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Research Article

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Breast Cancer Incidence After Risk-Reducing Salpingo-Oophorectomy in *BRCA1* and *BRCA2* Mutation Carriers

Ingrid E. Fakkert[1], Marian J.E. Mourits[2], Liesbeth Jansen[3], Dorina M. van der Kolk[4], Kees Meijer[3], Jan C. Oosterwijk[4], Bert van der Vegt[5], Marcel J.W. Greuter[6], and Geertruida H. de Bock[1]

Abstract

Premenopausal risk-reducing salpingo-oophorectomy (RRSO) in *BRCA1*/2 mutation carriers effectively reduces ovarian cancer risk, but also reduces breast cancer risk. Breast cancer risk reductions up to 50% have been reported for both *BRCA1* and *BRCA2* mutation carriers, but recent prospective studies were not able to reproduce this finding for *BRCA1* mutation carriers.

Breast cancer incidence after RRSO was assessed in a consecutive series of 104 *BRCA1* and 58 *BRCA2* mutation carriers. On the basis of data from our own centre, and assuming a 50% risk reduction through RRSO at premenopausal age, we expected to find 8 breast cancers (range 6–10) in this population for the reported screening period (532 women-years).

In 162 carriers with a median age of 41 years at RRSO, 13 incident breast cancers were diagnosed. In *BRCA1* mutation carriers, 12 incident breast cancers were found compared with 5 (range 3–6) expected and in *BRCA2* mutation carriers 1 breast cancer was found compared with 3 (range 2–5) expected.

Breast cancer incidence after premenopausal RRSO is still high, especially in *BRCA1* mutation carriers. Previously reported breast cancer risk reductions up to 50% were not confirmed. As a consequence, continued intensive screening for breast cancer is warranted in *BRCA1* and *BRCA2* mutation carriers after RRSO. *Cancer Prev Res; 5(11); 1291–7. ©2012 AACR.*

Introduction

Women with a proven *BRCA1* or *BRCA2* mutation have a risk for developing breast cancer of 40% to 80% by the age of 70 (1, 2). Ovarian cancer risk by the age of 70 is 40% for *BRCA1* and 18% for *BRCA2* mutation carriers (1, 2) A study by van der Kolk and colleagues (3) conducted at our centre found cumulative risks of breast cancer of 71% [95% confidence interval (CI), 67%–82%) in *BRCA1* and 88% (95% CI, 82%–93%) in *BRCA2* mutation carriers by the age of 70. These risks were at the high end of the spectrum compared with other studies, especially for *BRCA2* mutation carriers. The authors hypothesized that this could be due to skewing towards testing in women affected with cancer, competing risks of mortality from ovarian cancer in *BRCA1* mutation carriers, or missing of *BRCA2* mutation families with lower cancer penetrance that fail to meet the age-related criteria for mutation testing (3).

Authors' Affiliations: Departments of [1]Epidemiology, [2]Gynecology, [3]Surgery, [4]Genetics, [5]Pathology, and [6]Radiology, University Medical Center, University of Groningen, Groningen, The Netherlands.

Corresponding Author: G.H. de Bock, University Medical Center Groningen, University of Groningen, Department of Epidemiology, P.O. Box 30.001, 9700 RB Groningen, The Netherlands. Phone: 31-50-361-0739; Fax: 31-50-361-4493; E-mail: g.h.de.bock@umcg.nl

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BRCA1 and *BRCA2* mutation carriers are counseled on different risk-reducing strategies, either screening or prophylactic surgery. Breast cancer screening with clinical breast examination (CBE), mammography, and MRI is effective in detecting early-stage breast cancer in mutation carriers (4–8). For ovarian cancer, current screening protocols are ineffective in detecting early-stage ovarian cancer (9, 10). Risk-reducing salpingo-oophorectomy (RRSO) is effective in reducing the risk of ovarian cancer (HR, 0.21; 95% CI, 0.12–0.39) (11). After counseling, RRSO is chosen by almost all *BRCA1* and *BRCA2* mutation carriers at our centre.

Besides reducing ovarian cancer risk, RRSO has been shown to reduce breast cancer risk in mutation carriers. A large meta-analysis found risk reductions of 50% associated with RRSO in both *BRCA1* and *BRCA2* mutation carriers (*BRCA1*: HR, 0.47; 95% CI, 0.35–0.64; *BRCA2*: HR, 0.47; 95% CI, 0.26–0.84; ref. 11). The effect of RRSO on breast cancer risk was suggested to be stronger in women at premenopausal age, as greater risk reductions were found in women who had surgery before the age of 40 to 50 years (12, 13).

However, it has been suggested that the effect of RRSO differs between *BRCA1* and *BRCA2* mutation carriers (14, 15). In a study of Shah and colleagues (15), in 51 *BRCA1* and 41 *BRCA2* mutation carriers, 11 new breast cancers were found, all within *BRCA1* mutation carriers. The percentage of women with RRSO was equal in women who did and did not develop breast cancer (87% vs. 82%, $P = 0.754$; ref. 15).

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We aimed to study the incidence of breast cancer after RRSO at premenopausal age in *BRCA1* and *BRCA2* mutation carriers in the Northern Netherlands in a prospective cohort.

Materials and Methods

Study population

All women with 1 or 2 breasts *in situ*, who were 51 years old or younger (mean menopausal age in the Netherlands; ref. 16) at the time of RRSO, were consecutively selected from a prospective cohort of *BRCA1/2* mutation carriers who were enrolled in the surveillance program for hereditary breast and ovarian cancer at the University Medical Center Groningen (UMCG; Groningen, The Netherlands) from September 1995 until January 2011. Women with previous breast cancer were included, when breast cancer screening continued on the remaining breast tissue. Women in whom ovarian cancer was found on the RRSO specimen were not included. Before this study, we analyzed a previous version of this database (data up until 30 September, 2009) to determine the effectiveness of breast cancer screening after RRSO (17).

RRSO protocol

RRSO is advised from the age of 35 to 40 years in *BRCA1* mutation carriers and 40 to 45 years in *BRCA2* mutation carriers (18). However, patients are counseled individually, and actual timing of RRSO depends on personal circumstances such as previous breast cancer, family history of cancer, previous or planned pregnancies, and mental acceptance of this definitive procedure. The operative procedure is conducted by laparoscopy (19).

Breast cancer screening

Breast cancer screening in *BRCA1/2* mutation carriers was done according to the Dutch guidelines, with annual complete breast examination (CBE), and mammography and MRI alternating by 6 months since 2008 (18). Before 2008, CBE was conducted biannually and MRI was conducted in women participating in the MRISC trial (MRI screening for breast cancer in women with familiar or genetic predisposition, ref. 20).

Data collection

All *BRCA1/2* mutation carriers who visit our Family Cancer Clinic are consecutively included in a prospective cohort. If these women met our inclusion criteria, we retrospectively retrieved relevant data from the patient files in the hospital. Physician's letters, pathology reports, and imaging reports were used for data collection.

Information on the type of mutation, date of birth, date of RRSO, and ever-use of hormonal replacement therapy after RRSO was collected. For previous breast cancers, age of diagnosis and conducted surgical procedure (breast-conserving therapy or mastectomy) were recorded. For breast cancers diagnosed after RRSO, age at diagnosis and pathologic features were recorded: tumor type according to the WHO classification, tumor size in millimeters, tumor grade (Elston–Ellis modification of Bloom–Richardson grading system), receptor status [estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor], presence of ductal carcinoma *in situ* (DCIS), and presence of lymph node metastases. Patient data were entered into an SPSS database. Protection of the patient's identity was guaranteed by a patient-specific number. Those numbers were only retraceable to individual women when entered in the password-protected hospital database, which is only accessible for hospital employees who have a personal account. Complying with Dutch law, no further Institutional Review Board approval was needed.

Statistical analysis

To present the study population and characteristics of breast cancers discovered after RRSO, contingency tables were used. Breast cancers detected after RRSO could be prevalent, possibly prevalent or incident. Prevalent breast cancers were defined as breast cancers detected within 6 months after RRSO. Possibly prevalent breast cancers were defined as breast cancers detected more than 6 months after RRSO that we considered prevalent because the time after RRSO was shorter than the estimated growing time of the breast cancer. For all the invasive breast cancers diagnosed more than 6 months after RRSO, we estimated the duration of time a breast cancer had been growing and compared this with the time interval between RRSO and detection of breast cancer. To estimate this time, we used the formula for estimating tumor-doubling time in mutation carriers based on age at tumor diagnosis as presented by Tilanus-Linthorst and colleagues (21): $\log_2$ [doubling time (years)] $= -7.75 + 0.12$ age. On the basis of the tumor-doubling time, we estimated the time a tumor was growing from the theoretical size at baseline of 5 mm (which is the assumed detection threshold for invasive breast cancer on MRI; refs. 22, 23) to the size at detection. If this estimated time period was longer than the time period between RRSO and tumor detection, we considered a breast cancer possibly prevalent. Incident breast cancers were defined as breast cancers detected more than 6 months after RRSO and not possibly prevalent.

Duration of follow-up was calculated for each woman from RRSO to diagnosis of incident breast cancer, to prophylactic mastectomy, to one year after the last screening visit, or to January 1, 2011. The analyses were conducted using the SPAW software package, version 18.0 for Windows (SPSS).

Breast cancers expected

To estimate the number of women who develop incident breast cancer after RRSO based on womens' ages at RRSO and their ages during follow-up, we used the penetrance curves for breast cancer in mutation carriers in our centre as published by Van der Kolk and colleagues (3) and a 50% risk reduction for breast cancer expected after RRSO [*BRCA1/2*: HR, 0.49; (95% CI, 0.37–0.65); *BRCA1*: HR, 0.47; (95% CI, 0.35–0.64) and *BRCA2*: HR, 0.47 (95% CI 0.26–0.84); ref. 11].

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Results

Population characteristics

We analyzed the data of 162 women, 104 *BRCA1* mutation carriers and 58 *BRCA2* mutation carriers (Table 1). At the time of RRSO, median age was 41 years (range 30–51) for *BRCA1* mutation carriers and 42 years (range 33–51) for *BRCA2* mutation carriers ($P = 0.013$). At the time of RRSO, 25% of the *BRCA1* mutation carriers and 12% of the *BRCA2* mutation carriers had a history of breast cancer ($P = 0.066$). After RRSO, hormonal replacement therapy was prescribed to 47% (68/146) of the women, all without previous breast cancer. Total follow-up in this study was 6,389 months (532 women-years); 4,309 months (359 women-years), and 2,080 months (173 women-years) for *BRCA1* and *BRCA2* mutation carriers, respectively.

Breast cancers after RRSO

During the post-RRSO screening period, 18 breast cancers in 18 women were detected (34/1,000 women-years). Of these, 16 were found in *BRCA1* mutation carriers (45/1,000 women-years) and 2 in *BRCA2* mutation carriers (12/1,000 women-years).

Of the 18 breast cancers diagnosed after RRSO, 3 were found within 6 months after RRSO and were considered prevalent breast cancers. On the basis of tumor-doubling time calculations, we considered 2 breast cancers to be possibly prevalent (Table 2). Leaving out 3 prevalent breast cancers and 2 possibly prevalent breast cancers, there were at least 13 incident breast cancers (24/1,000 women-years) during the study period, 12 in *BRCA1* mutation carriers (33/1,000 women-years) and 1 in a *BRCA2* mutation carrier (6/1,000 women-years). Table 3 illustrates the number of women expected to develop breast cancer compared with the number observed. Table 4 illustrates the characteristics of women who did and did not develop incident breast cancer after RRSO.

Tumor characteristics

Of the 13 incident breast cancers detected after RRSO, 11 (86%) were invasive and 2 (15%) were DCIS (Table 5). In 4 of 11 (36%) invasive cancers, axillary lymph nodes were positive. Histologic grade was higher in breast cancers from *BRCA1* mutation carriers than from *BRCA2* mutation carriers (70% grade 3 vs. none, respectively). Of the 11 invasive breast cancers, 9 (82%) were ER, PR, and HER2 negative (triple negative), all in *BRCA1* mutation carriers.

Discussion

In a consecutive group of 104 *BRCA1* and 58 *BRCA2* mutation carriers with RRSO at premenopausal age, breast cancer screening at our Family Cancer Clinic revealed 18 breast cancers in 18 women during 532 women-years (34/1,000 women-years), of which, 13 were incident breast cancers (24/1,000 women-years). On the basis of breast

Table 1. Characteristics of the women at baseline ($N = 162$)

	BRCA1 ($N = 104$)	*BRCA2* ($N = 58$)	Total ($N = 162$)	Statistics
Age at RRSO in years				
Median (range)	40 (30–51)	42 (33–51)	41.0 (30–51)	$P = 0.013$[a]
≤40 years	50% (52/104)	28% (16/58)	42% (68/162)	$P = 0.006$[a]
Follow-up in months				
Total	4,309	2,080	6,389	
Median (range)	31 (3–228)	28 (2–159)	28 (2–228)	$P = 0.681$
Previous breast cancer				
No	75% (78/104)	88% (51/58)	80% (129/162)	$P = 0.066$
Yes unilateral	20% (21/104)	12% (7/58)	17% (28/162)	
Yes bilateral	5% (5/104)	-	3% (5/162)	
Age at onset of first breast cancer in years ($N = 33$)				
Median (range)	38 (29–49)	42 (32-50)	41.0 (29–50)	$P = 0.330$
Breast cancer therapy				
BCT unilateral	39% (10/26)	71% (5/7)	46% (15/33)	$P = 0.403$
Mast unilateral	42% (11/26)	29% (2/7)	39% (13/33)	
BCT bilateral	15% (4/26)	—	12% (4/33)	
BCT and Mast	4% (1/26)	—	3% (1/33)	
Hormonal replacement therapy use				
No	53% (49/92)	54% (29/54)	53% (78/146)	$P = 0.959$
Yes	47% (43/92)	46% (25/54)	47% (68/146)	

[a]$P < 0.05$ is significant. Mann–Whitney U test for continuous variables, Fisher exact test for proportions.

Abbreviations: BCT: Breast-conserving therapy; Mast, mastectomy; if noted as BCT and Mast, 1 breast is treated with BCT and 1 with Mast; after RRSO.

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Table 2. Estimated growing time and time to diagnosis in individual breast cancers after RRSO ($N = 15$)[a]

	Mutation	Age at detection of breast cancer	WHO tumor classification	Max. diameter (in mm)	Doubling time (in months)	Time to diagnosis (in months)	Estimated growing time (in months)
1	*BRCA1*	37	LC	7	1.2	54.8	1.8
2	*BRCA1*	38	DCIS	n.d.	n.d.	14.8	n.d.
3	*BRCA1*	45	IDC	25	2.4	27.4	19.1
4	*BRCA1*	45	IDC	14	2.4	12.6	10.6
5	*BRCA1*	43	IDC	3	2.0	7.2	-4.4
6	*BRCA2*	52	IDC	11	4.2	19.8	14.4
7	*BRCA1*	36	IDC	8	1.1	10.3	2.3
8	*BRCA1*	41	DCIS	13	1.7	12.4	n.d.
9	*BRCA1*	47	IDC	30	2.8	20.9	21.6[b]
10	*BRCA1*	55	IDC	16	5.4	228.4	27.2
11	*BRCA1*	42	IDC	9	1.8	42.5	4.7
12	*BRCA1*	53	IDC	11	4.6	48.3	15.7
13	*BRCA1*	52	GRCCC	11	4.2	95.5	14.4
14	*BRCA1*	41	IDC	20	1.7	6.7	10.2[b]
15	*BRCA1*	47	IDC	11	2.8	78.3	9.5

[a]Excluded were prevalent cancers found within 6 months of RRSO

[b]Possibly prevalent tumors based on tumor doubling time calculations.

Abbreviations: GRCCC, glycogen rich clear cell carcinoma; IDC, invasive ductal carcinoma; LC, lobular carcinoma; n.d, no data, tumor doubling time was not calculated for DCIS.

cancer incidence curves and a 50% risk reduction associated with RRSO, we expected to find 8 (range 6–10) incident breast cancers (15/1,000 women-years; refs. 3, 11). Several factors may have contributed to this difference in expected and observed breast cancer incidence after RRSO.

An important finding is that 12 incident breast cancers developed in *BRCA1* mutation carriers compared with 5 (range 3–6) expected. For *BRCA2* mutation carriers, 1 incident breast cancer developed compared with 3 (range 2–5) breast cancers expected. The risk reduction associated with RRSO might be smaller in *BRCA1* than in *BRCA2* mutation carriers. The same hypothesis was suggested by Shah and colleagues (15); they found 9 new tumors after RRSO in 45 *BRCA1* mutation carriers and none in 35 *BRCA2* mutation carriers. Kauff and colleagues (24) also showed a significant breast cancer risk reduction for *BRCA2* mutation

Table 3. Number of women with incident breast cancer expected versus observed

	Expected without RRSO[a]	Expected after RRSO[b]	Observed
All women			
($N = 162$, total follow-up 532 years)			
Number of women with incident breast cancer	16	8 (range 6–10)	13
In 1,000 women years	30	15	24
BRCA1 mutation			
($N = 104$, total follow-up 359 years)			
Number of women with incident breast cancer	10	5 (range 3–6)	12
In 1,000 women years	28	14	33
BRCA2 mutation			
($N = 58$, total follow-up 173 years)			
Number of women with incident breast cancer	6	3 (range 2–5)	1
In 1,000 women years	35	17	6

[a]Estimates based on the Van der Kolk penetrance curves (3).

[b]Risk reduction: 50% [*BRCA1/2:* HR, 0.49 (95% CI 0.37–0.65), *BRCA1*: HR, 0.47 (95% CI 0.35–0.63), and *BRCA2*: HR, 0.47 (95% CI 0.26–0.84; ref. 11].

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Table 4. Characteristics of women who did and did not develop incident breast cancer after RRSO

	Women with incident breast cancer ($n = 13$)	Women without incident breast cancer ($n = 149$)
Mutation		
BRCA1	92% (12/13)	62% (92/149)
BRCA2	8% (1/13)	38% (57/149)
Age at RRSO in years		
≤40 years	54% (7/13)	41% (61/149)
>40 years	46% (6/13)	59% (88/149)
Follow-up after RRSO in months		
Median (range)	28 (2–218)	27 (7–228)
Previous breast cancer		
No	69% (9/13)	77% (115/149)
Yes[a]	31% (4/13)	23% (34/149)
[b]Ever-use of hormonal replacement therapy		
No	62% (8/13)	51% (73/142)
Yes	38% (5/13)	49% (69/142)

[a]Prevalent and possibly prevalent cancers were considered previous breast cancer.
[b]HT: Hormonal replacement therapy after RRSO.

carriers but not for *BRCA1* mutation carriers [*BRCA1*: HR, 0.61 (95% CI, 0.30–122), *BRCA2*: HR 0.28 (95% CI, 0.08–0.92)] in a large prospective study with 190 *BRCA1* and 113 *BRCA2* mutation carriers at risk for breast cancer after RRSO.

One explanation for this difference is that the effect of RRSO might be less marked in *BRCA1* mutation carriers, because their breast cancers are often ER and PR negative (14, 24). Of the invasive breast cancers found in *BRCA1* mutation carriers in this study, 90% were ER and PR negative. Nevertheless, a protective effect of RRSO in *BRCA1* mutation carriers has been shown in several studies (12, 13).

Others suggested that RRSO might inhibit breast cancer growth in *BRCA1* mutation carriers at tumorigenesis: growth of ER and PR negative cells might be indirectly induced by paracrine signals from ER- and PR-positive cells that are influenced by estrogen and progesterone (15, 25). Thus, breast cancer risk reduction after RRSO may take longer to establish than the duration of follow-up in this study, which may be a second explanation why we saw more breast cancers than expected.

Another explanation for finding more breast cancers than expected may be the intensification of the breast cancer screening regime since 2008, when MRI screening for all *BRCA1/2* mutation carriers was introduced at our centre. Van der Kolks study contains information on breast cancer incidence up to March 2008. Before 2008, MRI screening was used in a small selection of women participating in the MRISC study. It is known that after introducing a new effective screening regimen, more breast tumors are found. Warner and colleagues found a higher incidence of breast cancer in the first 3 years after the introduction of MRI screening in *BRCA1/2* mutation carriers and an overall higher incidence of DCIS (26). This effect has also been shown in the general population after introduction of the population-based breast cancer screening with mammography (27, 28). This explanation is weakened by the fact that this effect was not seen in *BRCA2* mutation carriers.

Table 5. Characteristics of incident breast cancers detected after RRSO ($N = 13$)[a]

	N (%)
Mutation	
BRCA1	12/13 (92)
BRCA2	1/13 (8)
WHO tumor classification	
IDC	9/13 (69)
GRCCC	1/13 (8)
LC	1/13 (8)
DCIS	2/13 (15)
Tumor size[b]	
≤10 mm	4/12 (33)
10–20 mm	7/12 (58)
>20 mm	1/12 (8)
Histologic grade[c]	
Grade 1	1/11 (9)
Grade 2	3/11 (27)
Grade 3	7/11 (64)
ER status[c]	
Negative	9/11 (82)
Positive	2/11 (18)
PR status[c]	
Negative	9/11 (82)
Positive	2/11 (18)
HER2 status[c]	
Negative	10/11 (91)
Positive	1/11 (9)
DCIS	
Negative	7/13 (46)
Grade 1	—
Grade 2	1/6 (17)
Grade 3	5/6 (83)
Lymph node status[c]	
Negative	7/11 (64)
Positive	4/11 (36)

[a]Excluded were prevalent and possibly prevalent cancers
[b]Tumor size could not be measured in one DCIS case.
[c]Not determined for DCIS.
Abbreviations: GRCCC, glycogen rich clear cell carcinoma; IDC, invasive ductal carcinoma; LC, lobular carcinoma; WHO, World health organization.

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A fourth explanation might be that RRSO is chosen by women with especially high breast cancer risks. Although eventually RRSO is chosen by almost all mutation carriers at our centre, timing might be affected by family history and previous breast cancers. As can be seen in Table 4, of the women who developed breast cancer after RRSO, 54% were younger than 40 years and 31% had previous breast cancer, compared with 41% and 23% in the women who did not develop breast cancer.

A last explanation might be the use of hormonal replacement therapy after RRSO. In our study population, 47% of the women used hormonal replacement therapy after RRSO and this percentage was not higher in women with incident breast cancer. Although it has been shown that short-term use of hormonal replacement therapy does not negate the effect of RRSO (29) and one study found an inversed relation in hormonal replacement therapy use and breast cancer incidence in *BRCA1* mutation carriers (30), hormonal replacement therapy does increase the risk of new and recurrent breast cancer in women with previous breast cancer (31, 32). On the contrary, a higher mortality was seen in women with bilateral oophorectomy before the age of 45 who did not use hormonal replacement therapy, compared with those women who did (33). Theoretically, it is plausible that hormonal replacement therapy use after RRSO partially negates the risk-reducing effect of RRSO, but bias might be introduced if hormonal replacement therapy is more often prescribed to women with less breast cancer in their family, or if survival is shorter in women who do not use hormonal replacement therapy. Our study sample is too small and follow-up to short to draw conclusions on this issue. The effects of hormonal replacement therapy after RRSO on the long-term breast cancer risk and survival should be monitored carefully.

We aimed to study the incidence of breast cancer after RRSO at premenopausal age. The strength of this study is that we used an algorithm that incorporates an estimate of growing time to exclude the effect of prevalent breast cancer on the incidence of new breast cancers after RRSO. Small sample size and short follow-up limit the possibilities to identify risk factors for breast cancer after RRSO. Because menopausal status at RRSO was not known for all women, we chose to include all women with the age at RRSO of 51 years or younger, which can be a limitation. Although this is the mean age of menopause in the Netherlands, some of these women might have been postmenopausal at time of RRSO, either due to natural or chemotherapy-induced menopause. Furthermore, we estimated the amount of breast cancer after RRSO with breast cancer penetrance curves from our own centre. An ideal design would be a randomized controlled trial with a RRSO and a surveillance group. As surveillance is not effective and RRSO is chosen by almost all mutation carriers at our centre, this design would be unethical.

To conclude, the breast cancer incidence after premenopausal RRSO is still high, especially in *BRCA1* mutation carriers. We could not confirm the expected risk reduction as described by other authors. As a consequence, after RRSO, continued surveillance with mammography and MRI for breast cancer in *BRCA1* and *BRCA2* mutation carriers is warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: I.E. Fakkert, M.J.E. Mourits, J.C. Oosterwijk, G.H. de Bock

Development of methodology: I.E. Fakkert, M.J.E. Mourits, G.H. de Bock

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): I.E. Fakkert, M.J.E. Mourits, L. Jansen, K. Meijer, J.C. Oosterwijk, B. van der Vegt

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): I.E. Fakkert, L. Jansen, M.J.W. Greuter, G.H. de Bock

Writing, review, and/or revision of the manuscript: I.E. Fakkert, M.J.E. Mourits, L. Jansen, D.M. van der Kolk, K. Meijer, J.C. Oosterwijk, B. van der Vegt, M.J.W. Greuter

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): I.E. Fakkert, M.J.E. Mourits, G.H. de Bock

Study supervision: M.J.E. Mourits, M.J.W. Greuter, G.H. de Bock

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