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.

Factors* →	Higher grade tumours		Higher stage tumours		LN+ tumours		Large size tumours		ER+ tumours		CT received		HT received	
	N	*%*	N	*%*	N	*%*	N	*%*	N	*%*	N	*%*	N	*%*
BRCA1														
Studies describing differences of the factor* for *BRCA1* carriers compared to 'non-carriers'[a]	19	*4.2*	12	*26.7*	22	*48.9*	19	*42.2*	19	*42.2*	11	*24.4*	12	*26.7*
Studies reporting a lower percentage of the factor* in *BRCA1* carriers compared to 'non-carriers'	0	*0*	1	*8.3*	6	*27.3*	2	*10.5*	19	*100*	0	*0*	10	*83.3*
Studies reporting a equal distribution of the factor* in *BRCA1* carriers compared to 'non-carriers'	3	*15.8*	10	*83.3*	12	*54.5*	13	*68.4*	0	*0*	5	*45.5*	2	*16.7*
Studies reporting a higher percentage of the factor* in *BRCA1* carriers compared to 'non-carriers'	16	*84.2*	1	*8.3*	4	*18.1*	4	*21.1*	0	*0*	6	*54.5*	0	*0*
BRCA2														
Studies describing differences of the factor* for *BRCA2* carriers compared to 'non-carriers'[b]	7	*29.2*	8	*33.3*	13	*54.2*	9	*37.5*	12	*50*	4	*16.7*	5	*20.8*
Studies reporting a lower percentage of the factor* in *BRCA2* carriers compared to 'non-carriers'	0	*0*	0	*0*	1	*7.7*	0	*0*	1	*8.3*	0	*0*	1	*20*
Studies reporting a equal distribution of the factor* in *BRCA2* carriers compared to 'non-carriers'	4	*57.1*	4	*50*	6	*46.2*	6	*66.7*	8	*66.7*	3	*75*	4	*80*
Studies reporting a higher percentage of the factor* in *BRCA2* carriers compared to 'non-carriers'	3	*42.9*	4	*50*	6	*46.2*	3	*33.3*	3	*25*	1	*25*	0	*0*

[a]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]); [b]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 (HRunadjusted) and adjusted HR (HRadjusted). 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 (HRunadjusted>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 (HRadjusted<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' (HRunadjusted<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 (HRadjusted>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 (HRunadjusted>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 (HRunadjusted<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).

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