<tr>
<td>History of breast cancer</td>
<td>1.7</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1.6</td>
</tr>
<tr>
<td>Ever use of AI</td>
<td>1.2</td>
</tr>
<tr>
<td>Ever use of tamoxifen</td>
<td>1.7</td>
</tr>
<tr>
<td>Ever use of HT</td>
<td>0.7</td>
</tr>
<tr>
<td>Z-score BMD lumbar spine</td>
<td>1.0</td>
</tr>
<tr>
<td>Z-score BMD femoral neck</td>
<td>1.0</td>
</tr>
<tr>
<td>Corrected serum calcium</td>
<td>1.6</td>
</tr>
<tr>
<td>Serum 25(OH)D³</td>
<td>1.0</td>
</tr>
</tbody>
</table>

CI is confidence interval; RRSO is risk-reducing salpingo-oophorectomy; BMI is body mass index; AI is aromatase inhibitor; HT is hormonal replacement therapy; GCS is glucocorticosteroids; BMD is bone mineral density; AOD is anti-osteoporotic drugs.

a Adjusted for AOD/calcium/vitamin D3 supplement use.

b Use of prednisone 7.5 mg or equivalent >3 months or >3 oral prednisolone courses per years.

c * p < 0.05.
series of women with RRSO, which makes this study population representative for actual practice without selection bias.

In this study, women with RRSO at premenopausal age did not have lower BMD and higher fracture incidences compared to an age-matched control population. Based on these results, it cannot be advised to offer BMD measurements to all women after RRSO. Prospective research remains warranted to evaluate long-term fracture incidence after RRSO.

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**Conflict of interest statement**

The following authors disclosed possible conflicts of interest. Bruce H.R. Wolffenbuttel has received grant support for clinical studies and also consulting fees for serving on advisory boards and as a speaker for Eli Lilly and Company, GlaxoSmithKline, Novo Nordisk and Pfizer. He has also received consulting fees from Eli Lilly and Company as a member of the 4B study and the DURABLE Trial Data Monitoring Committee. Joop D. Lefrandt has received grant support from Boehringer Ingelheim. All remaining authors have declared no conflict of interest.

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**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2014.11.022.

**Reference**


