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Hormone replacement therapy after prophylactic risk-reducing salpingo-oophorectomy and breast cancer risk in BRCA1 and BRCA2 mutation carriers: A meta-analysis

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ABSTRACT

Background: Hormone replacement therapy (HRT) has been tested in women with BRCA1 and BRCA2 mutations who underwent risk-reducing salpingo-oophorectomy (RRSO), but its effect on breast cancer (BC) risk has never been appraised using meta-analysis comparison. We performed the first meta-analysis aimed to clarify whether HRT after RRSO could negatively impact on BC risk in women carriers of BRCA1 and BRCA2 mutations.
Methods and material: Pubmed and Scopus databases were searched to retrieve articles written in the English language. Trials comparing RRSO with or without HRT were identified and only those trials with available BC events were included. BC risk was the main endpoint.
Results: Three trials with 1100 patients were included. There was not a significantly higher BC risk in BRCA1 and BRCA2 mutation carriers receiving HRT after RRSO (HR = 0.98; 95% CI 0.63–1.52). There was a slightly but not significantly, benefit in BC risk reduction in favor of estrogen alone HRT versus estrogen plus progesterone HRT formulation (OR = 0.53; 95% CI 0.25–1.15).
Conclusion: HRT use after RRSO in BRCA 1 and BRCA2 mutation carries does not affect BC risk. Comparison of the different HRT types suggests that estrogen alone should be related to lowest BC risk.

1. Introduction

Mutations in DNA repair pathways, including breast-cancer susceptibility gene 1 (BRCA1) and breast-cancer susceptibility gene 2 (BRCA2) mutation carries, predispose women to an elevated lifetime risk for ovarian cancer (OC) and breast cancer (BC) (National Comprehensive Cancer Network Guidelines, 2018). While the role of bilateral risk-reducing mastectomy is still controversial, risk-reducing salpingo-oophorectomy (RRSO) represents nowadays the main effective prophylactic OC risk measure that should be proposed to BRCA carries, especially once childbearing is complete (National Comprehensive Cancer Network Guidelines, 2018; Paluch-Shimon et al., 2016; De Felice et al., 2015). In fact, in this setting of patients, prophylactic RRSO is associated with an OC risk-reduction of approximately 80% (hazard ratio, HR 0.19, 95% confidence interval, CI = 0.13 – 0.27) and it seems also to reduce BC risk by approximately 50% (HR 0.53, 95% CI = 0.33 – 0.84) (Rebbeck et al., 1999; Marchetti et al., 2014a). Subsequent hormone replacement therapy (HRT), including estrogen and progesterone alone or in combined therapy, remains a major concern, especially concerning its potential influence on BC risk. In clinical practice, HRT choice after RSSO is mainly driven by physician and patient preference to manage acute symptoms of surgically-induced menopause (De Felice et al., 2017).

This meta-analysis aims to stress the real impact of HRT after RSSO on BC risk in order to define the better standard of care for the management of BRCA1 and BRCA2 mutation carriers after prophylactic RSSO.

2. Methods and materials

2.1. Search strategy and selection criteria

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement was followed to perform this meta-

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analysis. It includes both prospective cohort trials and retrospective studies, written in English, without any restrictions on publication date. To be eligible, published and unpublished trials had to estimate BC incidence in BRCA1 and BRCA2 mutation carriers who underwent RRSO and received or not received HRT after prophylactic surgery. Systematic literature electronic search was conducted in Pubmed and Scopus databases, using the following combinations of research criteria: "mutation carriers", "BRCA", "ovarian cancer", "breast cancer", "risk", "prophylactic surgery", "hormone replacement therapy", "risk-reducing", "surgery", "oophorectomy". Hand searching (meeting proceedings of Society of Gynecologic Oncology, European Society of Medical Oncology and American Society of Clinical Oncology) was also used. The last literature search was done on May 2018. Reference lists of previously published reviews were explored. Review articles, case reports, commentaries and letters were not included. In closer evaluation of potentially eligible articles, when two articles appeared to report results with overlapping data, only the data representing the most recent publication were included.

2.2. Data extraction

Two independent investigators (CM and FDF) selected the identified studies based on title and abstract. If the study's topic could not be ascertained from its title or abstract, the full-text version would be retrieved for evaluation. Disagreement was resolved by discussion or consensus or with a third party (LM). Extracted data were recorded into standardized database. Data collected included first author's last name, publication year, sample size of cases, type of prophylactic surgery, HRT type and total months of use, data on BC event, follow-up time.

2.3. Outcomes

Primary end-point was BC risk. BC risk was defined as the time from the year HRT use began until a BC or other censoring event.

2.4. Statistical analysis

Statistical analysis was performed using Review Manager 5.0 (http://www.cochrane.org). It was exclusively based on full-text paper results. The analysis used hazard ratio (HR) or odds ratio (OR) to compare results for HRT group to no-HRT group. The pooled HR or OR was calculated using a random-effects model. Forest plots were used for graphical representation of each study and pooled analysis. The size of every box represents the weight that the corresponding study exerts in the meta-analysis; confidence intervals (CI) of each study are displayed as horizontal line through the box. The pooled HR or OR was symbolized by a solid diamond at the bottom of the forest plot and the width of the square represents the 95% CI of HR or OR. HR or OR, variance, 95% CI, log [risk ratio] and standard error for each study were calculated, based on Tierney et al. method (Tierney et al., 2007). A significant two-way p value for comparison was defined as $p < 0.05$. Statistical heterogeneity between studies was investigated using Cochrane Q statistic (significant at $p < 0.1$) and the I^2 value (significant heterogeneity if > 50%) (Higgins et al., 2003). Publication bias was examined using Egger et al. (Egger et al. (1997)) and Begg et al. (Begg and Mazumdar, 1994) analyses.

3. Results

A total of 3 studies were identified (Kotsopoulos et al., 2018; Rebbeck et al., 2005; Gabriel et al., 2009). The vast majority of articles were excluded due to different topic and format, such as review and case report/series. Of the 6 potentially eligible studies, 3 were excluded because of the absence of BC incidence data (n = 2) or overlapping data (n = 1). Overall, 3 studies representing 1100 patients were included in the meta-analysis. Details by study are presented in Table 1.

BC risk associated with HRT use after RRSO was 1.01 (95% CI 0.16–1.54) for the entire cohort (Fig. 1). Among prospective trials, the BC risk of HRT use was similar, without a negative impact in BRCA mutation carries who used HRT (HR = 0.98; 95% CI 0.63–1.52) (Fig. 2).

A subgroup analysis based on HRT formulation was also performed. In total, among the HRT users, 326 used estrogen alone (E) and 114 used estrogen plus progesterone (EP), for a mean duration of approximately 3.3 years (Table 1). There was no significant difference in BC risk comparing women who used E regimen and women who use EP formulation. But BC risk was lower for women who used E alone versus EP, both in overall population (OR = 0.62; 95% CI 0.29–1.31) (Fig. 3) and prospective studies only (OR = 0.53; 95% CI 0.25–1.15) (Fig. 4).

4. Discussion

We demonstrated that HRT seems to be a safe therapeutic option in BRCA 1 and 2 mutation carriers undergoing RRSO, regardless of the study design (HR = 0.98; 95% CI 0.63–1.52). Data were also confirmed in the subgroup analysis including only prospective/observational studies. Further, it seems that those who receive E-alone have a lower, not significant trend for BC risk compared with those who receive estrogen plus progesterone (OR = 0.53; 95% CI 0.25–1.15).

A woman identified as a BRCA mutation carrier faces a number of options to reduce her OC risk (De Felice et al., 2017). Nowadays, RRSO is recommended in BRCA1 and BRCA2 patients, especially once childbearing is complete, because of its proven efficacy in reducing OC risk and mortality in BRCA mutation carriers (Marchetti et al., 2014a). However, albeit the surgical procedure is rather feasible, RRSO has several short and long term clinical consequences (Birrer et al., 2018; Marchetti et al., 2014b). Among these consequences, the occurrence of early menopause is the most feared by both patient and physician. In fact, it has been demonstrated that early surgical menopause has an important impact on several aspects of premenopausal women's health, including her quality of life, sexual life, accelerated osteoporosis, cognitive impairment, cardiovascular disease, and a host of chronic conditions (Birrer et al., 2018; Parker et al., 2013; Rocca et al., 2008, 2006). To mitigate these adverse effects, exogenous hormone prescription has been proposed with a favorable clinical feedback also in healthy BRCA mutation carriers who underwent RRSO before natural menopause (Madalinska et al., 2006; Finch et al., 2011; Nathorst-Böös et al., 1993). A recent prospective study demonstrated that HRT use in the first year after RRSO had beneficial effects in reducing endocrine and sexual symptoms in premenopausal women who have undergone RRSO (Vermeulen et al., 2017).

Nonetheless, the use of HRT in BRCA mutation carriers remains controversial because of worry of an increased risk of BC onset, which is genetically higher in BRCA mutated women. The perplexity on HRT administration is partially based on data derived from HRT trials in the overall postmenopausal population. In the WHI randomized trial, a statistically significant increase in BC risk was observed among postmenopausal women submitted to estrogen plus progesterone therapy (HR, 1.24; 95% CI, 1.01–1.53) (Anderson et al., 2004). Similarly, the observational Million Women Study (MWS) found that HT users at recruitment were more likely to develop (RR, 1.66; 95% CI, 1.58–1.75) and die of BC (RR, 1.22; 95% CI, 1.00–1.48) than non-users, regardless of HRT type (Beral, 2003). But, it should be underlined that women enrolled in these studies were from the overall population and were also post-menopausal women who extended their lifelong hormone exposure after menopause. This clinical scenario is completely different from premenopausal BRCA mutated and oophorectomized women. In fact, these women are usually and reasonably younger than those involved in both WHI and MWS trials and experienced menopausal symptoms very earlier than natural. This assumption is confirmed in our meta-analysis. Globally, the mean age of HRT users is approximately 42 years, ranged from 42 years to 43.4 years, whereas the