# Is breast conservation a reasonable option for women with BRCA-associated breast cancer?

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A recent study has shown that women with *BRCA* mutations are as likely to achieve local control with breast-conserving treatment as women without mutations, but have increased long-term risk of ipsilateral and contralateral breast cancer.

When considering *BRCA1/2* testing, patients and physicians usually concentrate on defining and managing future cancer risks, but what about the woman with recently diagnosed breast cancer? Should germline *BRCA* status be taken into account when decisions are being made about her local and systemic treatment? Does the presence of a germline mutation have enough of an impact on treatment choices that peridiagnostic testing should be offered to women of unknown mutation status who are at a significant risk for these mutations, such as young women with 'triple-negative' disease? The paper by Pierce et al. (see opposite) bears strongly upon these questions.

Ten years after the discovery of *BRCA1* and *BRCA2*, breast-conservation therapy (BCT) for *BRCA*-associated breast cancer (BABC) remains controversial.[1] Studies examining the question are limited by ascertainment biases, small size and relatively short follow-up. Despite these limitations, most reports broadly agree that the short-term (five-year) risk of an in-breast tumour recurrence (IBTR) event after breast conservation for BABC is 12–15%, and that the actuarial risk over this time frame is not significantly greater than that for women without mutations; however, there are reports of higher rates of metachronous ipsilateral cancer with longer follow-up. Groups in the US and the Netherlands described actuarial risks as high as 49% at 12–15 years.[2,3] These alarming estimates might not be robust given the small number of patients at risk for more than 10 years in these studies, and it is reassuring that larger series from North America[4] and the Netherlands[5] confirm the findings of Pierce et al. – a 12% ipsilateral risk at 10 years. Even so, longer follow-up may yet reveal a greater risk. In the report by Pierce et al., for example, the rate of IBTR in carriers and non-carriers appeared to separate after 10 years of follow-up, and rose to 24% at 15 years in carriers. This increase is likely to reflect an ongoing risk of developing second ipsilateral primary cancers, a risk that may be deferred, but not eliminated, by adjuvant radiation.

Is breast conservation, therefore, appropriate for women with *BRCA* mutations? It seems that BABC and non-hereditary breast cancer are equally likely to be sterilised by local excision and adjuvant radiotherapy. So, for treatment of the established breast cancer, BCT is indeed a reasonable option; however, the significant risk of contralateral cancer and late ipsilateral metachronous primaries is not completely ameliorated by oophorectomy or tamoxifen. The substantial

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This article was first published in *Nature Clinical Practice Oncology* 2007 vol. 4 no. 1, and is reproduced with permission.
www.nature.com/clinicalpractice, doi:10.1038/ncponc0687, 

contralateral cancer risk, in particular, could lead carriers who are otherwise candidates for BCT to choose to undergo bilateral mastectomy to reduce these risks, recognising that the impact on survival is uncertain. Since adjuvant radiation may compromise reconstruction options, early genetic testing could benefit women who would consider preventive mastectomy if they were shown to carry a mutation, even if they may require postmastectomy radiotherapy on other grounds such as extent of nodal involvement. Successful communication of genetic prognostic information in the peridiagnostic setting remains a critical challenge, because of the psychological risks of 'information overload'.

*References*

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# Synopsis

*LJ Pierce, AM Levin, TR Rebbeck et al. (2006)* **Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer.** *J Clin Oncol 24:2437–2443*

**Background.** There is no consensus on the usefulness of a breast-conservation approach for *BRCA1/2* mutation carriers

**Objective.** To compare the outcomes of treatment with breast-conservation therapy (BCT) and radiotherapy in *BRCA1/2* mutation carriers with breast cancer compared with matched controls with sporadic breast cancer. The potential impact of oophorectomy and tamoxifen on rates of in-breast tumour recurrence (IBTR) and the development of contralateral breast cancer (CBC) was also studied.

**Design and intervention.** In this retrospective cohort study conducted in 11 institutions in the US, Canada and Israel, women with deleterious germline *BRCA1/2* mutations treated with BCT for a first primary breast cancer (stage I/II) were matched by age (within 2 years) and date of diagnosis (within 6 months) to controls with sporadic breast cancer (stage I/II). Patients who had a low probability of having a detectable mutation in either gene (<5%) were defined as having sporadic disease. Clinical data were retrieved through record review.

**Outcome measures.** Rates of IBTR and CBC were assessed.

**Results.** A total of 160 women with a deleterious germline *BRCA1/2* mutation and 445 controls were followed for median observation times of 7.9 and 6.7 years, respectively. No significant difference was found between carriers and controls for IBTR: 10-year and 15-year estimates were 12% (95% CI 9–15%) and 24% (95% CI 17–33%) for carriers and 9% (95% CI 7–10%) and 17% (95% CI 12–21%) for controls, respectively (hazard ratio [HR] 1.37, $P$=0.19). On multivariate analysis, excluding carriers who had undergone oophorectomy, *BRCA1/2* mutation status was an independent predictor of IBTR (HR 1.9; $P$=0.04). No significant difference was found between carriers who had undergone oophorectomy and sporadic controls for incidence of IBTR ($P$=0.37). Rates of CBC were greater in carriers versus controls: 10-year and 15-year estimates were 26% (95% CI 22–30%) and 39% (95% CI 31–47%) for carriers and 3% (95% CI 2–4%) and 7% (95% CI 5–10%) for controls, respectively (HR 9.57; $P$<0.0001). In mutation carriers who had not undergone oophorectomy, there were no local failures following tamoxifen treatment, in comparison with rates of 8%, 17% and 31% at 5, 10 and 15 years, respectively, without tamoxifen treatment. Tamoxifen use also reduced risk of CBCs in mutation carriers (HR 0.31; $P$=0.05).

**Conclusion.** The authors recommend considering bilateral oophorectomy and tamoxifen use in individuals with the *BRCA1* or the *BRCA2* mutation who prefer breast conservation, although additional risk reduction interventions are needed in these patients, particularly for long-term prevention of CBC.

*Acknowledgement:* The synopsis was written by Petra Roberts, Associate Editor, *Nature Clinical Practice*.