



# Risk of contralateral breast cancer amongst *BRCA1/2* mutation carriers

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Women harbouring a deleterious mutation in the high penetrance *BRCA1/2* genes have a lifetime risk of up to 85% of developing breast cancer (1). Once diagnosed, they have a significant risk of developing a contralateral breast cancer—approximately 2–3% per year. This risk persists for up to 30 years following an initial breast cancer diagnosis (2).

Management of this group of patients includes consideration of risk reducing strategies. Contralateral risk reducing mastectomy has been shown to improve survival amongst *BRCA1/2* carriers (3-5) but not the remainder of breast cancer patients (6) (discussed later). Rates of contralateral mastectomy have trebled over the last decade (7)—a trend observed in the non-high-risk group.

Stratification of risk is essential to formulate clinically useful guidance on managing this group of breast cancer patients (8). Individualised risk profiles can help determine those women who would derive the greatest benefit from contralateral risk-reducing mastectomy over surveillance strategies.

A recent meta-analysis (9) identified three factors associated with a lower risk of CBC amongst *BRCA* mutation carriers:

- (I) Age at first breast cancer diagnosis;
- (II) Oophorectomy;
- (III) Tamoxifen.

## Age of first breast cancer

One of the largest studies to date examined incidence of CBC amongst breast cancer patients with a *BRCA1* or

*BRCA2* mutation (2). The authors used a multivariable delayed entry cox regression model to confirm that young age (<40 years) at initial breast cancer diagnosis was the only consistent risk factor amongst this patient group. In addition, women with a *BRCA1* mutation had an approximately 3% higher cumulative rate of CBC compared to *BRCA2* carriers over a 30-year period—a finding substantiated in other studies (10).

A recent study from the Netherlands showed a survival benefit from CRRM amongst *BRCA* mutation carriers (5). The greatest survival benefit was derived amongst women diagnosed with their breast cancer before the age of 40 years as well as those not having chemotherapy and favourable histology (Grade 1/2 cancers and non-triple negative status).

## Oophorectomy

The impact of oophorectomy on breast cancer risk amongst this high-risk group is complex. The meta-analysis (9) showed that BRRSO was associated with a reduced risk of developing CBC (RR =0.52; 95% CI: 0.37–0.74). Similarly, BRRSO has been shown to reduce the risk of developing breast cancer amongst healthy *BRCA1/2* carriers by almost 50%.

However, a study from the Netherlands (11) has questioned whether previous studies including those used in the meta-analysis, had overestimated the breast cancer risk-reduction following BRRSO in healthy *BRCA1/2* mutation carriers. The main issue had been the use of different study designs and analytical methods resulting several forms of

selection bias (cancer induced testing bias, immortal person-time bias and informative censoring). The Dutch study showed no real protective effect from BRRSO when adjusting for the already described biases, but numbers of *BRCA2* carriers who develop predominantly ER+ breast cancers were small and follow up time was limited due to study design. A more recent study has shown a longer-term benefit from BRRO in *BRCA2* but not *BRCA1* carriers after appropriate censoring (12). Following on from this, a UK study assessed the role of BRRSO on CBC development amongst breast cancer patient harbouring a *BRCA* mutation (2). A standard Kaplan-Meier estimator showed that BRRSO had a significant effect on reducing CBC risk (HR =0.35; 95% CI: 0.2–0.61; P<0.001). Reanalysis taking into account the various biases showed no significant risk reduction (HR =0.83; 95% CI: 0.46–1.50; P=0.532). The authors concluded that caution should be exercised when counselling breast cancer patients with a *BRCA1/2* mutation on the expected breast cancer risk-reduction following BRRSO.

### Tamoxifen

Several randomised control studies have confirmed that tamoxifen and aromatase inhibitors are associated with a reduction in risk of CBC amongst breast cancer patients at general population risk (13,14). *BRCA1* associated breast cancers tend to be ER-ve (oestrogen receptor) compared to *BRCA2* where almost 80% are ER+ve (1).

Several studies have shown that tamoxifen use is associated with a reduction in CBC only in ER+ve tumours (15). The role of tamoxifen in reduction of CBC risk in *BRCA1/2* patients has been evaluated in a large international study (16). Tamoxifen use was associated with a reduction of CBC by almost a third—a trend seen irrespective of oestrogen receptor status. In addition, short-term use of tamoxifen (up to 1 year) offered equal or greater protection compared to the recommended use (5 years) (17).

Duration of use is of particular importance to women considering risk-reduction strategies. Short-term use of tamoxifen up to 1 year may be considered if women are uncertain of surgical options of risk-reduction (discussed later) or where the potential risk of side-effects (thromboembolism and endometrial cancer) needs to be minimised.

The CBC risk-reduction observed with tamoxifen use in *BRCA1* mutation carriers suggests that *BRCA1* related cancers may have an oestrogen sensitive phase—a theory supported by the reduction of breast cancer observed in pre-menopausal *BRCA* mutation carriers undergoing

BRRO. However, with further evidence of the BRRO effect being confined to *BRCA2* (12) this must also be treated with caution until left censoring is carried out to exclude bias in the tamoxifen studies also. Furthermore, the identification of 2 single nucleotide polymorphisms (discussed later) close to the *ESR1* gene (encodes ER1alpha) that are associated with increased breast cancer risk amongst *BRCA1* may account for the breast cancer risk reduction seen with tamoxifen use (if it is real) in *BRCA1* carriers.

### Other modifiers of CBC risk

#### SNPs

Considerable variations of risk exist amongst *BRCA1/2* mutation carriers. Through large scale GWAS, common SNPs associated with breast cancer risk in the general population have been studied and in particular modifiers of risk in *BRCA1/2* mutation carriers (18). Several of these SNPs have been shown to increase the risk of developing breast cancer. Amongst some *BRCA2* carriers the risk of developing breast cancer can be increased from as much as 42% to 96%, with several studies assessing the clinical utility of SNPs in risk prediction (19).

The WECARE study examined the role of 21 SNPs associated with increased breast cancer risk in a population based case-control setting comparing women who developed a CBC and those who had unilateral breast cancer only (20). Three SNPs were associated with an increased risk (RR =1.25) of CBC—10q26 (*FGFR2*), 8q24, and 2q35. In addition, particular combinations of SNPs and radiation doses were associated with an increased risk of CBC.

The role of SNPs in assessing the risk of CBC amongst *BRCA1* and *BRCA2* has recently been evaluated (2). Assessment of 18 validated SNPs associated with breast cancer risk was unable to differentiate CBC risk in these high-risk patients. The authors used weightings based on the general population of breast cancer that were less likely to be predictive for the ER negative breast cancers that account for up to 75% of *BRCA1* associated breast cancers. The authors concluded that continued international collaborations may unravel further SNPs that may be used to individualise CBC risk assessment amongst *BRCA* mutations carriers.

#### Contralateral risk reducing mastectomy

Three studies to date have shown a survival benefit for

CRRM amongst breast cancer patients with a *BRCA1/2* mutation (3-5). A study from Manchester followed up 718 *BRCA1/2* mutation carriers with unilateral breast cancer over a 10-year period (2). The 10-year survival amongst those who underwent CRRM (n=105) was 89% compared to 71% in a matched group who did not undergo CRRM (n=593).

This benefit was confirmed by a North American study (4) of 390 similar patients. At 20 years, 88% of those who underwent CRRM were alive compared to 66% of those who did not. Multivariate analysis controlling for several of the confounding factors showed that CRRM in this high-risk group was associated with a 48% reduction in mortality from breast cancer.

## Discussion

Breast cancer patients who are identified as carrying a *BRCA1/2* mutation are amongst those at highest risk of developing a contralateral breast cancer. Mainstream genetic testing has the potential unravel more breast cancer patients who harbour such a genetic mutation. As such, an objective assessment of risk factor for CBC is essential to make evidence based recommendation.

Following a diagnosis of breast cancer, these high-risk group patients will have a 2–3% per year risk of breast cancer—constant for almost 3 decades. Those whose breast cancer was diagnosed before the age of 40 years are at particularly heightened risk and would benefit most from risk-reducing strategies.

CRRM may half the risk of death from breast cancer over a 20-year period. In addition, the CBC risk reduction from BRRSO needs to be carefully assessed as it may have been overestimated especially for *BRCA1*. However, risk reduction from ovarian cancer should not be overlooked when considering BRRSO.

Chemoprevention for at least 1 year with tamoxifen may reduce the risk of CBC by a third. To our knowledge, the role of aromatase inhibitors in this population group has not been assessed.

Assessment of CBC risk amongst breast cancer patients with a *BRCA1/2* mutation should consider the above factors. Further efforts are required to unravel additional genetic and non-genetic modifiers of risk to offer personalised risk scores.

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