**Uptake and efficacy of bilateral risk reducing surgery in unaffected female *BRCA1* and *BRCA2* carriers**

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**ABSTRACT**

**Background:** Women testing positive for *BRCA1/2* pathogenic variants have high lifetime risks of breast and ovarian cancer. The effectiveness of risk reducing surgery (RRS) has been demonstrated in numerous previous studies. We evaluated long-term uptake, timing and effectiveness of risk reducing mastectomy (RRM) and bilateral salpingo-oophorectomy (RRSO) in healthy *BRCA1/2* carriers.

**Methods:** Women were prospectively followed-up from positive genetic test (GT) result to censor date. Chi-squared testing compared categorical variables; Cox regression model estimated hazard ratios and 95%CI for breast/ovarian cancer cases associated with RRS, and impact on all-cause mortality; Kaplan-Meier curves estimated cumulative RRS uptake. The annual cancer incidence was estimated by women-years at risk.

**Results:** In total, 887 women were included in this analysis.Mean follow-up was 6.26 years (range=0.01-24.3; total=4685.4 women-years). RRS was performed in 512 women, 73 before GT. Overall RRM uptake was 57.9% and RRSO uptake was 78.6%. The median time from GT to RRM was 18.4 months, and from GT to RRSO–10.0 months. Annual breast cancer incidence in the study population was 1.28%. Relative breast cancer risk reduction (RRM vs non-RRM) was 94%. Risk reduction of ovarian cancer (RRSO vs non-RRSO) was 100%.

**Conclusion:** Over a 24-year period we observed an increasing number of women opting for RRS. We showed that the timing of RRS remains suboptimal, especially in women undergoing RRSO. Both RRM and RRSO showed a significant effect on relevant cancer risk reduction. However, there was no statistically significant RRSO protective effect on BC.

**Key words:** risk reducing surgery, RRM, RRSO, *BRCA1, BRCA2*, breast cancer

**Introduction**

It is well established that pathogenic variants (path\_variants) in *BRCA1* and *BRCA2* (*BRCA1/2*) genes are strongly associated with a high lifetime risk of developing breast (BC) and/or ovarian cancer (OC). Whilst the lifetime risk of breast and ovarian cancer in the general population is 10%-12.5% and 1.5%-2%, respectively, various studies have shown that path\_variants in the *BRCA1/2* genes confer cumulative lifetime risk for developing BC of 35%-87% and 15%-60% for developing OC (1–3). Therefore, substantial effort has been deployed into developing specific surveillance and risk reducing strategies worldwide. Current risk management options for women with a *BRCA1/2* path\_variant include regular surveillance, chemoprevention and risk reducing surgery (RRS): risk reducing mastectomy (RRM), risk reducing salpingo-oophorectomy (RRSO), or both (4). Whilst breast surveillance, including regular breast self-examination, clinical breast examination, mammography and breast MRI, is effective for early BC detection (5), it is not effective in cancer risk reduction. Moreover, there is no effective surveillance for early detection of OC that decreases mortality, as regular transvaginal ultrasound and CA125 estimation are ineffective (6, 7). On the other hand, there is considerable evidence that RRS reduces breast (8–10) and ovarian (8, 11–13) cancer risks in *BRCA1/2* path\_variant carriers, albeit with negative consequences related to the surgery itself (14). Consequently, RRSO is widely recommended for *BRCA1/2* path\_variant carriers to reduce their risks of developing ovarian cancer. In addition, RRM is discussed in depth and offered as an option for *BRCA1/2* path\_variant carriers, taking into account the efficacy of early detection of BC.

Risk-reducing surgeries in *BRCA1/2* carriers have been shown to be both clinically effective (15) and cost effective (16). A meta-analysis of four prospective trials involving 2635 patients on the efficacy of RRM in *BRCA1/2* path\_variant carriers demonstrated a significant risk reduction in BC incidence (HR=0.06, 95%CI=0.01–0.41, p=0.005) (17). The efficacy of RRSO was demonstrated by meta-analysis of three prospective trials involving 9192 *BRCA1/2* path\_variant carriers with a significant risk-reduction in ovarian/primary peritoneal cancer incidence after surgery (HR=0.19, 95%CI=0.13–0.27, p<0.00001) (13).

Filippo-Morton and colleagues found a steady and significant increase in the uptake of RRS since 2006, reported in the literature (18). The growing proportion of women undergoing RRM (18%-50%) and RRSO (27%-78%) is thought to be related to improved surgical and reconstructive options and techniques, better education of *BRCA1/2* path\_variant carriers, and greater availability of genetic testing (GT) and counselling commensurate with cancer diagnosis (18). Moreover, women choosing one RRS are significantly more likely to then choose to undergo the other (19).

A recent study of 87 cancer-free *BRCA1/2* positive women found a 59% uptake of RRS with a median follow-up time to RRS of 4.8 months (median time to RRM=7.5 months; median time to RRSO=4.7 months; total follow-up time=30.4 months) (18).

Women are opting for early bilateral RRSO as a combined measure to reduce both breast and ovarian cancer risk, since many studies containing retrospective data have demonstrated an association between RRSO and BC risk reduction (20–22, 8). However, a prospective study by Heemskerk-Gerritsen et al. found no evidence of a short term protective effect on breast cancer risk after RRSO in BRCA1/2 path\_variant carriers (23).

In the present study we summarize the uptake, timing and effectiveness of RRM and bilateral RRSO in a large cohort of women with high lifetime risks of breast and ovarian cancer who were unaffected by either cancer at positive GT for a *BRCA1/2* path\_variant in the northwest of England.

**Materials and Methods**

Healthy women (unaffected with breast/ovarian cancer) with a confirmed family history for a *BRCA1/2* path\_variant are offered a targeted test, testing only for their familial variant. In contrast, unaffected women with strong family histories of BC and/or OC are offered full *BRCA1/2* path\_variant screening if an affected family member is unavailable for testing and their *a priori* likelihood of a pathogenic *BRCA1/2* variant is ≥10%.

Women with a lifetime BC risk >25%, including *BRCA1/2* path\_variant carriers, have been offered a discussion about bilateral RRM since 1994. *BRCA1/2* path\_variant carriers are also encouraged to undertake RRSO once their family is complete, ideally before 40 years of age for *BRCA1* and 45 years for *BRCA2*.

We used a prospective cohort design to evaluate the long-term uptake of RRM and RRSO among *BRCA1/2* path\_variant carriers, tested at the Manchester Centre for Genomic Medicine during the period November 1994–March 2019. The individuals were identified from the prospectively maintained Manchester Genetic Medicine Database (North Manchester Research Ethics Committee (reference 08/H1006/77)).

**Study Population**

A total of 887 women, born between 1930-2002 (median=1971), with a positive presymptomatic test for *BRCA1/2* gene path\_variants were included in our study. Only women without previous BC/OC diagnoses were included. GT was performed as per institutional guidelines and all patients received post-testing counselling to review medical management options, including RRS. We have included all RRM surgeries, regardless of type and technique used. Women participating in the MRI programme who developed BC and had contralateral RRM were described, but not included in our calculations. The characteristics of our study population are described in Table-1.

**Data Collection**

We retrieved data on date of birth, parity, date of individual DNA test result, gene with a path\_variant (*BRCA1* or *BRCA2*), date of RRM/RRSO, date of BC and/or OC diagnosis and tumour characteristics, date and cause of death. Follow-up was started from GT or 25th birthday (whichever was later – we used 25 years as cancer incidence before this age is very low) and censored at date of BC or OC diagnosis, date of death (DOD), whichever was earliest for each cancer. Time-dependent analysis was used for calculations – women were treated as unexposed to surgery before RRM/RRSO and exposed after they had RRM/RRSO. Women who underwent RRS were censored for follow-up for the relevant cancer at date of surgery but were assessed prospectively for cancer incidence and death. All individuals without censorship were counted as unaffected on prevalence day 01/03/2019.

**Statistical Analysis**

The statistical analyses were performed using the IBM SPSS Statistics 20.0 package. A Chi-squared test was used to compare categorical variables. A Cox regression model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of BC and OC cases associated with RRS, and the impact of RRS on all-cause mortality. Kaplan-Meier curves were used to estimate cumulative percentage uptake of RRS. Patients were censored at time of RRM and RRSO. The uptake of RRS among different age groups was compared using log rank test and ORs with 95% CI. Women who underwent RRS prior to receiving *BRCA1/2* test were excluded from Kaplan-Meier analysis. The annual BC incidence (%) was estimated by calculating the proportion of total women-years for the entire study population and the number of BC cases in the follow-up period. All p-values were based on two-sided tests and were considered statistically significant if <0.05.

**RESULTS**

**Study Population**

In total, 887 women underwent predictive *BRCA1/2* testing and tested positive for the path\_variant: 442 (49.8%) for *BRCA1* and 445 (50.2%) for *BRCA2* (Table-1). The highest proportion of those testing positive was observed in 30-39 year-old women; this group was described as a reference group for further analysis. The mean age at individual DNA test result was 39.5 years (range=15.3-85.3 years). In total 70 were tested positive before age 25 and only 4 over age 75 years. There were unusual circumstances that justified the unusual step of testing a minor with parental consent.

There have been 21 deaths (12 *BRCA1* path\_variant carriers and 9 *BRCA2* path\_variant carriers) during the study period. Three of them had undergone RRM, 4 –RRSO, 3–both RRSs, and 11 had no RRS. Cancer localisation profile: 3 BC (one of whom had previously had RRSO), 3 OC (one of whom had previously had RRM) and 6 other types of cancer (oesophagus, pancreas, liver, rectum, renal and non-Hodgkin's lymphoma). The mean age at death was 53.3 years (range=37.7-81.7 years).

There were 73/887 (8.2%) women who had RRS prior to GT, of which 22 (2.5%) had RRM (14 *BRCA1* path\_variant carriers and 8 *BRCA2* path\_variant carriers) and 56 (6.3%) underwent RRSO (35 *BRCA1* path\_variant carriers and 21 *BRCA2* path\_variant carriers) prior to GT. Five women underwent both surgeries prior to GT, all *BRCA1* path\_variant carriers.

Twenty-three originally healthy women (2.6%) (10 *BRCA1* path\_variant carriers and 13 *BRCA2* path\_variant carriers) underwent contralateral RRM after a prospective BC diagnosis.

At RRM, 5/306 (1.6%) women (3 *BRCA1* and 2 *BRCA2* path\_variant carriers) were found to have an occult BC (Supplementary table-1) and 2/414 (0.5%) women (1 *BRCA1* and 1 *BRCA2* path\_variant carriers) had an occult OC diagnosed at RRSO.

**Follow-up time**

The mean period of time from positive predictive GT result or 25th birthday (whichever was later) to the censor date (date of death, BC, OC or last follow-up, whichever was earliest) was 6.26 years (range=0.01-24.3). This constituted 4685.4-women-years (when women are censored for both cancers; Note: in BC/OC incidence calculations women are censored only for the relevant cancer). If time from RRS to GT was added in women who underwent RRS at an early age and prior to GT (two women had their RRSO surgery in 1970s), the total follow-up time would increase to 5339.9-women-years. This was not included in the follow-up calculations as study participants were followed from the date of GT or 25th birthday.

**RRM**

In total, 306/887 (34.5%) *BRCA1/2* path\_variant carriers underwent RRM (mean age at GT=37.9 years; mean age at RRM=39.2 years). *BRCA1* path\_variant carriers underwent RRM more frequently than *BRCA2* path\_variant carriers (165 and 141, respectively; p=0.04). RRM was most commonly performed in women aged 33-34 years. 269/306 women (87.9%) underwent RRM before the age of 50 years, 29 of whom (9.5%) were <30 years of age.

The 5/306 women (1.6%) with occult cancer at RRM were not considered to have had RRM in the BC incidence calculations.

*BRCA1/2* path\_variant carriers who underwent RRM after GT result (284 women), had their surgery within 0.2-177.6 months (mean=28.4; median=18.4); only 20 of whom (7.0%) had their surgery within 6 months after GT.

Overall RRM uptake in patients followed-up from GT to the censor date was 57.9% (Supplementary Figure-1). The distribution of different age groups undertaking RRM is shown in Figure-1. Women aged 50-59 had a statistically significantly lower RRM uptake rate 2, 5 and 10 years after GT, compared to the reference age group (30-39 years at GT) (Table-2). RRM was associated with a statistically significantly decreased BC risk (HR=0.061; 95%CI=0.02-0.20, p<0.001), but not with overall mortality (HR=0.32; 95%CI=0.09-1.17, p=0.09).

**RRSO**

In total, 414/887 (46.7%) *BRCA1/2* path\_variant carriers underwent RRSO (mean age at GT=43.8 years; mean age at RRSO=44.6 years; range=25.5-76.7).

RRSO after GT result was performed in 357/887 *BRCA1/2* path\_variant carriers, who had their surgery within 0.4-237.6 months (mean=29.5; median=10.0); 105 (29.4%) of whom had their surgery within 6 months after GT. The overall RRSO uptake in patients followed-up from GT to censor date was 78.6% (Figure-2 and Supplementary Figure-2). In 57 women RRSO was performed before their GT results and were not included in the calculations, therefore the actual percent of women undergoing RRSO is significantly higher. *BRCA1* path\_variant carriers underwent RRSO more frequently than *BRCA2* path\_variant carriers (226 versus 188, respectively; p=0.01). The majority of women (77%) underwent RRSO <50 years of age with surgery most commonly performed in women aged 39-40 years. Only 2.2% of women underwent RRSO at age <30-years.

Women having GT result at <30 years were less likely to undergo RRSO 2, 5 and 10 years after the GT, compared to the reference group. The reference age group was less likely to have RRSO within 2 years after GT, compared to other age groups, except the <30 group (Table-3).

A small proportion (14/887 (1.6%) originally healthy women) underwent RRSO after BC diagnosis (14/60 (23.3%) BC patients in this study). RRSO alone was not associated with a reduced risk of BC (HR=0.77; 95%CI=0.45-1.34, p=0.36), neither when stratified by gene (*BRCA1* *versus* *BRCA2*) nor age: <50years *versus* >50years at RRSO (data not shown).

OC incidence was not reduced in those undergoing RRSO (HR=0.02; 95%CI=0.000-5.9, p=0.17), possibly due to an extremely small incidence rate (0 in RRSO group *versus* 8 OC in non-RRSO; 2/8 OC cases were occult, therefore calculated as non-RRSO). This is perhaps unsurprising as the pre-symptomatic testing population is very young and RRSO would have little impact on incidence <35years in *BRCA1* and <45years in *BRCA2.* On the other hand, there was a 100% risk reduction of OC in RRSO group, compared to non-RRSO.

RRSO alone was not associated with a reduced risk of overall mortality in the total study population (HR=0.44; 95%CI=0.1-1.4, p=0.16).

**RRM and RRSO**

For every year increase in age (range=25–85years), women were more likely to undergo RRSO (HR=1.04; 95%CI=1.03-1.05, p<0.0001) but slightly less likely to undergo RRM (HR=0.98; 95%CI=0.97-0.99, p<0.0001).

In total 208/887 (23.5%) women (mean age at GT=39.9 years) underwent both RRSs. Of these, 106 (61 *BRCA1* and 45 *BRCA2* path\_variant carriers) underwent RRSO before RRM, 98 underwent RRSO after RRM (54 *BRCA1* and 44 *BRCA2* path\_variant carriers), and 4 underwent RRM and RRSO simultaneously (all *BRCA1* path\_variant carriers).

**Breast cancer**

Over the study period, 60 new first primary BC cases were diagnosed in the total study population (6.8%). Mean age at BC was 46.4 years (range=29.4-79.3). Mean time from GT to BC diagnosis was 4.5 years (range=0.02-14.7). The annual incidence of BC among all women in our study population during the 4702.9 women-years was 1.28%. The detailed BC incidence by RRS and *BRCA1/2* status is described in Table-4 and Supplementary Table-2.

**BC and contralateral RRM in the MRI programme**

There were 30 healthy *BRCA1/2* carriers detected with BC on the MRI programme during the study period (seven had ductal carcinoma in situ (DCIS), 22 had invasive ductal carcinoma (IDC), and one had invasive lobular carcinoma (ILC). Contralateral RRM after the BC diagnosis was performed in 23/30 (76.7%) patients (mean age at GT=40.6 years; mean age at RRM=44.8 years). The mean follow-up time from BC to contralateral RRM was 8.3 months (range=0.1-73.7 months). Tumour size ranged 2-29mm (median=9mm, mean=10.1mm). Following MRI screening one Stage 2+ patient died after three years, in a mean of 6.3 years of follow up post MRI screening diagnosis in our study population.

**Breast cancers after RRM**

There were three BC cases (two CIS) following RRM (two previously reported (25)); one on the chest wall 6.6 years after RRM in a *BRCA1* path\_variant carrier, the second behind a retained nipple in a *BRCA2* path\_variant carrier 9.9 years after RRM, and the third on the skin flap in a *BRCA2* path\_variant carrier 7 years after RRM.

**Ovarian cancer**

Over the study period, 8 new first primary OC cases were diagnosed among 887 (0.9%) women in our cohort. Mean age at OC diagnosis was 48.2 years (range=37.7-62.7). Mean time from GT to OC diagnosis – 2.32 years (range=0.4-9.3). The annual incidence of OC in our study population during 5084.1-women-years follow-up was 0.16%. The incidence of OC among women who had RRSO was 0%, compared to 0.31% in women without RRSO. The detailed OC incidence by RRS and *BRCA1/2* status is described in Supplementary Table-3.

**DISCUSSION**

This study assessed the uptake, timing and relative risk reduction from RRM and RRSO in 887 path\_variant carriers unaffected at GT. Most breast and ovarian cancers associated with germline *BRCA1/2* variants are diagnosed at younger ages with most ovarian being high-grade and advanced-stage serous carcinomas (26). The risk and age at onset of BC or/and OC depends on the gene and path\_variant involved, with *BRCA1* carriers affected more often and at younger ages than *BRCA2* carriers, which is in keeping with our results.

The decision to undergo RRS is undoubtedly difficult, especially in cases with a complex family history of cancer or unsatisfactory outcomes from RRS in the family. Moreover, physical, mental, and emotional consequences, which may result from RRS, should be taken into consideration. This makes pre-surgery genetic counselling, including psychological assessment for RRM, an essential part of the decision-making process. A woman who opts to undergo RRS must be fully prepared for all potential consequences. Howard et al. reviewed 43 studies on factors influencing the decision-making on risk-reducing strategies for women at high-risk for BC/OC. Key factors included medical and physical, psychological and social context (27). Tong and colleagues found that younger age, more years of education, higher cancer-related distress, and higher perceived risk of BC were independently associated with RRM intentions, whereas older age, perceived path\_variant risk, and perceived risk for OC were independently associated with RRSO intentions (28). Galmor at el. reported that being married and having a first-degree relative with BC were positively associated with RRM, while having a previous benign breast biopsy was negatively associated with RRM in cancer-free Israeli *BRCA1/2* path\_variant carriers (29).

 Evans et al. showed that RRS in unaffected women at high risk of breast and ovarian cancer are risk, time and age dependent (30). Thus, women continue to opt for RRM and RRSO many months and even years after their positive *BRCA1/2* path\_variant gene test result (12). In this cohort, the mean time from GT to RRM was 28.4 months (range=0.2-177.6) and 29.5 months (range=0.4-237.6) to RRSO, respectively. We did not evaluate reasons of uptake and timing of RRS; however the influence on decision making has been reported in detail previously (12, 31, 18) and reasons in our cohort were similar. In particular there is an appropriate delay in RRSO in the <30 years age group and much of the delay in the 30-39 age group may be explained by waiting until being over 35 years old or completion of childbirth.

Skytte et al. reported a higher rate of uptake of RRSO within the first 6 months after GT at 27% compared to 11.8% (105/887 women) in our population. We also observed a much lower rate of uptake of RRM with only 20 women (2.25%) within the first 6 months after receiving the GT result, compared to 11%, reported by Skytte et al (32). This lower short-term uptake of both RRM and RRSO is likely to be related with healthcare management and the patient preparation process for major surgery. This is particularly true of RRM which requires a psychological assessment and at least two surgical appointments (33–35). In terms of health economics, undergoing RRSO should be recommended to *BRCA1/2* path\_variant carriers due to its favourable comparative cost-effectiveness (36), with RRM being discussed as an option.

In our cohort of 887 healthy *BRCA1/2* path\_variant carriers the overall uptake of RRM and RRSO was 57.9% and 78.6% respectively. It is important to note that in our study only women who had their RRS after receiving GT results were included in uptake calculations and therefore the actual uptake of both RRSs in our Centre is higher. Skytte et al. reported similar data from 306 healthy *BRCA1/2* path\_variant carriers with 10-year RRM uptake of 50% and RRSO uptake of 75% by time to event analysis (32). Earlier studies report lower than 50% uptake of either RRS (30, 37, 31, 38). These findings are consistent with recent literature, reporting growing numbers of RRS uptake in unaffected high-risk *BRCA1/2* path\_variant carrier population (18). Galmor et al. reported that only 9.6% of cancer-free *BRCA1/2* path\_variant carriers underwent RRM in their institution over a median follow-up time of 4.4 years. This is significantly lower than we report and could relate to cultural differences (29). In reality, as demonstrated in our study, around 50% of RRM are undertaken in the first 2 years and later uptake may be driven by false positive screens, new BC diagnoses in the family or BC related deaths (30). Indeed, there are women who choose to undertake surgery more than 15 years post GT. As with prior studies that have examined RRM and RRSO in a single institution (39, 40, 19), we found a higher uptake of RRSO than RRM. Beattie and colleagues suggested cultural factors, different counselling practices, body image effects of RRS, and the greater accuracy of screening tests for BC compared with those for OC as the main determinants for decision making regarding uptake and timing of RRS (19).

Although the uptake of RRSO is high, the surgeries are performed later than recommended (37). RRSO should be performed shortly after GT if women are aged >40 years, or around 35 years of age (later in *BRCA2*), to get the optimal effect on cancer risk reduction, while reported uptake is still on average up to 10 years later (32). We found 2 occult OC cases on RRSO in women aged 35-39 years that potentially could have been avoided if RRSO was performed earlier, as both women had delayed surgery post GT. The decision to delay surgery is mostly related to later childbearing and concerns about early menopause with its consequences (41) despite the possibility of hormonal replacement therapy.

Garcia et al. reported that with increasing age women are more likely to undergo RRSO (OR=1.04, 95%CI=1.01–1.07) and less likely to undergo RRM (OR=0.94, 95%CI=0.91–0.97) in keeping with our results (30).

We did not include women with VUSs (variants-of-uncertain-significance). Welsh et al. reported RRS rates among unaffected women with *BRCA1/2* VUS as high as 39% (42).

RRM in high-risk *BRCA1/2* path\_variant carriers is clearly effective and this is supported by our data. Xiao Li et al. analysed six non-overlapping studies with 2,555 participants and showed that BC after RRM corresponded with a RR of 0.11 (95% CI=0.04–0.3) (43).

BC risk reduction after RRSO remains uncertain and most probably this is due to bias in previous studies. Stjepanovic and colleagues showed that premenopausal RRSO significantly decreased BC risk in local *BRCA1* path\_variant carriers, while both *BRCA1/2* carriers benefitted in their systematic review of published work (44). Eisen et al.previouslyreported that the BC risk reduction with RRSO was greater in *BRCA1/2* path\_variant carriers who underwent surgery <50 years compared to >50 years at surgery (45). However, Heemskerk-Gerritsen et al. reported no effect on BC risk and Kotosopoulos et al. found no effect of RRSO on premenopausal BC risk in *BRCA1* gene path\_variant carriers (23, 24). Terry at al. found no association of RRSO on BC risk when RRSO was used as a time-dependent variable (46). Similarly, our data do not support a reduction in BC risk for healthy *BRCA1/2* path\_variant carriers undergoing RRSO .

Schrag et al. reported that benefit for *BRCA1/2* path\_variant carriers, received from RRS, declined with age with little gain obtained from RRS after the age of 60 years (47). There are only a few reports on long-term follow-up of *BRCA1/2* carriers. It is therefore important to continue following-up our patients to determine the potential incidence and mortality from later cancer occurrences. Some cancer risk persists after RRS. Consequently, additional preventive and screening strategies are required to improve outcomes in high-risk *BRCA1/2* carriers (11).

In conclusion, this is one of the largest prospective studies evaluating healthy *BRCA1/2* path\_variant carriers. Despite the strong evidence for RRS effectiveness and rising uptake of RRM and RRSO compared to previous studies, women at high risk still need more encouragement to opt for RRS, especially RRSO. The timing of RRS is still suboptimal. Although RRM reduces BC incidence, we did not find a protective effect of RRSO on BC risk, similar to that observed by other groups. Further studies with long term follow up are needed.

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Literature Cited

1. Nasim Mavaddat, Susan Peock, Debra Frost, Steve Ellis, Radka Platte, Elena Fineberg, D Gareth Evans, Louise Izatt, Rosalind A Eeles, Julian Adlard, Rosemarie Davidson, Diana Eccles, Trevor Cole, Jackie Cook, Carole Brewer, Marc Tischkowitz, Fiona Douglas, Shirley Hodgson, Lisa Walker, Mary E Porteous, Patrick J Morrison, Lucy E Side, M John Kennedy, Catherine Houghton, Alan Donaldson, Mark T Rogers, Huw Dorkins, Zosia Miedzybrodzka, Helen Gregory, Jacqueline Eason, Julian Barwell, Emma McCann, Alex Murray, Antonis C Antoniou, Douglas F Easton, EMBRACE. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst 2013; 105(11):812–22.

2. D Gareth Evans, Andrew Shenton, Emma Woodward, Fiona Lalloo, Anthony Howell, Eamonn R Maher. Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family. BMC Cancer 2008; 8:155.

3. Karoline B Kuchenbaecker, John L Hopper, Daniel R Barnes, Kelly-Anne Phillips, Thea M Mooij, Marie-José Roos-Blom, Sarah Jervis, Flora E van Leeuwen, Roger L Milne, Nadine Andrieu, David E Goldgar , Mary Beth Terry, Matti A Rookus, Douglas F Easton, Antonis C Antoniou, BRCA1 and BRCA2 Cohort Consortium; Lesley McGuffog, D Gareth Evans, Daniel Barrowdale, Debra Frost, Julian Adlard, Kai-Ren Ong, Louise Izatt, Marc Tischkowitz, Ros Eeles, Rosemarie Davidson, Shirley Hodgson, Steve Ellis, Catherine Nogues, Christine Lasset, Dominique Stoppa-Lyonnet, Jean-Pierre Fricker, Laurence Faivre, Pascaline Berthet, Maartje J Hooning, Lizet E van der Kolk, Carolien M Kets, Muriel A Adank, Esther M John, Wendy K Chung, Irene L Andrulis, Melissa Southey, Mary B Daly, Saundra S Buys, Ana Osorio, Christoph Engel, Karin Kast, Rita K Schmutzler, Trinidad Caldes, Anna Jakubowska, Jacques Simard, Michael L Friedlander, Sue-Anne McLachlan, Eva Machackova, Lenka Foretova, Yen Y Tan, Christian F Singer, Edith Olah, Anne-Marie Gerdes, Brita Arver, Håkan Olsson. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA 2017; 317(23):2402–16.

4. NCCN. NCCN Guidelines Version 1.2020Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic; 2019. Available from: URL: https://www.nccn.org/professionals/physician\_gls/pdf/genetics\_bop.pdf.

5. Victor R Grann, Priya R Patel, Judith S Jacobson, Ellen Warner, Daniel F Heitjan, Maxine Ashby-Thompson, Dawn L Hershman, Alfred I Neugut. Comparative effectiveness of screening and prevention strategies among BRCA1/2-affected mutation carriers. Breast Cancer Res Treat 2011; 125(3):837–47.

6. Usha Menon, Michelle Griffin, Aleksandra Gentry-Maharaj. Ovarian cancer screening--current status, future directions. Gynecol Oncol 2014; 132(2):490–5.

7. B B J Hermsen, R I Olivier, R H M Verheijen, M van Beurden, J A de Hullu, L F Massuger, C W Burger, C T Brekelmans, M J Mourits, G H de Bock, K N Gaarenstroom, H H van Boven, T M Mooij, M A Rookus. No efficacy of annual gynaecological screening in BRCA1/2 mutation carriers; an observational follow-up study. Br J Cancer 2007; 96(9):1335–42.

8. Susan M Domchek, Tara M Friebel, Christian F Singer, D Gareth Evans, Henry T Lynch, Claudine Isaacs, Judy E Garber, Susan L Neuhausen, Ellen Matloff, Rosalind Eeles, Gabriella Pichert, Laura Van t'veer, Nadine Tung, Jeffrey N Weitzel, Fergus J Couch, Wendy S Rubinstein, Patricia A Ganz, Mary B Daly, Olufunmilayo I Olopade, Gail Tomlinson, Joellen Schildkraut, Joanne L Blum, Timothy R Rebbeck. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 2010; 304(9):967–75.

9. Allison W Kurian, Bronislava M Sigal, Sylvia K Plevritis. Survival analysis of cancer risk reduction strategies for BRCA1/2 mutation carriers. J Clin Oncol 2010; 28(2):222–31.

10. Allison W Kurian 1 , Diego F Munoz, Peter Rust, Elizabeth A Schackmann, Michael Smith, Lauren Clarke, Meredith A Mills, Sylvia K Plevritis. Online tool to guide decisions for BRCA1/2 mutation carriers. J Clin Oncol 2012; 30(5):497–506.

11. Timothy R Rebbeck, Noah D Kauff, Susan M Domchek. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst 2009; 101(2):80–7.

12. R Manchanda, M Burnell, A Abdelraheim, M Johnson, A Sharma, E Benjamin, C Brunell, E Saridogan, S Gessler, D Oram, L Side, A N Rosenthal, I Jacobs, U Menon. Factors influencing uptake and timing of risk reducing salpingo-oophorectomy in women at risk of familial ovarian cancer: a competing risk time to event analysis. BJOG 2012; 119(5):527–36.

13. Claudia Marchetti, Francesca De Felice, Innocenza Palaia, Giorgia Perniola, Angela Musella, Daniela Musio, Ludovico Muzii, Vincenzo Tombolini, Pierluigi Benedetti Panici. Risk-reducing salpingo-oophorectomy: a meta-analysis on impact on ovarian cancer risk and all cause mortality in BRCA 1 and BRCA 2 mutation carriers. BMC Womens Health 2014; 14:150.

14. Gabriel A Del Corral, Ari M Wes, John P Fischer, Joseph M Serletti, Liza C Wu. Outcomes and Cost Analysis in High-Risk Patients Undergoing Simultaneous Free Flap Breast Reconstruction and Gynecologic Procedures. Ann Plast Surg 2015; 75(5):534–8.

15. M J Bermejo-Pérez, S Márquez-Calderón, A Llanos-Méndez. Effectiveness of preventive interventions in BRCA1/2 gene mutation carriers: a systematic review. Int J Cancer 2007; 121(2):225–31.

16. Kristin Anderson 1 , Judith S Jacobson, Daniel F Heitjan, Joshua Graff Zivin, Dawn Hershman, Alfred I Neugut, Victor R Grann. Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation. Ann Intern Med 2006; 144(6):397–406.

17. Francesca De Felice, Claudia Marchetti, Angela Musella, Innocenza Palaia, Giorgia Perniola, Daniela Musio, Ludovico Muzii, Vincenzo Tombolini, Pierluigi Benedetti Panici. Bilateral risk-reduction mastectomy in BRCA1 and BRCA2 mutation carriers: a meta-analysis. Ann Surg Oncol 2015; 22(9):2876–80.

18. Teresa Flippo-Morton, Kendall Walsh, Karinn Chambers, Lisa Amacker-North, Brook White, Terry Sarantou, Danielle M Boselli, Richard L White Jr. Surgical Decision Making in the BRCA-Positive Population: Institutional Experience and Comparison with Recent Literature. Breast J 2016; 22(1):35–44.

19. Mary S. Beattie, Beth Crawford, Feng Lin, Eric Vittinghoff, and John Ziegler. Uptake, time course, and predictors of risk-reducing surgeries in BRCA carriers. Genet Test Mol Biomarkers 2009; 13(1):51–6.

20. T R Rebbeck, A M Levin, A Eisen, C Snyder, P Watson, L Cannon-Albright, C Isaacs, O Olopade, J E Garber, A K Godwin, M B Daly, S A Narod, S L Neuhausen, H T Lynch, B L Weber. Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. J Natl Cancer Inst 1999; 91(17):1475–9.

21. Joan L Kramer, Isela A Velazquez, Bingshu E Chen, Philip S Rosenberg, Jeffery P Struewing, Mark H Greene. Prophylactic oophorectomy reduces breast cancer penetrance during prospective, long-term follow-up of BRCA1 mutation carriers. J Clin Oncol 2005; 23(34):8629–35.

22. Noah D Kauff, Susan M Domchek, Tara M Friebel, Mark E Robson, Johanna Lee, Judy E Garber, Claudine Isaacs, D Gareth Evans, Henry Lynch, Rosalind A Eeles, Susan L Neuhausen, Mary B Daly, Ellen Matloff, Joanne L Blum, Paul Sabbatini, Richard R Barakat, Clifford Hudis, Larry Norton, Kenneth Offit, Timothy R Rebbeck. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. J Clin Oncol 2008; 26(8):1331–7.

23. B A M Heemskerk-Gerritsen, C Seynaeve, C J van Asperen, M G E M Ausems, J M Collée, H C van Doorn, E B Gomez Garcia, C M Kets, F E van Leeuwen, H E J Meijers-Heijboer, M J E Mourits, T A M van Os, H F A Vasen, S Verhoef, M A Rookus, M J Hooning, Hereditary Breast and Ovarian Cancer Research Group Netherlands. Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. J Natl Cancer Inst 2015; 107(5).

24. Joanne Kotsopoulos, Tomasz Huzarski, Jacek Gronwald, Christian F Singer, Pal Moller, Henry T Lynch, Susan Armel, Beth Karlan, William D Foulkes, Susan L Neuhausen, Leigha Senter, Nadine Tung, Jeffrey N Weitzel, Andrea Eisen, Kelly Metcalfe, Charis Eng, Tuya Pal, Gareth Evans, Ping Sun, Jan Lubinski, Steven A Narod, Hereditary Breast Cancer Clinical Study Group. Bilateral Oophorectomy and Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers. J Natl Cancer Inst 2017; 109(1).

25. D Gareth Evans, Elaine Harkness, Fiona Lalloo, Anthony Howell. Long-term prospective clinical follow-up after BRCA1/2 presymptomatic testing: BRCA2 risks higher than in adjusted retrospective studies. J Med Genet 2014; 51(9):573–80.

26. Mohamed Salhab, Selina Bismohun, Kefah Mokbel. Risk-reducing strategies for women carrying BRCA1/2 mutations with a focus on prophylactic surgery. BMC Womens Health 2010; 10:28.

27. A Fuchsia Howard, Lynda G Balneaves, Joan L Bottorff. Women's decision making about risk-reducing strategies in the context of hereditary breast and ovarian cancer: a systematic review. J Genet Couns 2009; 18(6):578–97.

28. Angie Tong, Scott Kelly, Rachel Nusbaum, Kristi Graves, Beth N Peshkin, Heiddis B Valdimarsdottir, Marie Wood, Wendy McKinnon, Judy Garber, Shelley R McCormick, Lina Jandorf, Marc D Schwartz. Intentions for risk-reducing surgery among high-risk women referred for BRCA1/BRCA2 genetic counseling. Psychooncology 2015; 24(1):33–9.

29. Lee Galmor, Rinat Bernstein-Molho, Miri Sklair-Levy, Dana Madoursky-Feldman, Dov Zippel, Yael Laitman, Eitan Friedman. Time trends in uptake rates of risk-reducing mastectomy in Israeli asymptomatic BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat 2020.

30. D Gareth R Evans, Fiona Lalloo, Linda Ashcroft, Andrew Shenton, Tara Clancy, Andrew D Baildam, Anne Brain, Penelope Hopwood, Anthony Howell. Uptake of Risk-Reducing Surgery in Unaffected Women at High Risk of Breast and Ovarian Cancer Is Risk, Age, and Time Dependent. Cancer Epidemiology Biomarkers & Prevention 2009; 18(8):2318–24.

31. Christine Garcia, Jacqueline Wendt, Liisa Lyon, Jennifer Jones, Ramey D Littell, Mary Anne Armstrong, Tina Raine-Bennett, C Bethan Powell. Risk management options elected by women after testing positive for a BRCA mutation. Gynecol Oncol 2014; 132(2):428–33.

32. A-B Skytte, A-M Gerdes, M K Andersen, L Sunde, K Brøndum-Nielsen, M Waldstrøm, S Kølvraa, D Crüger. Risk-reducing mastectomy and salpingo-oophorectomy in unaffected BRCA mutation carriers: uptake and timing. Clin Genet 2010; 77(4):342–9.

33. NICE guideline CG164: Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer; 2019. Available from: URL: https://www.nice.org.uk/Guidance/CG164.

34. F Lalloo, A Baildam, A Brain, P Hopwood, D G Evans, A Howell. A protocol for preventative mastectomy in women with an increased lifetime risk of breast cancer. Eur J Surg Oncol 2000; 26(7):711–3.

35. A. Mcintosh, C. Shaw, G. Evans, N. Turnbull, N. Bahar, M. Barclay, D. Easton, Jon Emery, J. Gray, J. Halpin, P. Hopwood, J. Mckay, C. Sheppard, M. Sibbering, W. Watson, A. Wailoo, A. Hutchinson, NCCPC. Clinical Guidelines and Evidence Report for The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care; 2004 (updated 2006 and 2013).

36. Dirk Müller, Marion Danner, Kerstin Rhiem, Björn Stollenwerk, Christoph Engel, Linda Rasche, Lisa Borsi, Rita Schmutzler, Stephanie Stock. Cost-effectiveness of different strategies to prevent breast and ovarian cancer in German women with a BRCA 1 or 2 mutation. Eur J Health Econ 2018; 19(3):341–53.

37. Xinglei Chai, Tara M. Friebel, Christian F. Singer, D. Gareth Evans, Henry T. Lynch, Claudine Isaacs, Judy E. Garber, Susan L. Neuhausen, Ellen Matloff, Rosalind Eeles, Nadine Tung, Jeffrey N. Weitzel, Fergus J. Couch, Peter J. Hulick, Patricia A. Ganz, Mary B. Daly, Olufunmilayo I. Olopade, Gail Tomlinson, Joanne L. Blum, Susan M. Domchek, Jinbo Chen, and Timothy R. Rebecck. Use of risk-reducing surgeries in a prospective cohort of 1,499 BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat 2014; 148(2):397–406.

38. Long J, Evans TG, Bailey D, Lewis MH, Gower-Thomas K, Murray A. Uptake of risk-reducing surgery in BRCA gene carriers in Wales, UK. Breast J 2018; 24(4):580–5.

39. Jeffrey R Botkin, Ken R Smith, Robert T Croyle, Bonnie J Baty, Jean E Wylie, Debra Dutson, Anna Chan, Heidi A Hamann, Caryn Lerman, Jamie McDonald, Vickie Venne, John H Ward, Elaine Lyon. Genetic testing for a BRCA1 mutation: Prophylactic surgery and screening behavior in women 2 years post testing. Am. J. Med. Genet. 2003; 118A(3):201–9.

40. Kram V, Peretz T, Sagi M. Acceptance of preventive surgeries by Israeli women who had undergone BRCA testing. Fam Cancer 2006; 5(4):327–35.

41. Martha Hickey, Ines Rio, Alison Trainer, Jennifer L Marino, C David Wrede, Michelle Peate. Exploring factors that impact uptake of risk-reducing bilateral salpingo-oophorectomy (RRBSO) in high-risk women. Menopause 2020; 27(1):26–32.

42. Jessemae L Welsh, Tanya L Hoskin, Courtney N Day, Abigail S Thomas, Jodie A Cogswell, Fergus J Couch, Judy C Boughey. Clinical Decision-Making in Patients with Variant of Uncertain Significance in BRCA1 or BRCA2 Genes. Ann Surg Oncol 2017; 24(10):3067–72.

43. Xiao Li, Ran You, Xinwei Wang, Congxin Liu, Zicheng Xu, Jin Zhou, Bin Yu, Ting Xu, Hongzhou Cai, Qing Zou. Effectiveness of Prophylactic Surgeries in BRCA1 or BRCA2 Mutation Carriers: A Meta-analysis and Systematic Review. Clin Cancer Res 2016; 22(15):3971–81.

44. Neda Stjepanovic, Guillermo Villacampa, Kevin T. Nead, Sara Torres-Esquius, Guadalupe G. Melis, Katherine L. Nathanson, Alexandre Teule, Joan Brunet, Teresa R y Cajal, Gemma Llort, Rodrigo Dienstmann, Montserrat Rue, Susan M. Domchek, Judith Balmana . Association of premenopausal risk-reducing salpingo-oophorectomy with breast cancer risk in BRCA1/2 mutation carriers: Maximising bias-reduction. Eur J Cancer 2020; 132:53–60.

45. Andrea Eisen, Jan Lubinski, Jan Klijn, Pal Moller, Henry T Lynch, Kenneth Offit, Barbara Weber, Tim Rebbeck, Susan L Neuhausen, Parviz Ghadirian, William D Foulkes, Ruth Gershoni-Baruch, Eitan Friedman, Gadi Rennert, Teresa Wagner, Claudine Isaacs, Charmaine Kim-Sing, Peter Ainsworth, Ping Sun, Steven A Narod. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. J Clin Oncol 2005; 23(30):7491–6.

46. Mary Beth Terry, Mary B. Daly, Kelly Anne Phillips, Xinran Ma, Nur Zeinomar, Nicole Leoce, Gillian S. Dite, Robert J. MacInnis, Wendy K. Chung, Julia A. Knight, Melissa C. Southey, Roger L. Milne, David Goldgar, Graham G. Giles, Prue C. Weideman, Gord Glendon, kConFab Investigators, Richard Buchsbaum, Irene L. Andrulis, Esther M. John, Saundra S. Buys, John L. Hopper Risk-Reducing Oophorectomy and Breast Cancer Risk Across the Spectrum of Familial Risk. J Natl Cancer Inst 2019; 111(3):331–4.

47. D Schrag, K M Kuntz, J E Garber, J C Weeks. Decision analysis--effects of prophylactic mastectomy and oophorectomy on life expectancy among women with BRCA1 or BRCA2 mutations. N Engl J Med 1997; 336(20):1465–71.

Table 1. Characteristics of the study population

|  |  |
| --- | --- |
| Characteristics | Number of pathogenic variant carriers |
| *BRCA1* | *BRCA2* | Total |
| All study population | 442 | 445 | 887 |
| Age at individual DNA test result (years) |
| <30 | 111 | 88 | 199 |
| 30-39 | 167 | 146 | 313 |
| 40-49 | 96 | 117 | 213 |
| 50-59 | 47 | 55 | 102 |
| ≥60 | 21 | 39 | 60 |
| Mean | 38.0 | 41.0 | 39.5 |
| Median | 36.8 | 39.3 | 37.6 |
| Range | 15.3-85.3 | 19.1-84.0 | 15.3-85.3 |
| Parity status (No. of women) |
| Nulliparous | 124 | 103 | 227 |
| Parous | 304 | 307 | 611 |
| Unknown | 14 | 35 | 49 |
| Mean No. of children | 1.5 | 1.7 | 1.6 |
| Median No. of children | 2 | 2 | 2 |
| Range No. of children | 0-9 | 0-12 | 0-12 |
| Deaths (No. of women) | 12 | 9 | 21 |
| Mean age at death | 54.6 | 51.6 | 53.3 |
| Median age at death | 53.7 | 53.0 | 53.0 |
| Age range at death | 37.9-81.7 | 37.7-69.8 | 37.7-81.7 |
| RRM (total) | 165 | 141 | 306 |
| Mean age at RRM | 38.3 | 41.3 | 39.7 |
| Median age at RRM | 36.5 | 39.9 | 38.7 |
| Age range at RRM | 22.5-65.3 | 20.9-68.5 | 20.9-68.5 |
| Mean time (months) from GT to RRM (RRM before GT not included) | 29.8 | 26.8 | 28.4 |
| Median time (months) from GT to RRM (RRM before GT not included) | 18.1 | 19.3 | 18.4 |
| Time range (months) from GT to RRM (RRM before GT not included) | 0.2-177.6 | 1.6-114.5 | 0.2-177.6 |
| RRSO (total) | 226 | 188 | 414 |
| Mean age at RRSO | 43.1 | 46.3 | 44.6 |
| Median age at RRSO | 41.8 | 44.7 | 43.2 |
| Age range at RRSO | 25.5-76.7 | 30.5-73.6 | 25.5-76.7 |
| Mean time (months) from GT to RRSO (RRSO before GT not included) | 29.7 | 29.3 | 29.5 |
| Median time (months) from GT to RRSO (RRSO before GT not included) | 12.0 | 9.5 | 10.0 |
| Time range (months) from GT to RRSO (RRSO before GT not included) | 1.3-237.6 | 0.4-163.6 | 0.4-237.6 |

Acronyms: RRM – risk reducing mastectomy, RRSO – risk reducing salpingoophorectomy, GT – genetic test.

Table 2. RRM uptake (years after genetic test) compared to the reference age group (30-39 years at genetic test) (Actual and ORs with 95%CI).

|  |  |
| --- | --- |
| Age group (age at genetic test) | RRM uptake (years after genetic test) compared to reference age group (30-39 years at genetic test); OR, (95% CI).  |
| 2 years | 5 years | 10 years |
| Actual RRM uptake |
| All age groups | 29.2% | 43.7% | 54.1% |
| <30 | 26.7% | 45.1% | 61.3% |
| 30-39 (Reference) | 37.2% | 55.4% | 64.2% |
| 40-49 | 29.4% | 41.7% | 49.8% |
| 50-59 | 18.0% | 22.5% | 32.8% |
| >60 | 12.4% | 12.4% | 12.4% |
| Odds ratios (95% CIs) |
| <30 | 0.61 (0.37-0.99)  | 0.73 (0.43-1.22)  | 0.97 (0.45-2.1)  |
| 30-39 (Reference) | 1.00  | 1.00  | 1.00  |
| 40-49 | 0.75 (0.48-1.18)  | 0.62 (0.38-1.01)  | 0.62 (0.32-1.22)  |
| 50-59 | 0.37 (0.19-0.72)  | 0.28 (0.14-0.56)  | 0.38 (0.15-0.95)  |
| >60 | 0.33 (0.12-0.91)  | 0.39 (0.13-1.17)  | 0.36 (0.08-1.55)  |

Acronyms: RRM – risk reducing mastectomy, OR – odds ratio, CI – coincidence interval.

Table 3. RRSO uptake (years after genetic test) compared to the reference age group (30-39 years at genetic test) (Actual and ORs with 95%CI).

|  |  |
| --- | --- |
| Age group (age at genetic test) | RRSO uptake (years after genetic test) compared to reference age group (30-39 years at genetic test); OR, (95% CI).  |
| 2 years | 5 years | 10 years |
| Actual RRSO uptake |
| All age groups | 37.3% | 49.9% | 63.7% |
| <30 | 1.4% | 4.3% | 24.8% |
| 30-39 (Reference) | 34.7% | 53.7% | 71.8% |
| 40-49 | 61.0% | 71.7% | 78.4% |
| 50-59 | 61.8% | 74.9% | 77.7% |
| >60 | 47.6% | 55.1% | 55.1% |
| Odds ratios (95% CIs) |
| <30 | 0.03 (0.01-0.12)  | 0.04 (0.02-0.11)  | 0.11 (0.05-0.22)  |
| 30-39 | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| 40-49 | 3.03 (2.0-4.65)  | 2.20 (1.36-3.58)  | 1.64 (0.79-3.37)  |
| 50-59 | 3.36 (1.89-5.99)  | 2.8 (1.39-5.6)  | 1.32 (0.53-3.26)  |
| >60 | 3.01 (1.21-7.51)  | 3.23 (0.9-11.55)  | 2.61 (0.33-20.76)  |

Acronyms: RRSO – risk reducing salpingoophorectomy, OR – odds ratio, CI – coincidence interval.

Table 4. Breast cancer incidence during the follow-up (person-years) stratified by *BRCA1/2* pathogenic variant status, BC status and RRM status

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **Number of cases** | **Person-years of follow-up** | **Number of breast cancer cases** | **Breast cancer annual incidence (%)** |
| ***BRCA1*** | ***BRCA2*** | **Total** | ***BRCA1*** | ***BRCA2*** | **Total** | ***BRCA1*** | ***BRCA2*** | **Total** | ***BRCA1*** | ***BRCA2*** | **Total** |
| All study population | 541 | 546 | 1087 | 2505.6 | 2197.4 | 4702.9 | 31 | 29 | 60 | 1.24 | 1.32 | 1.28 |
| Post RRM | 147 | 122 | 269 | 1234.7 | 941.1 | 2175.8 | 1 | 2 | 3 | 0.08 | 0.21 | 0.14 |
| No RRM | 394 | 424 | 818 | 1270.9 | 1256.2 | 2527.2 | 30 | 27 | 57\*  | 2.36 | 2.15 | 2.26 |

Acronyms: RRM – risk reducing mastectomy, BC – breast cancer. \*Including 14 occult and 23 with contralateral RRM.