Do all \textit{BRCA1/2} carriers with breast cancer benefit from bilateral mastectomy?

Riccardo Ponzone

Candiolo Cancer Institute, FPO – IRCCS, Candiolo, TO 10060, Italy

\textit{Correspondence to:} Riccardo Ponzone, MD, PhD. Gynecological Oncology, Candiolo Cancer Institute, FPO – IRCCS, Strada Provinciale 142, Km 3.95, Candiolo, TO 10060, Italy. Email: riccardo.ponzone@ircc.it.

\textbf{Abstract:} Surgical management of hereditary breast cancer is influenced by several variables pertaining tumor biology as well as patients’ physical and psychological characteristics. The prevalence of \textit{BRCA1/2} mutations among breast cancer patients is low, but many carriers are not diagnosed according current criteria of access to genetic testing. This is becoming even more relevant as specific drugs for carriers have now been included in the armamentarium of medical oncologists. Indeed, the whole therapeutic strategy, including pros and cons of radiotherapy, is influenced by \textit{BRCA1/2} status. Although no major differences have been reported between the outcome of \textit{BRCA1/2} negative vs. \textit{BRCA1/2} positive patients, the latter carry a substantially higher cumulative risk of metachronous breast and ovarian cancers. It is then mandatory that the complex interplay between clinical, biological and treatment variables be fully taken into account when cancer develops in these women.

\textbf{Keywords:} Hereditary breast cancer; \textit{BRCA1/2} mutation; bilateral mastectomy; breast conserving surgery

Received: 29 August 2019; Accepted: 25 September 2019; Published: 15 October 2019.

doi: 10.21037/abs.2019.09.01

View this article at: https://dx.doi.org/10.21037/abs.2019.09.01

Which breast cancer patients should undergo \textit{BRCA} testing?

Since the discovery of the \textit{BRCA1} (1) and \textit{BRCA2} genes (2) over 25 years ago, understanding and management of hereditary breast and ovarian cancer patients have been constantly evolving. In the general population \textit{BRCA1/2} mutations occur in 1 every 300 to 500 women and account for 5% and 15% of breast and ovarian cancer cases, respectively. \textit{BRCA1} and \textit{BRCA2} carriers exhibit a similar cumulative breast cancer risk to the age of 80 (72% and 69%, respectively), while both ovarian cancer risk (44% vs. 17%) and contralateral cumulative breast risk 20 years after breast cancer diagnosis (40% vs. 26%) are higher for \textit{BRCA1} vs. \textit{BRCA2} carriers (3). Given the substantial risk of subsequent breast and ovarian cancers, knowledge of \textit{BRCA1/2} mutation status may be important when cancer develops as it may influence the attitude of patients towards surveillance and preventive options (4).

The prevalence of \textit{BRCA} pathogenic variants in unselected breast cancer patients is less than 2%, yet up to 60% of carriers are not diagnosed according current criteria of access to genetic testing (5). This gap of knowledge is becoming a critical issue in breast cancer care. Indeed, the relevance of \textit{BRCA} status is increasing not only from the surgical standpoint, but also to tailor medical therapies as it predicts responsiveness to platinum-based chemotherapy and poly(ADP-ribose) polymerase (PARP) inhibitors (6). Therefore, universal genetic testing for ovarian cancer patients and a broadening of criteria to genetic testing for breast cancer patients have been suggested (7). This change of practice is reflected in the recently published US Preventive Services Task Force statement on genetic testing for \textit{BRCA}-related cancer (8).

Neoadjuvant chemotherapy vs. primary surgery

The available scientific evidence on breast cancer overall survival of \textit{BRCA} carriers as compared to non-carriers is conflicting, although large differences are unlikely to
exist (Table 1) (9-14). A recently published prospective study assessed the relationship between germ-line BRCA mutation and outcome in a large cohort of young-onset breast cancer patients in the UK (15). Overall, patients with a BRCA mutation had similar survival as non-carriers [hazard ratio (HR) 0.96, 95% confidence interval (CI): 0.76–1.22; P=0.76]; nevertheless, carriers with triple-negative (TN) breast cancer had a survival advantage during the first few years after diagnosis compared with non-carriers (HR 0.59, 95% CI: 0.35–0.99; P=0.047), likely due to the greater sensitivity of BRCA-mutant breast cancers to chemotherapy. Indeed, a systematic review and meta-analysis by Caramelo et al. suggests that the addition of platinum to chemotherapy regimens in the neoadjuvant setting increases the complete pathological response (pCR) rate in BRCA-mutated as compared to wild-type TNBC patients (16). Neoadjuvant chemotherapy (NACT) is particularly attractive in suspected BRCA carriers with TN tumors primarily due the expected chemosensitivity of their tumors. In addition, NACT provides time to get the result of genetic testing if not yet available, and to consider pros and cons of prophylactic surgery if the test is positive. Furthermore, tumor response may help to tailor further adjuvant regional and systemic treatments, as well as the opportunity to undergo prophylactic surgery based on the expected outcome of the patient (Figure 1).

### Table 1 Meta-analyses and systematic reviews and on overall survival of breast cancer in BRCA carriers

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Main results</th>
</tr>
</thead>
</table>
| Lee, 2010 (9) | • BRCA1 mutation decreases short-term and long-term OS and short-term PFS  
• BRCA2 mutation does not affect either short-term or long-term survival rate |
| Zhong, 2015 (10) | • Among patients with breast cancer, BRCA1 mutation carriers had worse OS than non-carriers  
• BRCA2 mutation was not associated with breast cancer prognosis |
| van den Broek, 2015 (11) | • Current evidence does not support worse breast cancer survival of BRCA1/2 carriers |
| Templeton, 2016 (12) | • BRCA mutations were not associated with worse overall survival |
| Bernier, 2015 (13) | • There is currently no evidence that, provided adequate systemic treatment is part of the therapeutic management, significant differences in both BCSS and OS |
| Hallam, 2015 (14) | • In most studies there was no significant difference in survival for BRCA1/2 carriers |

OS, overall survival; PFS, progression free survival; BCSS, breast cancer specific survival.

**Figure 1** Treatment tailoring with neoadjuvant chemotherapy for triple negative breast cancer in BRCA carries. CT, chemotherapy; TN, triple negative; BCS, breast conserving surgery; RT, radiotherapy; NACT, neoadjuvant chemotherapy; cCR, clinical complete response. +, pros; −, cons.
Breast conserving surgery (BCS) vs. mastectomy

The role of breast conserving surgery followed by radiotherapy (RT) in BRCA carriers has long been debated. It has been suggested that, as BRCA mutations may predispose carriers to higher cellular sensitivity to ionizing radiation, tumors responses may be better, but toxicity and radiation-induced malignancies may also be increased. Fortunately, the available data on complications are reassuring and there appears to be no increase in contralateral breast cancer (CBC) risk from scatter radiotherapy (RT) (13,17).

As tumor control is concerned, most studies do not show significant differences of ipsilateral breast tumor recurrences (IBTR) in BRCA carriers treated by BCS + RT as compared to non-carriers (Table 2) (17-26). The metanalysis by Valachis et al. confirms this finding [relative risk (RR) 1.45, 95% CI: 0.98–2.14], yet shows a significant higher risk for ipsilateral breast tumor recurrences (IBTR) among BRCA-mutation carriers in studies with a median follow-up ≥7 years (RR 1.51, 95% CI: 1.15–1.98) (27). The latter finding, coupled with the observation that BRCA carriers develop more new events elsewhere in the breast (i.e., not in the quadrant where the original tumor was located) than non-carriers (19), suggests that these “late” IBTR are likely new primaries and not local recurrences.

The same explanation may underlie the increased risk of local failure in BRCA carriers treated with BCS + RT vs. mastectomy (Table 3) (26,28,29). Importantly, in none of these studies significant differences for overall survival (OS), breast cancer death, or distant recurrence have been reported according to type of surgery performed.

Contralateral prophylactic mastectomy vs. surveillance

It has been repeatedly substantiated that the risk of CBC in BRCA1/2 carriers is significantly higher as compared to non-carriers. In the meta-analysis by Valachis et al., the number of CBCs was significantly greater in carriers versus

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Studies of ipsilateral breast tumor recurrences (IBTR) after BCT + RT in</th>
<th>BRCA carriers vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, year</td>
<td>BRCA carriers</td>
<td>Controls</td>
</tr>
<tr>
<td>Pierce, 2000 (17)</td>
<td>71</td>
<td>203</td>
</tr>
<tr>
<td>Haffty, 2002 (18)</td>
<td>22</td>
<td>105</td>
</tr>
<tr>
<td>Seynaeve, 2004 (19)</td>
<td>26</td>
<td>174</td>
</tr>
<tr>
<td>Robova, 2005 (20)</td>
<td>56</td>
<td>440</td>
</tr>
<tr>
<td>Kirova, 2005 (21)</td>
<td>29</td>
<td>271</td>
</tr>
<tr>
<td>Pierce, 2006 (22)</td>
<td>170</td>
<td>469</td>
</tr>
<tr>
<td>Brekelmans, 2007 (23)</td>
<td>109</td>
<td>410</td>
</tr>
<tr>
<td>Garcia Etienne, 2009 (24)</td>
<td>54</td>
<td>162</td>
</tr>
<tr>
<td>Kirova, 2010 (25)</td>
<td>29</td>
<td>58</td>
</tr>
<tr>
<td>van den Broek, 2019 (26)</td>
<td>55</td>
<td>1,510</td>
</tr>
</tbody>
</table>

FU, follow up; IBTR, ipsilateral breast tumor recurrence; BCS, breast conserving surgery; RT, radiotherapy.

| Table 3 | Studies comparing local failures after BCS + RT vs. mastectomy in BRCA carriers |
|---------|-------------------------------------------------|---------------------------|
| Author, year | BCS | M | Median FU (years) | BCS vs. M at 10 yrs | Local failure (%) | P | BCS vs. M at 15 yrs | Local failure (%) | P |
| Pierce, 2010 (28) | 302 | 353 | 8.2/8.9 | 10.5 vs. 3.5 | 0.0001 | – | 23.5 vs. 5.5 | 0.0001 |
| Nilsson, 2104 (29) | 45 | 118 | 14.9/12.1 | 25 vs. 9 | 0.03 | – | 32 vs. 9 | 0.03 |
| van den Broek, 2019 (26) | 91 | 49 | – | 7.3 vs. 1.5 | – | – | – | – |

FU, follow up; IBTR, ipsilateral breast tumor recurrence; BCS, breast conserving surgery; RT, radiotherapy; M, mastectomy.
controls (RR 3.56, 95% CI: 2.50–5.08) (27). In a more recent meta-analysis, the cumulative 5-year risk of CBC for BRCA1 and BRCA2 mutation carriers was 15% (95% CI: 9.5–20%) and 9% (95% CI: 5–14%), respectively and the 10-year risk increased up to 27% and 19%, respectively (30).

Similarly to the general population, family history of breast cancer and young age at primary breast cancer diagnosis increase CBC risk also in BRCA carriers, while endocrine therapy and risk reducing salpingo-oophorectomy (RRSO) decrease the risk (31). Somehow unexpectedly, while the type of surgery on the primary tumor (BCS vs. mastectomy) does not influence overall survival, several studies suggest that contralateral prophylactic mastectomy (CPM) may improve OS, likely through the prevention of new contralateral tumors (Table 4) (32-35). In the most recent of such studies the mortality was lower in the CPM group than in the surveillance group (adjusted HR 0.49, 95% CI: 0.29–0.82) and the survival benefit was especially seen in patients <40 years of age, with grade 1/2 and/or no TN tumors and if were not treated with adjuvant chemotherapy (35).

### Table 4 Studies on survival after contralateral prophylactic mastectomy (CPM) in BRCA carriers with unilateral breast cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>CPM/no-CPM</th>
<th>Mean FU (yrs)</th>
<th>No. CBC</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Sprundel, 2005 (32)</td>
<td>78/69</td>
<td>3.5</td>
<td>1 vs. 6 (1 vs. 8.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Evans, 2013 (33)</td>
<td>105/473</td>
<td>9.7/8.6</td>
<td>6 vs. 118 (6 vs. 25)</td>
<td>–</td>
</tr>
<tr>
<td>Metcalfe, 2014 (34)</td>
<td>181/209</td>
<td>14.3</td>
<td>1 vs. 70 (0.6 vs. 33.5)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Heemskerk-Gerritsen, 2105 (35)</td>
<td>242/341</td>
<td>11.4</td>
<td>4 vs. 64 (2 vs. 19)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*No longer significant after adjustment for BPO in a multivariate Cox analysis; °The survival advantage remained after matching for oophorectomy, gene, grade and stage; §In a propensity score adjusted analysis of 79 matched pairs, the association was not significant (P=0.08). CPM, contralateral prophylactic mastectomy; FU, follow up; CBC, contralateral breast cancer; OS, overall.

The mutation in either BRCA1 or BRCA2 and patient’s age are important factors to consider when deciding the optimal surgical approach. For example, it has been shown that 62.9% of BRCA1 carriers less than 40 years of age at first breast cancer developed a CBC vs. 19.6% of those who were older than 50 years and that BRCA1 carriers had a 1.6-fold (95% CI: 1.2- to 2.3-fold) higher risk of CBC than BRCA2 carriers after 25 years of follow up (38). The risk-benefit ratio of prophylactic surgery may also be influenced by a history of previous breast irradiation. Radiotherapy may in fact exert a preventive effect on the development of new primaries (39), but it increases the likelihood of complications and unfavorable outcomes of reconstructive surgery (40). Finally, the decision should always respect patients’ preferences, taking into account that the latter can be heavily influenced by perceived physician recommendation for CPM, greater perceived contralateral breast cancer risk, and greater perceived benefits of CPM (41,42) (Figure 2).

### Variables in the surgical decision-making process

In BRCA carriers who develop breast cancer, similarly to all breast cancer patients, the risks of ipsilateral, contralateral and distant new events are significantly modified by several factors. With regard to local control, in patients undergoing BCT the risk of a second in-breast event is significantly reduced by chemotherapy (17). Risk reducing salpingo-oophorectomy (RRSO) has a protective effect against recurrences [hazard ratio (HR) 0.50; 95% CI: 0.31 to 0.69], but it also reduces the risk of death (HR =0.33; 95% CI: 0.28 to 0.38) (36). Also tamoxifen is associated with a reduction in CBC risk both for BRCA1 (HR 0.38, 95% CI: 0.27 to 0.55) and BRCA2 carriers (HR 0.33; 95% CI: 0.22 to 0.50) (37).

Conclusions

BRCA1/2 carriers who develop breast cancer face difficult decisions regarding their surgical options mainly due to their increased lifetime risk of developing other breast and ovarian cancers. In carriers, BCS and mastectomy provide the same survival, as well as in the general population, yet the risk of late new ipsilateral breast cancers after BCS is increased. This event is a source of severe psychological distress by itself and, as it requires a mastectomy, exposes these patients to higher risk of surgical complications and unfavorable reconstructive results due to the previous breast RT. Furthermore, the lifetime risk of CBC is significantly
increased, especially in very young and *BRCA1*-positive patients. Therefore, as CPM in this setting may even improve overall survival, a thorough discussion of pros and cons of BCS + RT vs. therapeutic mastectomy and CPM is warranted in all *BRCA1/2* carriers with unilateral breast cancer (*Figure 3*).

Expedited genetic testing is becoming a critical issue for many newly diagnosed breast cancer patients; fortunately, a broadening of indications to gene counseling and the rapid analysis of gene panels are now possible thanks to the introduction of next generation sequencing (NGS). A negative *BRCA1/2* test may provide reassurance on the

---

*Figure 2* Factors to be considered when choosing between breast conserving surgery and bilateral mastectomy in *BRCA*-carriers with early stage unilateral breast cancer. BCS, breast conserving surgery; RT, radiotherapy; T, tumor diameter; N+, node positive; cCR, clinical complete response; CT, chemotherapy; BSO, bilateral salpingo-oophorectomy.

*Figure 3* Different attitudes of physicians towards breast conserving surgery and bilateral mastectomy in *BRCA*-carriers with early stage unilateral breast cancer. BCS, breast conserving surgery; RT, radiotherapy; IBTR, ipsilateral breast tumor recurrence; BSO, bilateral salpingo-oophorectomy.
Figure 4 Proposal of a decision-making/aiding algorithm in patients with early stage hereditary breast cancer. BCS, breast conserving surgery; RT, radiotherapy; APBI, accelerated partial breast irradiation.

safety of BCS + RT, while limiting the unjustified increase of bilateral mastectomies that took place over the last 15 years worldwide. Conversely, the awareness of a positive test may help patients to choose their favorite surgical option and physicians to tailor neoadjuvant and adjuvant therapies. Large scale genetic testing with NGS will provide more in depth information on the risks associated with variants of unknown significant (VUS) of BRCA1/2 and with other cancer predisposing genes. Better knowledge may hopefully lead to the creation of decision-making/aiding algorithms that will better take into account the complex interplay between clinical, biological and treatment variables (Figure 4) that characterizes the care of these patients.

Acknowledgments

This study is supported by FPRC 5xmille Ministero della Salute 2015 (Strategy); FPRC 5xmille Ministero della Salute 2013; Ricerca Corrente 2019.

Funding: None.

Footnote


Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References


