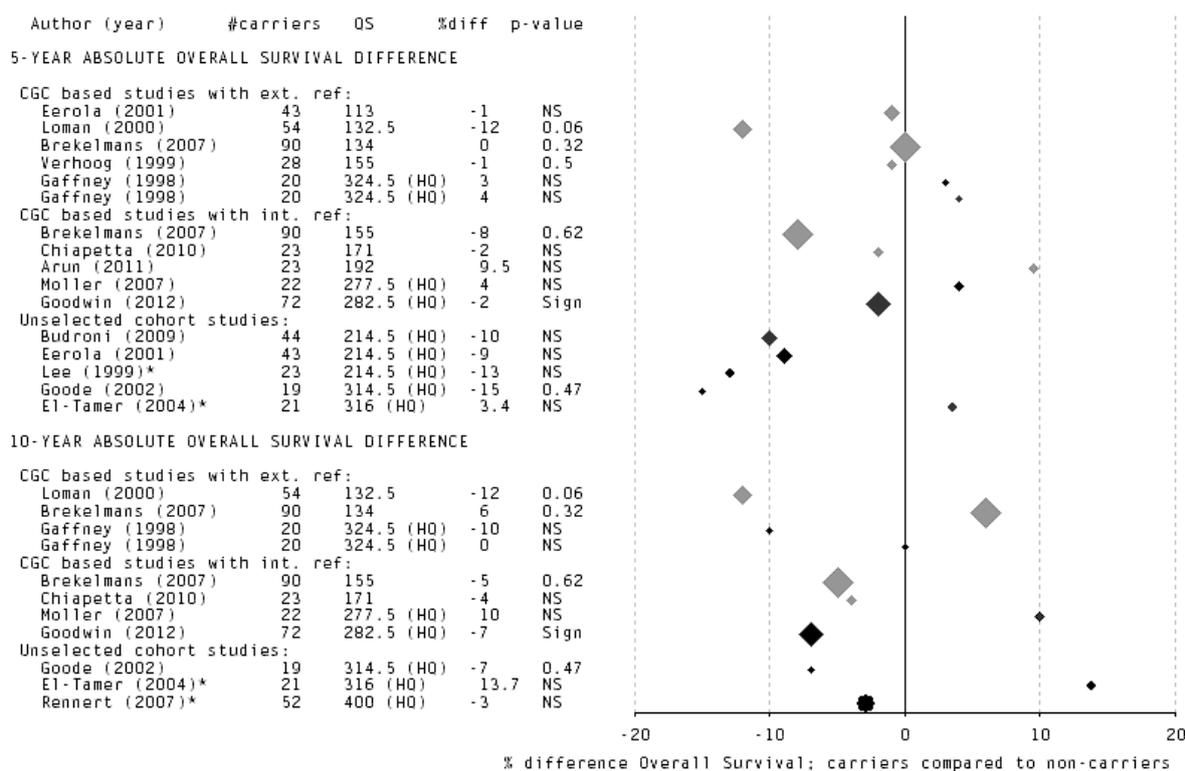


S5 Supporting Information. Results *BRCA2* mutation carriership.

Forest plots (the forest plots are also shown outside the Supporting information (Figs. 4A-D), but are repeated here for readability): size of the bullet represents the number of included carriers; black bullet = HQ study; round bullet (●) and * = A. Jewish study population, only founder mutations tested; square bullet (■) and ** = specific study population (but not A. Jewish), in which only founder mutations were tested; — = 95% Confidence interval (only for hazard ratios); CGC based studies with ext. ref. = CGC based studies with external reference group; CGC based studies with int. ref. = CGC based studies with internal reference group; Sign = statistically significant ($P < 0.05$); NS = not statistically significant; NR = not reported; †Adjusted for clinico-pathological characteristics and/or treatment.

A. *BRCA2* mutation carriership and overall survival (OS)

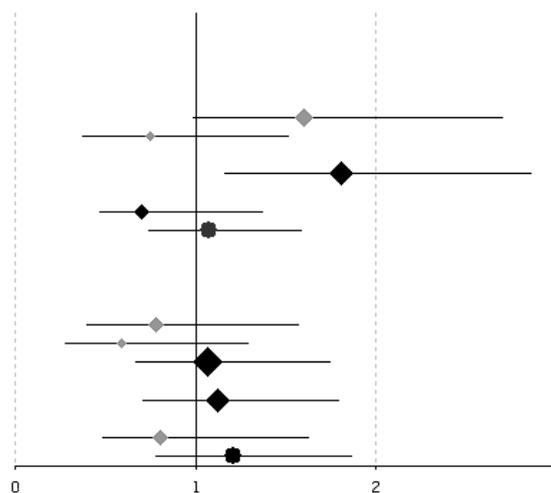
Absolute OS differences: *BRCA2* mutation carriers compared to ‘non-carriers’



The forest plot above shows the absolute OS differences of *BRCA2* compared to ‘non-carriers’ reported by studies included in this review. Five studies [1-4] (31%) reported a better 5-year absolute OS for *BRCA2* compared to ‘non-carriers’, but four [1,2,4] of these studies reported survival differences smaller than 5%. On the other hand, ten studies [5-13] (63%) reported a worse 5-year absolute OS, with differences ranging from 1% to 15% including one [13] statistically significant difference of 2%. Three studies [2,3,12] (27%) reported a better 10-year absolute OS for *BRCA2* compared to ‘non-carriers’, with differences of 6% and 13.7%. Comparable to the 5-year results, more studies (seven [1,7,9,11-14] (64%)) reported again a worse OS, with 10-year absolute OS differences ranging from 3% to 12%; including the same study [13] reporting a statistically significant difference of 7%.

Hazard ratios for OS: *BRCA2* mutation carriers compared to ‘non-carriers’

Author (year)	#carriers	OS	HR	CI95%
UNADJUSTED HAZARD RATIO FOR OVERALL SURVIVAL				
CGC based studies with ext. ref:				
Loman (2000)	54	132.5	1.6	0.98-2.7
Verhoog (1999)	28	155	0.75	0.37-1.51
CGC based studies with int. ref:				
Goodwin (2012)	72	282.5 (HQ)	1.81	1.15-2.86
Unselected cohort studies:				
Budroni (2009)	44	214.5 (HQ)	0.7	0.46-1.37
Rennert (2007)*	52	400 (HQ)	1.07	0.73-1.58
ADJUSTED† HAZARD RATIO FOR OVERALL SURVIVAL				
CGC based studies with ext. ref:				
Eerola (2001)	43	172	0.78	0.39-1.57
Verhoog (1999)	28	275	0.59	0.27-1.29
Brekelmans (2007)	90	310 (HQ)	1.07	0.66-1.74
CGC based studies with int. ref:				
Goodwin (2012)	72	458.5 (HQ)	1.12	0.7-1.79
Unselected cohort studies:				
Budroni (2009)	44	288.5	0.8	0.48-1.62
Rennert (2007)*	52	538 (HQ)	1.2	0.77-1.86



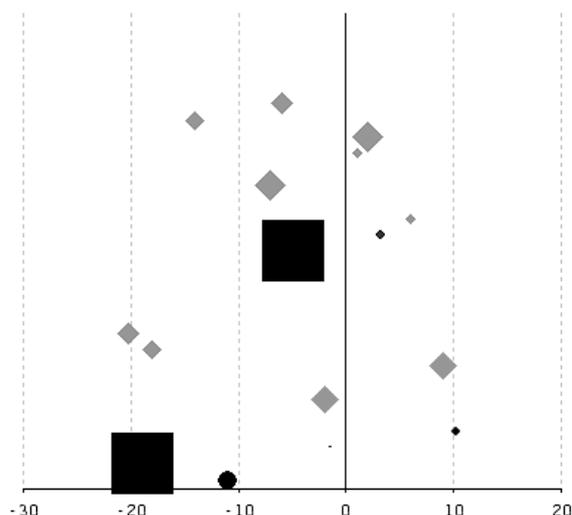
Hazard ratio for Overall Survival; carriers compared to non-carriers

The forest plot above shows the seven studies [6-8,10,12-14] reporting adjusted and/or unadjusted HRs for OS for *BRCA2* compared to ‘non-carriers’. Three [7,13,14] (60%) of the five studies [6,7,10,13,14] reporting an unadjusted HR found a worse OS for *BRCA2* mutation carriers; one study [14] only observed a slight increased HR (1.07), however, another study [13] observed a HR which was statistically significant. The other two studies [6,10] (40%) reported a non-significant better unadjusted OS for *BRCA2* mutation carriers. For the adjusted OS for *BRCA2* compared to ‘non-carriers’, three studies [6,8] (50%) reported a better adjusted OS, while three other studies [12,14] (50%) reported a worse OS. None of these results were statistically significant.

B. *BRCA2* mutation carrier and breast cancer-specific survival (BCSS)

Absolute BCSS differences: *BRCA2* mutation carriers compared to ‘non-carriers’

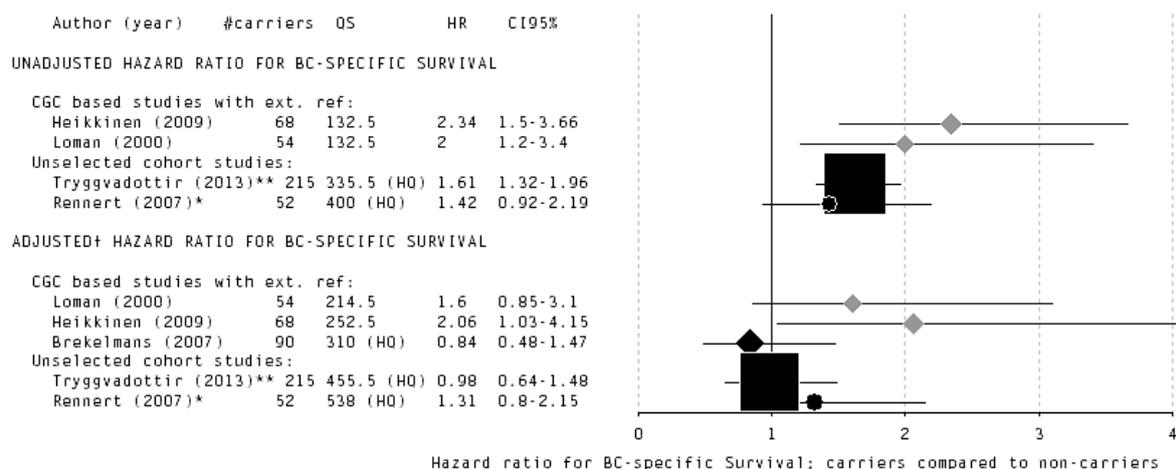
Author (year)	#carriers	OS	%diff	p-value
5-YEAR ABSOLUTE BC-SPECIFIC SURVIVAL DIFFERENCE				
CGC based studies with ext. ref:				
Heikkinen (2009)	68	132.5	-6	0.00
Loman (2000)	54	132.5	-14	0.00
Brekelmans (2007)	90	134	2	0.17
Verhoog (1999)	28	155	1	0.4
CGC based studies with int. ref:				
Brekelmans (2007)	90	155	-7	0.92
Unselected cohort studies:				
Xu (2012)	28	171	6	NS
E1-Tamer (2004)*	21	316 (HQ)	3.1	NS
Tryggvadottir (2013)**	215	335.5 (HQ)	-5	0.00
10-YEAR ABSOLUTE BC-SPECIFIC SURVIVAL DIFFERENCE				
CGC based studies with ext. ref:				
Heikkinen (2009)	68	132.5	-20.3	0.00
Loman (2000)	54	132.5	-20	0.00
Brekelmans (2007)	90	134	9	0.17
CGC based studies with int. ref:				
Brekelmans (2007)	90	155	-2	0.92
Unselected cohort studies:				
E1-Tamer (2004)*	21	316 (HQ)	10.1	NS
Robson (2004)*	14	316 (HQ)	-1.5	0.76
Tryggvadottir (2013)**	215	335.5 (HQ)	-19	0.00
Rennert (2007)*	52	400 (HQ)	-11	NS



% difference BC-specific Survival; carriers compared to non-carriers

The forest plot above shows the absolute BCSS differences of *BRCA2* compared to ‘non-carriers’ reported by studies included in this review. Four studies [2,6,12,15] (50%) reported a better 5-year absolute BCSS for *BRCA2* compared to ‘non-carriers’, though all reported survival differences were less than 6%. The other four studies [7,12,16,17] (50%) reported a 5% to 14% worse 5-year BCSS for *BRCA2* mutation carriers, including three [7,16,17] statistically significant results. Only two studies [2,12] (25%) reported a better 10-year absolute BCSS for *BRCA2* compared to ‘non-carriers’ with absolute differences of 9% and 10.1%, while six studies [7,12,14,16-18] (75%) reported a worse 10-year BCSS for *BRCA2* mutation carriers, with differences ranging from 1.5% to 20.3% including three [7,16,17] statistically significant results.

Hazard ratios for BCSS: *BRCA2* mutation carriers compared to ‘non-carriers’



The forest plot above shows the univariate and multivariate hazard ratios for BCSS of *BRCA2* compared to ‘non-carriers’ reported by studies included in this review. For BCSS of *BRCA2* compared to ‘non-carriers’, only five studies [7,12,14,16,17] reported an HR; all four studies [7,14,16,17] reporting an unadjusted HR observed a worse BCSS for *BRCA2* mutation carriers, with HRs ranging from 1.42 to 2.34 and three [7,16,17] statistically significant results. On the other hand, three [7,14,17] (60%) of the five studies [7,12,14,16,17] reporting an adjusted HR found a worse adjusted BCSS for *BRCA2* compared to ‘non-carriers’; also only one [17] of these studies reported a statistically significant result. Two studies [12,16] (40%) reported a better adjusted BCSS for *BRCA2* mutation carriers (HR 0.98 and 0.84).

C. *BRCA2* mutation carriership and metastasis-free survival (MFS)

There were only three studies [12,13] which reported the 5 and 10-year absolute MFS differences for *BRCA2* compared to ‘non-carriers’ (no figures shown). One substudy by Brekelmans and colleagues [12] did not find any difference, though the other substudy [12] reported a respectively 9% and 11% 5- and 10-year better absolute MFS for *BRCA2* mutation carriers. The HQ study by Goodwin and colleagues [13] reported a statistically significant 11% and 6% 5- and 10-year worse absolute MFS for *BRCA2* mutation carriers and also a statistically significant unadjusted HR of 1.63 (95% CI 1.02-2.6). In contrast, the adjusted HR which this study [13] reported was 1 (95% CI 0.62-1.61). The adjusted HR reported in the substudy of Brekelmans and colleagues [12] was 0.75 (95% CI 0.44-1.29).

D. *BRCA2* mutation carriership and recurrence-free survival (RFS)

Five studies [2,4,6,12] (one HQ study [2]) reported 5-year absolute RFS differences for *BRCA2* compared to ‘non-carriers’ (no figure shown); three studies [2,12] (60%) observed a 5% to 9% worse absolute RFS for *BRCA2* mutation carriers. The substudies of Brekelmans and colleagues [12] also reported 10-year absolute RFS differences, i.e. 4% (better survival) and 2% (worse survival) for *BRCA2* compared to ‘non-carriers’. On the other hand, Arun and colleagues [4] observed a 19.4% better 5-year absolute RFS for *BRCA2* mutation carriers. Another study by Verhoog and colleagues [6] did not find any difference in 5-year absolute RFS between *BRCA2* and ‘non-carriers’, and additionally reported an unadjusted HR of 0.92 (95% CI 0.52-1.63). Adjustment of this HR made it stronger (HR 0.84, 95% CI 0.44-1.63). One substudy of Brekelmans and colleagues [12] also reported an adjusted better RFS for *BRCA2* mutation carriers (HR 0.85, 95% CI 0.26-2.77). None of the above results were significant.

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