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REVIEW ARTICLE – BREAST ONCOLOGY

Bilateral Risk-Reduction Mastectomy in BRCA1 and BRCA2 Mutation Carriers: A Meta-analysis

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ABSTRACT

Background. Women with BRCA1 and BRCA2 mutations have substantially elevated risk of developing breast cancer. The aim of this study was to clarify the role of bilateral risk-reducing mastectomy (BRRM) in reducing breast cancer risk in women carriers of BRCA1 and BRCA2 mutations.

Methods. The Pubmed, MEDLINE and Scopus databases were searched to retrieve articles written in the English language. Two investigators independently extracted the characteristics and results of the selected studies. Only prospective trials with available absolute numbers of breast cancer and death events were included. Pooled hazard ratio (HR) with 95 % confidence interval (CI) was calculated using fixed or random effects model.

Results. Meta-analysis of four prospective studies, including 2635 patients, demonstrated a significant risk reduction of breast cancer incidence in BRCA1 and BRCA2 mutation carriers receiving BRRM (HR 0.07; 95 % CI 0.01–0.44; $p = 0.004$). Among patients without previous risk-reducing salpingo-oophorectomy, a significant benefit was similarly recorded (HR 0.06; 95 % CI 0.01–0.41; $p = 0.005$).

Conclusions. Performing BRRM may lead to highly significant risk reduction of breast cancer in BRCA1 and BRCA2 mutation carriers. These data allow clinicians to discuss more in-depth with patients all the available options in order to design better management strategies.

It is now well-established that mutations in BRCA1 and BRCA2 confer 80 % lifetime risk for breast cancer (BC).[1] Recent advances in understanding the genetics of BC have provided enormous opportunities for the development of risk-reduction therapies in BRCA1 and BRCA2 mutation carriers.[2] Risk-reducing salpingo-oophorectomy (RRSO) is recommended to prevent ovarian cancer/fallopian tube cancer (OC) in these women by 40 years of age or after completion of childbearing.[3] There are several options to reduce BC risk, including regular surveillance with magnetic resonance imaging and mammography, chemoprevention, and bilateral risk-reducing mastectomy (BRRM).[2,4] Several authors have supported the use of BRRM to significantly reduce the risk of BC.[5–7] Nonetheless, data are non-homogeneous and are only derived from retrospective or prospective studies in the absence of randomized trials that would probably be unethical to perform. Finally, some authors have underlined the lack of survival advantage, at the cost of a highly aggressive procedure with potential psychosocial effects, including negative impact on the body's perception and loss of sexual organ.[8]

The aim of this meta-analysis was to report the BC risk-reduction estimates following BRRM in BRCA1 and BRCA2 mutation carriers, and to help clinicians and women in making evidence-based decisions.

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METHODS

Data Extraction and Trials Selection

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement was followed to perform the meta-analysis, which included trials without any restrictions on publication date. The last search was carried out on October 2014. The title and abstract fields of the electronic databases Pubmed, MEDLINE, and Scopus were searched using the terms 'prophylactic bilateral' or 'risk-reduction', 'mastectomy' 'BRCA1', and 'BRCA2'. Trials that compared preventive mastectomy with follow-up policy in women with a mutation in BRCA1 and/or BRCA2 genes were eligible. Prospective clinical trials, written in English, were included, and reference lists of previously published reviews and meta-analyses were explored. Review articles, case reports, commentaries, and letters were not included, and conference abstracts were not considered because of the insufficient data provided by the authors.

Two independent reviewers (FDF and CM) selected the identified studies based on the title and abstract. If the topic of the study could not be ascertained from its title or abstract, the full-text version was retrieved for evaluation. Disagreement was resolved by discussion or consensus or with a third party (LM).

Trials were eligible if patients had a proven mutation status and were cancer-free at study entry.

In closer evaluation of potentially eligible articles, and because large collaborations are needed to study BRCA1 and BRCA2 carriers, many of the studies had overlapping centers. When two articles appeared to report results with overlapping data, only the data representing the most recent publication or with the larger sample size were included in the meta-analysis. Although every attempt was made to eliminate redundancy in the data represented in our meta-analysis, we cannot rule out the possibility that a few individuals participated in more than one study. The following information was obtained from all included studies: first author's surname, publication year, sample size of cases and controls, treatment, duration of follow-up, and detection rate.

Endpoints

The primary endpoint was the risk of developing BC in BRCA1 and BRCA2 mutation carriers.

A subgroup analysis—in patients with or without previous risk-reduction salpingo-oophorectomy (RRSO)—was performed; this data analysis related to two studies (1758 patients).

Statistical Analysis

Cancer risk was stratified by studies and hazard ratio (HR), and the pooled HR was calculated using a fixed- or random-effects model. Forest plots were used for graphical representation of each study and pooled analysis. The size of each box represents the weight that the corresponding study exerts in the meta-analysis; confidence intervals (CIs) for each study are displayed as a horizontal line through the box. The pooled HR is symbolized by a solid diamond at the bottom of the forest plot, and the width of the square represents the 95 % CI of the HR. HR, variance, 95 % CI, log [risk ratio] and standard error for each study were extracted or calculated, based on the published studies, according to the methods described by Tierney et al. in 2007.[9] A significant two-way p value for comparison was defined as $p < 0.05$. Statistical heterogeneity among studies was examined using both the Cochrane Q statistic (significant at $p < 0.1$) and the I^2 value (significant heterogeneity if >50 %).[10] Statistical analysis was performed using Review Manager 5.0 (http://www.cochrane.org). Publication bias was examined using analyses described by Egger et al.[11] and Begg and Mazumdar.[12]

RESULTS

The literature search identified a total of 210 potentially relevant articles. Articles were excluded because the subject matter was not related to the study ($n = 123$) or the article was not published in English ($n = 15$) or was a review ($n = 61$). Of 11 applicable clinical studies, seven were eliminated due to different endpoint analysis.

At the end of the review process, we included results reported from four studies, with a total of 2635 patients, including 631 (23.95 %) who underwent BRRM and 2004 (76.05 %) who received regular surveillance.[5–8] Table 1 illustrates our opinion regarding each item of bias risk for the included studies; the vast majority of items were 'low risk' (according to the Cochrane handbook, version 5.1.0), suggesting a high standard of studies.[13] A flowchart of the meta-analysis process is shown in Fig. 1.

Bilateral Risk-Reduction Mastectomy and Breast Cancer Risk

In all published studies, the BRRM consistently reduced BC risk compared with control patients. The summary BC risk after BRRM, expressed as HR, was 0.07 (95 % CI 0.01–0.44; $p = 0.004$; $I^2 = 59$ %) (Fig. 2).

TABLE 1 Risk of bias for each study

Type of bias	Study			
	Heemskerk-Gerritsen et al.[5]	Skytte et al.[8]	Meijers-Heijboer et al.[6]	Domchek et al.[7]
Selection bias				
Sequence generation	Low risk	Unclear risk	Unclear risk	Unclear risk
Detection bias				
Blinding of outcome assessment	Low risk	Low risk	Low risk	Low risk
Attrition bias				
Incomplete outcome data	Low risk	Low risk	Low risk	Low risk
Reporting bias				
Selective reporting	Low risk	Low risk	Low risk	Low risk

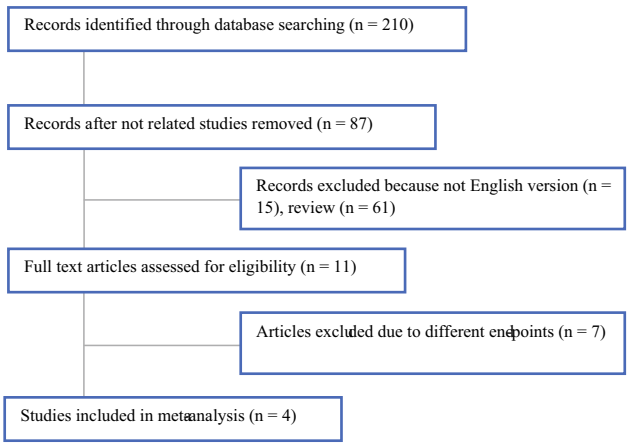

FIG. 1 Meta-analysis process

Risk-Reducing Salpingo-Oophorectomy Subgroup Analysis

The following analysis related to two studies including 1758 patients (1027 submitted to RSO) with a mean follow-up of 3 years.

Among patients without previous RRSO, a significant benefit was recorded (HR 0.06; 95 % CI 0.01–0.41; $p = 0{\cdot}005$) (Fig. 3). Among patients who received both RRSO and BRRM, the benefit was also confirmed (HR 0.11; 95 % CI 0.01–0.86; $p = 0{\cdot}03$) (Fig. 4). There was no significant heterogeneity in the subgroup analysis.

DISCUSSION

BRCA1 and BRCA2 mutation carriers are exposed to a 65–85 % lifetime risk of BC and 25–65 % risk of OC. Within this framework, risk-reducing surgery is one of the most effective options to decrease the risk of developing cancer.[2] The effectiveness of BRRM in reducing the risk of BC has been suggested by several authors, showing a protection against BC of at least 90 %.[14] On the other hand, other authors have claimed that the risk of BC is not completely eliminated after prophylactic surgery due to the probable residual of mammary-gland tissue.[8] Furthermore, randomized data regarding survival after BRRM in healthy BRCA1 and BRCA2 mutation carriers are not yet available.

Furthermore, RRSO seems to ensure an 80 % reduction in OC and a 46 and 56 % decrease in BC incidence and BC-specific mortality, respectively.[15–17] This probably explains why RRSO is generally considered as a preference strategy, more so than BRRM.

This meta-analysis was initially performed to confirm the success or failure of BRRM in preventing BC in all

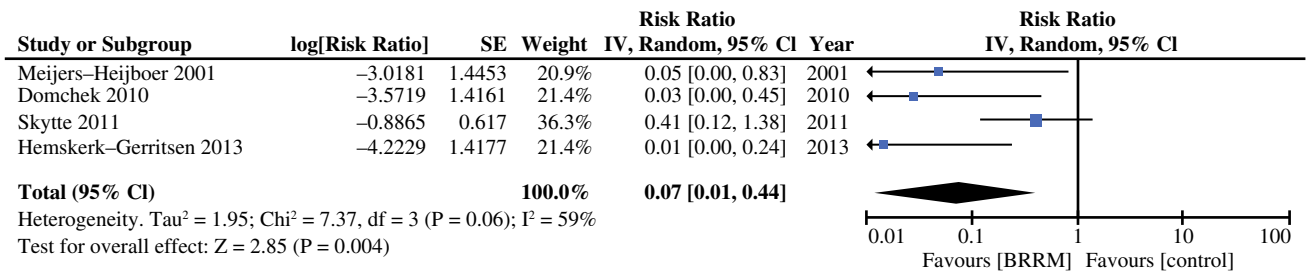

FIG. 2 Relative risk estimates for risk reduction of breast cancer associated with BRRM in the overall population of BRCA1 and BRCA2 mutation carriers. *BRRM* bilateral risk-reducing mastectomy, *CI* confidence interval, *df* degrees of freedom, *IV* inverse variance, *SE* standard error

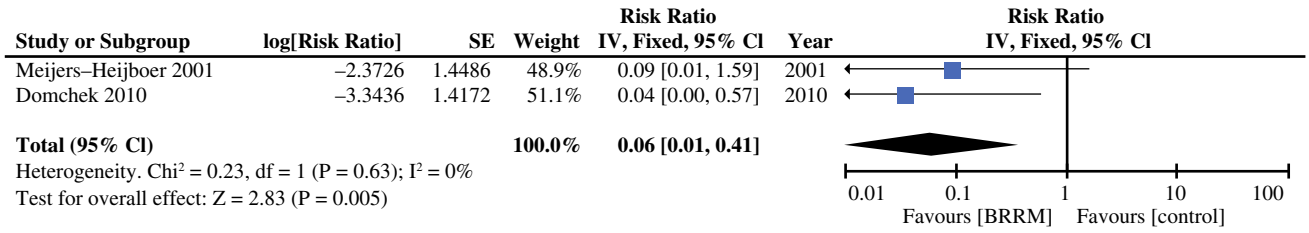

FIG. 3 Relative risk estimates for risk reduction of breast cancer associated with BRRM in BRCA1 and BRCA2 mutation carriers, without risk-reducing salpingo-oophorectomy. *BRRM* bilateral risk-reducing mastectomy, *CI* confidence interval, *df* degrees of freedom, *IV* inverse variance, *SE* standard error

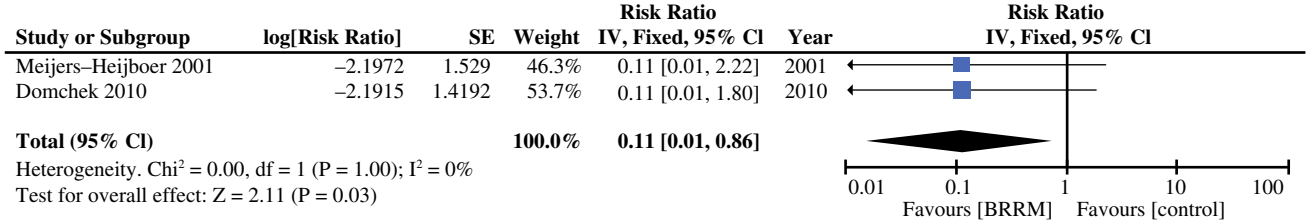

FIG. 4 Relative risk estimates for risk reduction of breast cancer associated with BRRM and risk-reducing salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers. *BRRM* bilateral risk-reducing mastectomy, *CI* confidence interval, *df* degrees of freedom, *IV* inverse variance, *SE* standard error

BRCA1- and BRCA2-mutated healthy patients. To our knowledge, this is the first meta-analysis of BRRM focusing on BRCA mutation carriers.

Our results have clearly shown the clinical benefit of performing BRRM; we found that BRRM reduced the risk of developing BC in these patients by 93 %. Due to the high heterogeneity ($I^2 = 59$ %) we performed further subgroup analysis, evaluating only patients who underwent BRRM without RRSO (subanalysis 1) and only those who received both procedures (subanalysis 2). In fact, we noticed that RRSO had been carried out in 38–82 % of women belonging to the control group and in 18–69 % of women who underwent BRRM. We supposed that this imbalance could have represented a confounding factor for the actual estimation of BC incidence because those who had received RRSO had an 'a priori' potential 46 % risk reduction of developing BC.[15–17]

Based on these evidences, we found that in patients who underwent BRRM plus RRSO the benefit was confirmed (HR 0.11; $p = 0.03$) but was slightly lower than the one recorded in patients receiving BRRM without RRSO (HR 0.06; $p = 0.005$).

Our study may be accompanied by several limitations. First, it was not possible to delineate a correct standardization by age; this would have been interesting due to the characteristic peak of the incidence of BC.[18] Second, the mean follow-up of the analyzed studies is short, and data regarding survival cannot be extrapolated; reasonably, longer follow-up would be useful to better understand the impact of this procedure. Finally, we only analyzed studies of a prospective nature because randomized studies have not been published in this setting, probably because they are ethically unacceptable.

Controversies still exist, such as the need for BRRM in association with RRSO, the timing of procedures, as well as whether BRRM could improve survival. The next research steps should consider long-term follow-up to determine the incidence of late occurrences, the survival and the reduction in BC mortality, according to management's option. Furthermore, future analysis should also focus on the impact of different types of prophylactic surgical procedures in reducing BC risk, such as radical mastectomy, nipple-sparing mastectomy, or skin-sparing mastectomy.

Nonetheless, while waiting for these future trials, patients need to be counseled, and we hope that our results could influence behaviors more rationally than celebrity disclosures.[19]

The decision to opt for BRRM must obviously be driven by the patient's choice; this, in turn, should be performed according to evidenced-based knowledge of the risks and benefits of prophylactic surgical procedures.

As far as we are concerned, it is therefore paramount to discuss several aspects with women.

First, BC and OC have different peaks of incidence, with a 10-year delay: 20 and 3 % of BRCA-mutated women aged in their 40 s will receive a diagnosis of BC or OC, respectively.[18]

Second, BRRM and RRSO are both definitive procedures. BRRM can impair body image, whereas RRSO

limits reproductive choices and may impose health risks due to early menopause.[20]

Nonetheless, after the recent anesthesiological and surgical improvements, BRRM with breast reconstruction, and RRSO, can nowadays be performed easily, with a low rate (2 %) of complications.[21] Furthermore, the level of patients' satisfaction after receiving these procedures increased with time.[22] Finally, in BRCA1 and BRCA2 mutation carriers without a personal history of BC, short-term hormonal replacement therapy could be reasonably proposed, considering its use in improving quality of life, without any impact on oncologic outcomes.[20]

Third, the risk reduction of BC is estimated to be 94–95 % when BRRM is performed (unpublished observations), nearly 89 % in patients who received BRRM plus RRSO, and 46 % when RRSO alone is carried out, suggesting that RRSO alone cannot replace the beneficial impact of BRRM in BC occurrence.

As a consequence, BRRM should be discussed more carefully with patients, and it is of paramount importance that clinicians became familiar with the estimation of risk reduction.

The results of our meta-analysis indicated that performing BRRM might achieve a highly significant risk reduction of breast cancer in BRCA1 and BRCA2 mutation carriers. These data allow clinicians to discuss more in-depth with women all the available options, in order to really help them in the complex process of decision making.

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