

# Breast and ovarian cancer risks to carriers of the BRCA1 5382insC and 185delAG and BRCA2 6174delT mutations: a combined analysis of 22 population based studies

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A recent report estimated the breast cancer risks in carriers of the three Ashkenazi founder mutations to be higher than previously published estimates derived from population based studies. In an attempt to confirm this, the breast and ovarian cancer risks associated with the three Ashkenazi founder mutations were estimated using families included in a previous meta-analysis of population based studies. The estimated breast cancer risks for each of the founder BRCA1 and BRCA2 mutations were similar to the corresponding estimates based on all BRCA1 or BRCA2 mutations in the meta-analysis. These estimates appear to be consistent with the observed prevalence of the mutations in the Ashkenazi Jewish population.

We recently reported the average risks of breast and ovarian cancer associated with BRCA1 and BRCA2 mutations, using a meta-analysis of pedigree data from 498 BRCA1 and BRCA2 mutation carriers identified through population based studies of women with breast and ovarian cancer.<sup>1</sup> King *et al*<sup>2</sup> estimated the risks to carriers in the three Ashkenazi founder mutations (BRCA1 185delAG and 5382insC, and BRCA2 6174delT) by genotyping the relatives of 104 mutation carriers. They concluded that the risks are higher than both our estimates or other previously published estimates.<sup>3–6</sup> To provide a more direct comparison between the two studies, we estimated the breast and ovarian cancer risks associated with the three Ashkenazi founder mutations using families included in our meta-analysis.

Among the index cases studied by Antoniou *et al*,<sup>1</sup> 75 were BRCA1 185delAG carriers, 69 were BRCA1 5382insC carriers, and 52 were BRCA2 6174delT carriers. Sixty three (84%) of the 185delAG mutation carriers and 42 (81%) of the 6174delT mutation carriers were identified through studies of Ashkenazi Jewish populations. However, only 22 (32%) of

the 5382insC carriers were identified through such studies, while 34 carriers (49%) were of eastern European origin.

We estimated the age specific breast and ovarian cancer incidences in mutation carriers for each mutation separately using the maximum likelihood approach described in Antoniou *et al*.<sup>1</sup> The estimated cumulative breast and ovarian cancer risks are shown in table 1. The breast cancer risks by age 70 were similar in carriers of the 185delAG mutation (64%; 95% confidence interval (CI), 34% to 80%) and the 5382insC mutation (67%, 95%CI, 36% to 83%) ( $p = 0.53$  by likelihood ratio test), although the risks by age 50 were somewhat higher for 5382insC carriers (46% *v* 27%). The breast cancer risks for carriers of the 6174delT mutation were, however, lower (43% by age 70, 95% CI, 14% to 62%;  $p = 0.007$  compared with all BRCA1 mutation carriers). The difference is particularly marked at age 50 (8% *v* 36% for BRCA1 mutations combined). The corresponding ovarian cancer risks were 14% (95% CI, 2% to 24%), 33% (8% to 50%), and 20% (2% to 35%) in carriers of the 185delAG, 5382insC and 6174delT mutations, respectively.

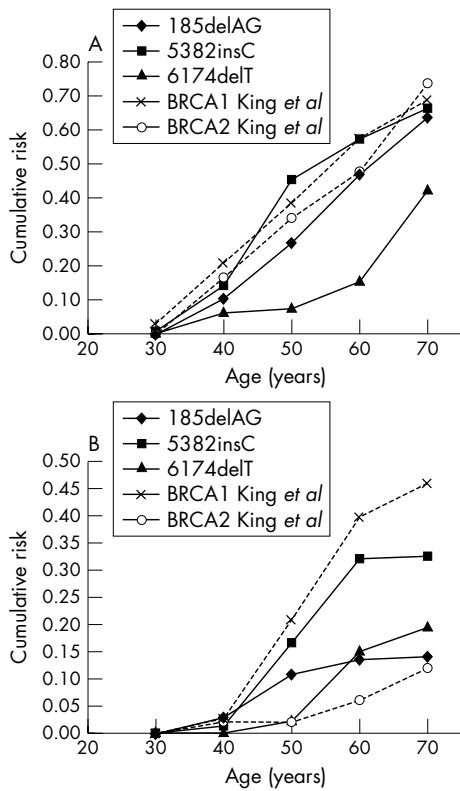
Figure 1 illustrates our penetrance estimates and those obtained by King *et al*.<sup>2</sup> The estimated breast cancer risks in BRCA1 mutation carriers are similar in the two studies (67% by age 70 from our study, for 185delAG and 5382insC combined, compared with 69% obtained by King *et al*<sup>2</sup>). However, there was a substantial difference in the breast cancer risk in BRCA2 6174delT mutation carriers (43% *v* 74%;  $p = 0.016$ ). The 95% confidence intervals for the estimated breast cancer cumulative risks in BRCA2 mutation carriers exclude the corresponding point estimates of King *et al*<sup>2</sup> at all ages. Our lower estimate is more consistent with estimates obtained by other studies.<sup>4–5</sup> The difference in risks between BRCA1 and BRCA2 carriers also appears more consistent with the observed prevalence of the founder mutations among breast cancer cases in the Ashkenazi Jewish population.<sup>7</sup>

Our estimated breast cancer risks for the Ashkenazi founder mutations were similar to the estimates obtained

**Table 1** Estimated cumulative risks of breast and ovarian cancer in carriers of the 185delAG, 5382insC, and 6174delT mutations

Age (years)	Cumulative risks (%) (95% CI)					
	185 del AG		5382insC		6174delT	
	Breast cancer	Ovarian cancer	Breast cancer	Ovarian cancer	Breast cancer	Ovarian cancer
40	10 (3 to 18)	3 (0 to 7)	14 (5 to 23)	2 (0 to 5)	7 (0 to 14)	0
50	27 (13 to 38)	11 (2 to 19)	46 (29 to 59)	17 (4 to 28)	8 (0 to 16)	2 (0 to 7)
60	47 (26 to 62)	14 (2 to 24)	57 (35 to 72)	32 (8 to 50)	16 (1 to 28)	15 (1 to 28)
70	64 (34 to 80)	14 (2 to 24)	67 (36 to 83)	33 (8 to 50)	43 (14 to 62)	20 (2 to 35)

CI, confidence interval.



**Figure 1** Estimated cumulative risks of breast and ovarian cancer (A and B, respectively) in carriers of the 185delAG and 5382insC BRCA1 and 6174delT BRCA2 mutations. The estimates of King *et al*<sup>2</sup> are also included.

from our meta-analysis of population based studies for all BRCA1 and BRCA2 mutations combined.<sup>1</sup> The ovarian cancer risks in 6174delT carriers were somewhat higher than the average BRCA2 risks (20% *v* 11%), consistent with the observation that mutations within the ovarian cancer cluster region are associated with a higher ovarian cancer risk.<sup>8</sup> The ovarian cancer risk in carriers of the 185delAG mutation is lower than expected, but the confidence limits are wide. Moreover, the risks conferred by this mutation are not significantly different from the risks conferred by 5382insC ( $p = 0.53$ ). Given the much larger number of families studied, the overall estimates of Antoniou *et al*<sup>1</sup> probably provide a more reliable basis for risk assessment for carriers of BRCA1 and BRCA2 mutations identified through population studies than estimates based on individual mutations.

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