S10 Supporting Information. Confounding and/or mediating factors.

A. Differences in confounders and mediating factors between BRCA1 and BRCA2 mutation carriers compared to ‘non-carriers’ reported in studies included in this review.

<table>
<thead>
<tr>
<th>Factors* →</th>
<th>Higher grade tumours</th>
<th>Higher stage tumours</th>
<th>LN+ tumours</th>
<th>Large size tumours</th>
<th>ER+ tumours</th>
<th>CT received</th>
<th>HT received</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td><strong>BRCA1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies describing differences of the factor* for BRCA1 carriers compared to ‘non-carriers’</td>
<td>19</td>
<td>4.2</td>
<td>12</td>
<td>26.7</td>
<td>22</td>
<td>48.9</td>
<td>19</td>
</tr>
<tr>
<td>Studies reporting a lower percentage of the factor* in BRCA1 carriers compared to ‘non-carriers’</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>8.3</td>
<td>6</td>
<td>27.3</td>
<td>2</td>
</tr>
<tr>
<td>Studies reporting a equal distribution of the factor* in BRCA1 carriers compared to ‘non-carriers’</td>
<td>3</td>
<td>15.8</td>
<td>10</td>
<td>83.3</td>
<td>12</td>
<td>54.5</td>
<td>13</td>
</tr>
<tr>
<td>Studies reporting a higher percentage of the factor* in BRCA1 carriers compared to ‘non-carriers’</td>
<td>16</td>
<td>84.2</td>
<td>1</td>
<td>8.3</td>
<td>4</td>
<td>18.1</td>
<td>4</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies describing differences of the factor* for BRCA2 carriers compared to ‘non-carriers’</td>
<td>7</td>
<td>29.2</td>
<td>8</td>
<td>33.3</td>
<td>13</td>
<td>54.2</td>
<td>9</td>
</tr>
<tr>
<td>Studies reporting a lower percentage of the factor* in BRCA2 carriers compared to ‘non-carriers’</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>7.7</td>
<td>0</td>
</tr>
<tr>
<td>Studies reporting a equal distribution of the factor* in BRCA2 carriers compared to ‘non-carriers’</td>
<td>4</td>
<td>57.1</td>
<td>4</td>
<td>50</td>
<td>6</td>
<td>46.2</td>
<td>6</td>
</tr>
<tr>
<td>Studies reporting a higher percentage of the factor* in BRCA2 carriers compared to ‘non-carriers’</td>
<td>3</td>
<td>42.9</td>
<td>4</td>
<td>50</td>
<td>6</td>
<td>46.2</td>
<td>3</td>
</tr>
</tbody>
</table>

*Selection of studies included in this review and reporting any risk estimate for survival (independent of the type) of BRCA1 mutation carriers compared to ‘non-carriers’ (total n = 45 [1-38]). Selection of studies included in this review and reporting any risk estimate for survival (independent of the type) of BRCA2 mutation carriers compared to ‘non-carriers’ (total n = 24 [5,6,9,12,14,16,19,21,22,26,27,29,30,32,35,36,38-42]). LN+ tumours = tumours with spread to the lymph nodes at diagnosis; ER+ tumours = tumours which have expression of the estrogen receptor; CT received = chemotherapy received as adjuvant treatment; HT received = hormonal therapy received as adjuvant treatment.

The differences in tumour characteristics of BRCA1 and BRCA2 mutation carriers compared to ‘non-carriers’ are described in about half of the studies included in this review (depending on the type of tumour characteristic, table above). When reported, mostly differences in grade and/or stage (defined as stage and/or lymph node status and/or size of the tumour) and/or estrogen receptor status were determined. Most of the studies [5,7,8,11,13,16-18,24-26,32,35,36,38] reporting differences in grade of tumours in BRCA1 mutation carriers compared to ‘non-carriers’ [5,7,8,11,13,16-18,23-26,28,32,34-36,38] observed that the percentage of high grade tumours was larger in BRCA1 mutation carriers compared to ‘non-carriers’ (84.2% of the studies; table above). For BRCA2 mutation carriers, of the studies reporting differences in grade of tumours in BRCA2 mutation carriers compared to ‘non-carriers’ [5,6,9,12,14,16,19,21,22,26,27,29,30,32,35,36,38-42], most [5,6,9,12,14,16,19,21,22,27,29,30,40-42] observed an equal distribution of high grade tumours in BRCA2 mutation carriers and ‘non-carriers’ (57.1% of the studies), although none of the studies reported a lower percentage (table above). In contrast, most studies [4,14,25,27,34-38] reporting differences in stage of tumours observed an equal distribution of high stage tumours in BRCA1 mutation carriers compared to ‘non-carriers’. For BRCA2 mutation carriers half [14,16,41] of the studies reported a higher percentage of high stage tumours in BRCA2 mutation carriers compared to ‘non-carriers’, while none of the studies reported a lower percentage (table above). All studies reporting differences in estrogen receptor status of tumours in BRCA1 mutation carriers compared to ‘non-carriers’ [3-5,7,13,17,18,21,22,24-27,32,35-38] observed a higher percentage of estrogen receptor negative tumours in BRCA1 mutation carriers compared to ‘non-carriers’. This was not observed for BRCA2 mutation carriers (table above) [21,22,26,27,32,35,36,38-40,42].

A small part of the studies included in this review also reported differences in therapy given for breast cancer in BRCA1 and BRCA2 mutation carriers compared to ‘non-carriers’ (table above). About half of the studies [3,21,22,25,43] observed that a higher percentage of BRCA1 mutation carriers received chemotherapy compared to non-carriers (none of the studies reported that a lower percentage of BRCA1 mutation carriers received chemotherapy). Furthermore, most of the studies [3,18,21,24,25,32,34,36,38] (83.3%) reported that a lower percentage of hormone therapy was given to BRCA1 mutation carriers compared to ‘non-carriers’. Such differences were not seen when looking at studies reporting differences in treatment given to BRCA2 mutation carriers compared to ‘non-carriers’ (table above) [21,22,32,36,38].
B. Effect of adjustment for tumour characteristics and/or treatment on Hazard ratios.

To examine the effect of adjustment for confounders on the prognosis of BRCA1 and BRCA2 mutation carriers, we compared pairs of unadjusted HR (HR\text{unadjusted}) and adjusted HR (HR\text{adjusted}). Because of the low numbers of HR pairs per outcome and the large differences in confounders/mediating variables adjusted for, we could not stratify for these factors in the analysis.

Twenty-three unadjusted plus adjusted HR pairs have been reported for the relation between BRCA1 carriership and survival [3,4,13,16,18,24,25,27,32,34,38]. In 13 HR pairs [3,4,13,16,18,24,27,32,38] a worse unadjusted survival for BRCA1 mutation carriers compared to ‘non-carriers’ was reported (HR\text{unadjusted}>1); after adjustment for confounders/mediating variables, in nine pairs [13,16,18,24,27,38] (75%) the HR became weaker (but still in the same direction) or changed to the direction of a better prognosis (HR\text{adjusted}<1). For the other four HR pairs [3,4,27,32] (31%), the adjusted estimates were equal (difference HRs<0.1) (n=1 [27]) or became stronger (n=3 [3,4,32]). Furthermore, there were nine HR pairs [25,32,34] with a better unadjusted survival for BRCA1 mutation carriers compared to ‘non-carriers’ (HR\text{unadjusted}<1). In the majority of these pairs the effect was still in the same direction after adjustment; stronger in three pairs [25] (33%), equal (difference HRs<0.1) in two pairs [32,34] (22%) and weaker in two pairs [34] (22%). In two pairs [32] (22%) the effect changed to a worse prognosis (HR\text{adjusted}>1) (Table 4).

Ten unadjusted plus adjusted HR pairs have been reported for the relation between BRCA2 carriership and survival [27,29,38-42]. In seven HR pairs [27,29,38,39,41] a worse unadjusted survival for BRCA2 mutation carriers compared to ‘non-carriers’ was observed (HR\text{unadjusted}>1); six of these [27,29,38,39,41] (86%) reported a weaker effect in the same direction or even to the direction of a better prognosis after adjustment. Only in one [27] (14%) of these HR pairs the adjusted estimate was stronger. For the three other HR pairs [40,42] with a better unadjusted survival for BRCA2 mutation carriers (HR\text{unadjusted}<1), one [40] showed a stronger effect after adjustment; in the two others [40,42] the effect was equal (difference HRs<0.1) (Table 4).
References


