Association of premenopausal risk-reducing salpingo-oophorectomy with breast cancer risk in BRCA1/2 mutation carriers: Maximising bias-reduction

Neda Stjepanovic a, j, Guillermo Villacampa a, Kevin T. Nead b, c, k, Sara Torres-Esquius a, Guadalupe G. Melis d, Katherine L. Nathanson b, c, Alexandre Teule e, Joan Brunet c, f, Teresa R. y Cajal g, Gemma Llort h, Rodrigo Dienstmann a, Montserrat Rue i, Susan M. Domchek b, c, l, Judith Balmaña a, *, 1

a Vall d’Hebron University Hospital and Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain
b Basser Center for BRCA and Abramson Cancer Center, University of Pennsylvania, Philadelphia, USA
c Perelman School of Medicine at the University of Pennsylvania, Philadelphia, USA
d Universitat Politécnica de Catalunya, Barcelona, Spain
e Catalan Institute of Oncology, IDIBELL, Barcelona, Spain
f Catalan Institute of Oncology, IDIBGI, Girona, Spain
g Hospital Sant Pau, Barcelona, Spain
h Hospital Universitari, Parc Taullí Sabadell, Consorci Sanitari de Terrassa, Barcelona, Spain
i University of Lleida-Lleida Biomedical Research Institute (UdL-IRBLleida), Lleida, Spain
j Sunnybrook Health Sciences Centre, Toronto, Canada
k Anderson Cancer Centre, Houston, TX, USA
l Both authors to be considered senior authors.

Received 8 December 2019; received in revised form 28 February 2020; accepted 9 March 2020

KEYWORDS
BRCA1/2; Breast cancer risk; Salpingo-

Abstract  Background: Whether risk-reducing salpingo-oophorectomy (RRSO) in BRCA1/2 carriers reduces the breast cancer (BC) risk is conflicting, potentially due to methodological issues of prior analysis. We analysed the association between premenopausal RRSO and BC risk in BRCA1/2 carriers after adjusting for potential biases.

* Corresponding author: Medical Oncology Department, Vall d’Hebron University Hospital and Vall d’Hebron Institute of Oncology, Passeig de la Vall d’Hebron, 119, 129, 08035, Barcelona, Spain.
E-mail address: neda.stjepanovic@sunnybrook.ca (N. Stjepanovic), gvillacampa@vhio.net (G. Villacampa), ktnead@mdanderson.org (K.T. Nead), storres@vhio.net (S. Torres-Esquius), lupe.gomez@upc.edu (G.G. Melis), knathans@upenn.edu (K.L. Nathanson), ateule@iconcologia.net (A. Teule), jbrunet@iconcologia.net (J. Brunet), tramon@santpau.cat (T.R. y Cajal), gliort@tauli.cat (G. Llort), rdienstmann@vhio.net (R. Dienstmann), montserrat.rue@udl.cat (M. Rue), susan.domchek@uphs.upenn.edu (S.M. Domchek), jbalmana@vhio.net (J. Balmaña).

https://doi.org/10.1016/j.ejca.2020.03.009
0959-8049/ © 2020 Elsevier Ltd. All rights reserved.
1. Background

Women with germline BRCA1/2 mutations have an estimated cumulative risk of breast cancer (BC) of 72% for BRCA1 and 69% for BRCA2 carriers, and of ovarian cancer of 44% for BRCA1 and 17% for BRCA2 carriers [1]. While the effectiveness of the risk-reducing salpingo-oophorectomy (RRSO) in reducing the ovarian cancer risk has been demonstrated [2], the impact of RRSO on BC risk is conflicting [3]. Prior observational studies have potential methodological issues and biases such as immortal person-time bias or informative censoring [4].

Prolonged exposure to endogenous oestrogens has been related to increased risk of premenopausal and postmenopausal female BC [8–10]. The levels of oestrogen synthesised by the ovaries decrease rapidly after RRSO in premenopausal BRCA1/2 carriers, but the magnitude of BC risk reduction may vary depending on the age and the history of exposure to female hormones. Mavaddat et al. showed that RRSO performed before age 45 compared to after age 45 was associated with a greater reduction in BC risks in both BRCA1 and BRCA2 carriers [3]. Kotsovolos et al. analysed the impact of RRSO on BC risk censoring at age 50, and the protective effect was observed only in BRCA2 carriers [6].

Currently, RRSO as an ovarian cancer-preventive measure is recommended between ages 35 and 40 [11,12] and may be postponed to ages between 40 and 45 for BRCA2 carriers. RRM or breast surveillance with annual contrast-enhanced magnetic resonance imaging (MRI) and mammography are offered to premenopausal BRCA1/2 carriers. Knowing the impact of premenopausal RRSO on BC risk may be critical for women deciding between surveillance and prophylactic surgery.

In this new multicentre international observational study, we estimated the association between premenopausal RRSO and BC risk, taking into consideration previously described and additional potential biases. Additionally, the results of the current study were integrated with published studies in a systematic review that elucidates the association of RRSO with BC risk in BRCA1/2 mutation carriers, focusing on the premenopausal population.

2. Methods

2.1. Study subjects

Women with BRCA1/2 germline mutations were identified from five prospectively maintained clinical cancer databases from Catalonia (Spain) and Pennsylvania (United States of America, USA). All participants underwent an informed consent process for participation in research, approved by each institution’s ethics committee. Genetic testing and counselling were performed as per respective institutional guidelines. Women who did not undergo RRM were counselled to undergo breast surveillance with annual MRI and mammography.

Women were eligible for inclusion in the study analysis if they met the following criteria: (1) DNA testing prior to age 51, considered as a median age of menopause [13]; (2) no prior bilateral oophorectomy or bilateral mastectomy; (3) no cancer diagnosis prior to DNA testing or within 6 months after the DNA testing, except in-situ cervical cancer and non-melanoma skin cancer (to avoid the cancer-induced testing bias and the prevalent cancer bias, respectively); and (4) more...
than 6 months of follow-up. The flow chart of study population selection is available in Fig. S1.

2.2. Study design

We conducted a retrospective analysis of prospectively collected data. The observation period started on the date of DNA test result or the age of 30 years, whichever occurred last (because the earliest RRSO was performed at age 30 and for risk comparison at least one case is required in both groups), and ended at BC or other cancer diagnosis (except in-situ cervical cancer and non-melanoma skin cancer), RRM, death or last follow-up, whichever occurred first. For data analysis, the first 6 months of follow-up after the DNA test result date were omitted, because cancer diagnosis during this period was an exclusion criterion (to avoid event-free time bias). Only RRSO under age 51 years (considered premenopausal [13]) were accounted for in the analysis and were coded as a time-dependent variable (to avoid immortal person-time bias) with the allocation of follow-up time prior to RRSO to the non-RRSO group. The non-RRSO period also included the latency period of 3 months after RRSO (to avoid prevalent cancer bias). Women who did not undergo RRSO prior to age 51 remained in the non-RRSO group until the end of observation period (Fig. 1) (Details of bias definition are available in Supplementary Methodology).

2.3. Statistical analysis

A Markov multistate model [14] with four states (non-RRSO, RRSO, RRM and BC) and five transitions was used for statistical analysis (Fig. 2). Stratified Cox proportional hazard models were fitted for each transition to estimate covariate effects [15]. Additionally, stratified Cox proportional hazard models were fitted to compare transition intensities in order to estimate BC risk reduction related to premenopausal RRSO (using RRSO as a time-dependent covariate). As a sensitivity analysis, we estimate the impact of premenopausal RRSO on premenopausal BC risk was calculated after censoring follow-up at age 51 and excluding patients who underwent RRM. All models were built using age as the time-scale, stratified by centre and applying robust variance estimation. Hazard ratios (HRs) with 95% confidence intervals (95% CI) were reported. No data imputation was performed. All analyses were undertaken using R statistical software version 3.4.1 (R packages mstate, survival and Epi).

2.4. Systematic review

Studies that assess the association of RRSO and BC risk in BRCA1/2 carriers were identified in PubMed database. Search terms BRCA1 and BRCA2 or BRCA1/2, salpingo-oophorectomy or ovariectomy and BC risk were used to identify studies published until 1st May 2019. Studies whose methodology did not account for cancer-induced testing bias and immortal person time bias were excluded. We used meta-analysis to summarise the association between RRSO (premenopausal and regardless the menopausal status) and BC risk in BRCA1/2 carriers. The summary measure was hazard ratio (HR) with 95% confidence interval (95% CI). Fixed and random effects models were fitted to estimate the overall impact, and heterogeneity across studies was quantified through the I² statistic. This systematic review...
was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Complete details are available in Supplementary Methodology.

3. Results

A total of 853 women (444 BRCA1 and 409 BRCA2 carriers) met the inclusion criteria and were analysed in this study. Recruitment lasted from January 1, 1996 to December 31, 2018, with mean follow-up of 4.3 years (Table 1). Overall, 337 (39.5%) women underwent premenopausal RRSO prior to mastectomy and prior to a cancer diagnosis at a median age of 42.0 years (range 30.5–50.8) among BRCA1 carriers and 43.5 years (range 33.7–50.9) among BRCA2 carriers (Table S1). A complete overview of study population characteristics is shown in Table 1, S1 and S2. Uptake of premenopausal RRSO was similar between BRCA1 and BRCA2 carriers (HR = 0.98 [95% CI: 0.77–1.25], Transition 1–2 in Table 2A).

Regarding BC prophylactic strategies, 240 women (28.1%) underwent RRM at a median age of 40.6 years (30.3–57.6) for BRCA1 carriers and 40.7 years (30.0–61.7) for BRCA2 carriers (Table S1). No differences were observed between BRCA1 and BRCA2 carriers with respect to RRM strategy among individuals who did not undergo premenopausal RRSO (HR = 0.93 [95% CI: 0.64–1.36], Transition 1–3 in Table 2A), and those who did (HR = 1 [95%CI: 0.69–1.44], Transitions 2–3 in Table 2A).

A total of 96 women (11.3%) were diagnosed with BC (54 BRCA1 and 42 BRCA2) at a median age of 40.1 years (30.7–59.6) and 41.4 years (30.4–61.5), respectively (Table S1). Among women who did not undergo premenopausal RRSO, we found a trend towards lower BC risk in BRCA2 carriers compared to BRCA1 carriers (HR = 0.7 [95%CI: 0.44–1.12], Transition 1–4 in Table 2A and Figs. S2–C). After premenopausal RRSO, the risk of BC was similar for BRCA1 and BRCA2 carriers (HR = 1.15 [95% CI: 0.48–2.75], Transition 2–4 in Table 2A and Figs. S2–D).

For BRCA1 carriers, premenopausal RRSO was associated with BC risk reduction with a HR = 0.45 [95% CI: 0.22–0.92] (Table 2B). The BC incidence rates were 19.4 and 37.4 per 1000 person years of observation for RRSO and non-RRSO groups respectively (Table S3). For BRCA2 carriers, no statistically significant reduction in BC risk was found after the premenopausal RRSO with a HR = 0.77 [95% CI: 0.35–1.67] (Table 2B), and a similar BC incidence rate was observed regardless of the premenopausal RRSO with 25.1 and 27.3 per 1000 person years of observation for RRSO and non-RRSO groups respectively (Table S3).

We performed a sensitivity analysis to determine the association between RRSO and BC risk in the following settings: (1) after censoring follow-up at age 51, which showed similar results in terms of HR estimation and incidence rate and remained statistically significant among BRCA1 carriers with a HR = 0.35 [95% CI: 0.15–0.82] (Tables S4 and S5) and (2) after excluding women who have had RRM, which showed a similar point estimation compared to the primary analysis (Table S4).

3.1. Systematic review

The literature search identified 303 entries; 15 were assessed for eligibility out of which five articles met the eligibility criteria (see Supplementary Methodology) and were included in the analysis [3–7] (Fig. S3). Among the included articles, one contained updates with methodology changes of two published studies [5]. Information related to study designs, exclusion criteria and observational period considerations is summarised in Table S6.
Table 1
Study population characteristics according to RRSO status.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Non-RRSO</th>
<th>RRSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n (%)</td>
<td>853 (100)</td>
<td>503 (59)</td>
<td>350 (41)</td>
</tr>
<tr>
<td>Mean FU time, y (range)</td>
<td>4.3 (0.1−16.9)</td>
<td>3.6 (0.1−14.7)</td>
<td>5.2 (0.5−16.9)</td>
</tr>
<tr>
<td>Age at DNA test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 y, n (%)</td>
<td>580 (68)</td>
<td>430 (85.5)</td>
<td>150 (42.9)</td>
</tr>
<tr>
<td>≥40 y, n (%)</td>
<td>273 (32)</td>
<td>73 (14.5)</td>
<td>200 (57.1)</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>36.2 (19.6−50.9)</td>
<td>32.9 (19.6−50.6)</td>
<td>41.2 (22.9−50.9)</td>
</tr>
<tr>
<td>Year of DNA test result</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2010</td>
<td>404 (47.4)</td>
<td>247 (49.1)</td>
<td>157 (44.9)</td>
</tr>
<tr>
<td>≥ 2010</td>
<td>449 (52.6)</td>
<td>256 (50.9)</td>
<td>193 (55.1)</td>
</tr>
<tr>
<td>BRCA mutation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1, n (%)</td>
<td>444 (52.1)</td>
<td>264 (52.5)</td>
<td>180 (51.4)</td>
</tr>
<tr>
<td>BRCA2, n (%)</td>
<td>409 (47.9)</td>
<td>239 (47.5)</td>
<td>170 (48.6)</td>
</tr>
<tr>
<td>Cohorts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catalonia - Spain, n (%)</td>
<td>486 (57)</td>
<td>300 (59.6)</td>
<td>186 (53.1)</td>
</tr>
<tr>
<td>Pennsylvania – USA, n (%)</td>
<td>367 (43)</td>
<td>203 (40.4)</td>
<td>164 (46.9)</td>
</tr>
<tr>
<td>RRSO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>350 (41)</td>
<td>—</td>
<td>350 (100)</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>43 (30.5−56.5)</td>
<td>—</td>
<td>43 (30.5−56.5)</td>
</tr>
<tr>
<td>Premenopausal RRSO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>337 (39.5)</td>
<td>—</td>
<td>337 (96.3)</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>42.8 (30.5−50.9)</td>
<td>—</td>
<td>42.8 (30.5−50.9)</td>
</tr>
<tr>
<td>Mean FU time for RRSO period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-RRSO period, y (range)</td>
<td>2 (0.1−11.3)</td>
<td>—</td>
<td>2 (0.1−11.3)</td>
</tr>
<tr>
<td>RRSO period, y (range)</td>
<td>3.2 (0−15.6)</td>
<td>—</td>
<td>3.2 (0−15.6)</td>
</tr>
<tr>
<td>RRM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>240 (28.1)</td>
<td>106 (21.1)</td>
<td>134 (38.3)</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>40.7 (30−61.7)</td>
<td>35.8 (30.03−51.8)</td>
<td>44.2 (30.5−61.7)</td>
</tr>
<tr>
<td>BC diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>96 (11.3)</td>
<td>73 (14.5)</td>
<td>23 (6.6)</td>
</tr>
<tr>
<td>Median, y (range)</td>
<td>40.4 (30.4−61.5)</td>
<td>39 (30.4−59.6)</td>
<td>46.5 (34.1−61.5)</td>
</tr>
<tr>
<td>Mean FU: BC diagnosis, y (range)</td>
<td>4.4 (0.4−14.1)</td>
<td>3.9 (0.4−13.7)</td>
<td>5.9 (0.6−14.1)</td>
</tr>
</tbody>
</table>

* The reported FU is the individual time included in data analysis not the total observational time.

* All RRSO under age 51 were considered premenopausal. BC: breast cancer; FU: Follow-up; n: number; RRM: risk-reducing mastectomy; RRSO: Risk-reducing salpingo-oophorectomy.

For the meta-analysis evaluating the BC risk associated with premenopausal RRSO, two cohorts and the current study were selected, accounting for a total of 376 BC diagnosis. The overall estimation in the random effects model showed a BC risk reduction after premenopausal RRSO for both *BRCA1* carriers with HR = 0.61 (95% CI: 0.36–1.02) and *BRCA2* carriers with HR = 0.43 (95% CI: 0.18–1.01) (Fig. 3).

For the meta-analysis of RRSO regardless of the menopausal status the included cohorts account for a total of 1076 BC diagnosis. The overall random effect had a HR = 0.81 (95% CI: 0.61–1.08) for *BRCA1* carriers and HR = 0.64 (95% CI: 0.47–0.87) for *BRCA2* carriers (Fig. S4) with a higher heterogeneity across studies in the *BRCA1* setting (*I²* = 45%). There is some indication for potential publication bias, although not conclusive (Fig. S5).

4. Discussion

In this study, a BC risk reduction was observed among women with inherited *BRCA1* mutations who underwent premenopausal RRSO. When follow-up was censored at age 51 to analyse the association with premenopausal BC risk, the RRSO remained protective among *BRCA1* carriers. We consider that this protective effect is plausible in the context of preclinical studies showing that *BRCA1*-associated mammary tumorigenesis is highly dependent on hormone signalling [16–18]. In the clinical setting the findings are not consistent, even when taking into account only the studies that analysed premenopausal RRSO. Mavaddat *et al.* found an association between RRSO prior to age 45 and BC incidence in *BRCA1* carriers with a HR = 0.38 (95% CI: 0.13–1.13), while Kotsopoulos *et al.* [6] observed a HR = 0.84 (95% CI: 0.58–1.21) when censoring follow-up at age 50.

In carriers of *BRCA2* mutation, our study was not conclusive for BC risk reduction associated with premenopausal RRSO, probably because of BC risk at older age, even postmenopausal period. However Kotsopoulos *et al.* [6] observed an association between RRSO and BC incidence prior to age 50 with HR = 0.17 (95% CI: 0.05–0.59), while Mavaddat *et al.* found HR = 0.44 (95% CI: 0.14–1.38). These
Table 2
Stratified cox proportional hazard model fitted in multistate model transitions.

### A: Comparison of prophylactic strategies and BC risk in BRCA1 vs. BRCA2 carriers

<table>
<thead>
<tr>
<th>BRCA2 vs. BRCA1</th>
<th>N events</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transition 1 → 2 (Non-RRSO → RRSO)</td>
<td>337</td>
<td>0.98</td>
<td>0.77–1.25</td>
<td>0.89</td>
</tr>
<tr>
<td>Transition 1 → 3 (Non-RRSO → RRM)</td>
<td>111</td>
<td>0.93</td>
<td>0.64–1.36</td>
<td>0.72</td>
</tr>
<tr>
<td>Transition 1 → 4 (Non-RRSO → BC)</td>
<td>74</td>
<td>0.7</td>
<td>0.44–1.12</td>
<td>0.14</td>
</tr>
<tr>
<td>Transition 2 → 3 (RRSO → RRM)</td>
<td>129</td>
<td>1</td>
<td>0.69–1.44</td>
<td>0.99</td>
</tr>
<tr>
<td>Transition 2 → 4 (RRSO → BC)</td>
<td>22</td>
<td>1.15</td>
<td>0.48–2.75</td>
<td>0.75</td>
</tr>
</tbody>
</table>

### B: Association of premenopausal RRSO on BC risk according to BRCA mutation status

<table>
<thead>
<tr>
<th>RRSO vs. NON-RRSO</th>
<th>N events</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 (n = 853)</td>
<td>96</td>
<td>0.57</td>
<td>0.32–1.00</td>
<td>0.05</td>
</tr>
<tr>
<td>BRCA2 (n = 444)</td>
<td>54</td>
<td>0.45</td>
<td>0.22–0.92</td>
<td>0.03</td>
</tr>
<tr>
<td>BRCA2 (n = 409)</td>
<td>42</td>
<td>0.77</td>
<td>0.35–1.67</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Note: Table 2A results correspond to stratified Cox model fitted in each transition of the multistate model to compare risks in BRCA1 vs. BRCA2 carriers. Table 2B results correspond to the comparison of instantaneous hazard in transitions 1 → 4 and 2 → 4 (Fig. 2) to assess the association between premenopausal RRSO and BC risk. The MM estimation provides the same results (HR) that the extended Cox model with RRSO as a time-dependent covariate. Initial analyses of RRSO as a BC risk-reducing factor that included patients with history of BC prior to DNA testing (cancer-induced testing bias) and did not take into account RRSO as a time-dependent covariate (immortal person-time bias) had an over selection of BC cases in the non-RRSO group and less observation time in the non-RRSO group, respectively, which may have led to an overestimation of the protective effect of RRSO.

In the RRSO group, the DNA testing was performed at an older age, and the RRM rate was 17% higher compared to the non-RRSO group, hypothetically driven by the desire to make an informed decision regarding immediate prophylactic surgeries. Additionally, 51.5% of the women who were censored because of RRM had less than one year of follow-up after the RRSO (data not shown). The sensitivity analysis excluding women who underwent RRM showed consistent results with the primary analysis. Therefore, these results provide an indirect evidence that censoring for RRM was not informative.

Our study was limited by the small number of incident cancers (54 BRCA1 cases and 42 BRCA2 cases), relatively short follow-up duration (4.3 years on average) and the fact that we had to infer the menopausal status according to the individual’s age. Additionally, we were unable to control for family history of cancer, hormone replacement therapy or other risk factors as potential confounders and the hormonal status of the BCs. In the systematic review our analyses lacked individual patient-data. On the other hand, our study has many strengths. We performed strict control of biases including: (1) cancer-induced testing bias by excluding individuals with history of cancer; (2) prevalent cancer bias by adding a latency period to each group; (3) event-free time bias by starting the observational time 6 months after the DNA testing date; and (4) immortal person-time bias by taking RRSO into account as a time-dependent covariate. Initial analyses of RRSO as a BC risk-reducing factor that included patients with history of BC prior to DNA testing (cancer-induced testing bias) and did not take into account RRSO as a time-dependent covariate (immortal person-time bias) had an over selection of BC cases in the non-RRSO group and less observation time in the non-RRSO group, respectively, which may have led to an overestimation of the protective effect of RRSO.

Differences among studies may be due to small number of BC events in the RRSO group which precluded conclusive statements.

The results of the systematic review suggested that the premenopausal RRSO is effective in BC risk reduction in both BRCA1 and BRCA2 carriers. The meta-analysis including all studies regardless of the menopausal status at RRSO also showed a protective, but weaker effect on the reduction of BC risk. However, caution is advised when interpreting these results given the methodological heterogeneity among included studies and the possibility of publication bias.

For the BRCA1 carriers who underwent premenopausal RRSO for ovarian cancer risk reduction, the results of our study could influence patient’s preferences regarding breast screening versus prophylactic surgery. RRSO is strongly advised for reduction of ovarian cancer risk. Although several studies of premenopausal RRSO in unaffected BRCA1 carriers have demonstrated that the use of hormone replacement therapy does not increase the risk of BC [19,20], the consequences of an early menopause on other aspects of long-term quality health need to be considered. Compared to BRCA1, the BRCA2 carriers have a lower risk of ovarian cancer and a subsequent age of diagnosis. Because of this difference, RRSO is recommended for ovarian cancer risk reduction between ages 35–40 for BRCA1 mutation carriers but can be delayed up to ages 40–45 for BRCA2 mutation carriers. Further data are needed on optimal timing of RRSO related to breast cancer risk reduction. Studies are underway examining whether salpingectomy with delayed oophorectomy is safe and effective; if proven as such, they may be considered. Compared to BRCA1, the BRCA2 carriers have a lower risk of ovarian cancer and a subsequent age of diagnosis. Because of this difference, RRSO is recommended for ovarian cancer risk reduction between ages 35–40 for BRCA1 mutation carriers but can be delayed up to ages 40–45 for BRCA2 mutation carriers. Further data are needed on optimal timing of RRSO related to breast cancer risk reduction. Studies are underway examining whether salpingectomy with delayed oophorectomy is safe and effective; if proven as such, they may be considered. Compared to BRCA1, the BRCA2 carriers have a lower risk of ovarian cancer and a subsequent age of diagnosis. Because of this difference, RRSO is recommended for ovarian cancer risk reduction between ages 35–40 for BRCA1 mutation carriers but can be delayed up to ages 40–45 for BRCA2 mutation carriers.
overestimation of BC risk reduction after RRSO. When controlling for the above mentioned biases some more recent studies observed that RRSO is effective in reducing BC risk [3,5], while other studies did not observe this association [4,7]. The event-free time bias, controlled for in the current study, could have led to an underestimation of BC risk in the non-RRSO period, and consequently to an underestimation of the BC risk reduction after RRSO in prior studies. After controlling for all above mentioned biases, our analysis demonstrated an association between premenopausal RRSO and BC risk reduction in BRCA1 carriers. Another important strength of this study is the statistical approach that attempted to provide a better understanding of real world risk-reducing strategies in BRCA1/2 carriers. The use of multistate models allows a more flexible analysis to model complex data with intermediate and multiple end-points. This model better accounts for differences in the BC risk before and after premenopausal RRSO among BRCA1 and BRCA2 carriers. Prior to premenopausal RRSO the risk of BC was higher for BRCA1 carriers compared to BRCA2 carriers, while after premenopausal RRSO the BC risk was similar in both groups. These observations may help understand why premenopausal RRSO was more effective in BRCA1 carriers in terms of BC risk reduction.

5. Conclusion

The results from our study provide further evidence of BC risk reduction following the premenopausal RRSO in BRCA1 carriers, using rigorous methodology that may better account for the inherent biases of observational studies. Considering all available preclinical and epidemiological evidence, the added benefit on BC risk reduction should be included in the discussion of premenopausal RRSO when counselling BRCA1 mutation carriers.

Sources of support

Spanish Instituto de Salud Carlos III (ISCIII) - supported by European Regional Development FEDER funds: FIS PI16-11363 (to JB), Breast Cancer Research Foundation (to SMD and KLN), Komen Foundation for the Cure (to SMD), MTM2015-64465-C2-1-R (MINECO/FEDER) and MDM-2014-0445 of the Ministerio de Economía y Competitividad (Spain) and 2017 SGR 622 (GRBIO) (to GG).

Funding and acknowledgements

The Spanish cohort of this study included patients from the Vall d’Hebron University Hospital-Barcelona, the Catalan Institute of Oncology, IDIBELL-Barcelona, the Catalan Institute of Oncology, IDIBGI-Girona, Sant Pau University Hospital-Barcelona and Corporació Sanitària Parc Taulí-Barcelona. This work was partially granted by Spanish Instituto de Salud Carlos III (ISCIII) funding, an initiative of the Spanish Ministry of Economy and Innovation partially supported by European Regional Development FEDER funds: FIS PI16-11363 (to J. Balmaña). The University of
Pennsylvania (UPenn) cohort included patients from the Basser Center for BRCA - Philadelphia, USA and the Abramson Cancer Center—Philadelphia, USA and was supported by grants from the Breast Cancer Research Foundation (SMD, KLN), and the Komen Foundation for the Cure (SMD). Guadalupe Gómez research was partially supported by grants MTM2015-64465-C2-1-R (MINECO/FEDER) and MDM-2014-0445 of the Ministerio de Economía y Competitividad (Spain) and 2017 SGR 622 (GRBIO).

Conflict of interest statement

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at [https://doi.org/10.1016/j.ejca.2020.03.009](https://doi.org/10.1016/j.ejca.2020.03.009).

References