Breast Cancer Prevention in Women with a BRCA1 or BRCA2 Mutation

Kelly A. Metcalfe[1,2] & Steven A. Narod[2]

[1]Faculty of Nursing, University of Toronto; [2]Women's College Hospital, Toronto, Ontario

## Introduction

Genetic testing for BRCA1 and BRCA2 mutations has been available for over ten years. Using this technology, we are able to identify women who are at significantly increased risk of developing breast and ovarian cancer. Over the past decade, several advances have been made in the area of cancer prevention. Ultimately, the value of genetic testing for BRCA1 and BRCA2 mutations comes from reducing the number of women who develop breast cancer and the number of women dying of the disease. For BRCA1 carriers, the estimated cumulative risks to age 70 years are 65% for breast cancer and 39% for ovarian cancer. The corresponding risks for BRCA2 carriers are 45% for breast cancer and 11% for ovarian cancer [1] (in comparison, the average woman in the general population has an 11 percent lifetime risk of developing breast cancer and a 1.5 percent risk of developing ovarian cancer). After the initial diagnosis of breast cancer in a *BRCA1* or *BRCA2* carrier, the risk of cancer in the opposite breast is approximately 3% per year.[2-4]. About one in 200 women in North America carries a BRCA1 or BRCA2 mutation [5-7], but among several ethnic groups the prevalence is considerably higher. Notably, the frequency in those of Ashkenazi Jewish ancestry is one in 50 [7, 8]. Other groups with high frequencies of mutations include women from Iceland [9] and Poland [10]. These high prevalence rates are due to the presence of founder mutations (founder mutations are one or more specific mutations in a population which have been inherited from a common ancestor, and which have become amplified through chance effects, often aided by geographical isolation of the population).

-

## Cancer Prevention Options

Women with a BRCA1 or BRCA2 mutation may consider several options for breast cancer prevention. The three main options are prophylactic mastectomy, prophylactic oophorectomy, and chemoprevention (tamoxifen or raloxifene). In addition, a woman may elect to undergo screening (secondary prevention). However, the goal of screening is to detect cancers at an early treatable stage, not to prevent cancer.

*Prophylactic Mastectomy*

A prophylactic mastectomy involves the removal of both breasts in the absence of disease. The goal of prophylactic mastectomy is to prevent breast cancer, thereby eliminating the potential for metastatic spread and death from breast cancer. The effectiveness of prophylactic mastectomy in preventing breast cancer has been established in a small prospective study, and in historical cohort studies of primary and contralateral breast cancers. Meijers-Heijboer and colleagues observed no cases of breast cancer after three years among 76 women who underwent prophylactic mastectomy [11]. Rebbeck and colleagues observed two cases of breast cancer in 191 women after mastectomy, compared to 184 of 378 women who retained their breasts [12]. Metcalfe and colleagues studied contralateral breast cancer in 491 women treated for hereditary breast cancer [2]. Only one contralateral breast cancer was observed among 146 women who had undergone a contralateral mastectomy, versus 33 expected ($P < 0.0001$). These studies suggest that the residual breast cancer risk following mastectomy approaches zero. Currently, total mastectomy is generally recommended over subcutaneous, or nipple-sparing mastectomy, but there are few data about failures of subcutaneous mastectomy and these reports are based on old literature [13]. Technical advances in skin-sparing techniques and the availability of approaches such as muscle-containing flaps or implantable prostheses have broadened the surgical options available to women [14].

*Prophylactic Oophorectomy*

To date, most of the established cofactors for *BRCA1*- associated breast cancers are hormonally-associated [15]. The purpose of an anti-hormonal therapy is to eliminate, or to block the effect of ovarian estrogen, and probably progesterone, or to prevent aromatization of androgen to estrogen. Anti-hormonal approaches include tamoxifen, raloxifene and other SERM's, ovarian ablation (oophorectomy,

radiation or chemical ablation) and aromatase inhibition. Of these, only tamoxifen and oophorectomy have been well studied in women with *BRCA1* or *BRCA2* mutations.

The rationale for the anti-hormonal approach comes from the observation that oophorectomy prevents breast cancer in *BRCA1* and *BRCA2* carriers. Cohort studies estimate the reduction in hereditary breast cancer risk associated with a pre-menopausal oophorectomy to be about 50% [16-18]. A recent case-control study reported that the risk reduction might be even greater if the oophorectomy is performed before age 40 and that the duration of protection is approximately 15 years [19]. Short-term use of estrogen in young women following oophorectomy might abrogate some of the breast cancer protection associated with oophorectomy; however, such interventions in symptomatic young women may be of benefit in improving quality of life. In one study the effectiveness of prophylactic oophorectomy was not reduced by the addition of hormone replacement therapy [18]. There are no comparable data on the degree of protection against breast cancer offered by other forms of ovarian ablation such as radiation or GNRH agonists. A GNRH agonist may be preferred by a woman who wishes to preserve her fertility, but the use of these drugs in *BRCA* carriers is not widespread and their effectiveness in reducing breast cancer risk is unknown. There remains the concern that these non-surgical approaches to ovarian ablation do not address risk for ovarian of fallopian tube cancers.

*Tamoxifen*

Tamoxifen is a selective estrogen receptor modulator (SERM) that competes with estrogen for binding to the estrogen receptor. In humans, tamoxifen acts as an estrogen antagonist in breast tissue, inhibiting the growth of estrogen-dependent breast tumors [20]. On theoretical grounds, tamoxifen should not reduce the incidence of estrogen-receptor negative breast cancers – and most breast cancers which occur in *BRCA1* (but not *BRCA2*) carriers are estrogen-receptor negative. An attempt to address this issue was made in the NSABP P1 trial; however only eight *BRCA1* carriers with breast cancer were identified in the follow-up period [21]. No protective effect was seen with tamoxifen for BRCA1

carriers, but the number of cases is too small for the study to be definitive. In a large case-control study tamoxifen was found to reduce the incidence of contralateral breast cancer in affected *BRCA1* and *BRCA2* carriers by about one-half (OR = 0.5; 95% CI 0.30-0.85)[22]. To the extent that contralateral cancers in carriers are representative of all new primary breast cancers, the results of this study might be extrapolated to the prevention of first primary breast cancers. But this conclusion would be invalid if the two primary cancers were not independent; for example if tamoxifen were given only to ER-positive patients, and if the ER status of bilateral cancers were highly correlated. In a recent study by Weitzel et al, the majority of contralateral breast cancers following ER-positive breast cancer were in fact, ER-negative, suggesting that tamoxifen prevents ER-negative contralateral breast cancers [23].

Recent research with the drug raloxifene has demonstrated that this drug reduces the risk of developing breast cancer in post-menopausal women (NSABP). However, it has not been tested in women with a BRCA1 or BRCA2 mutation. This form of chemoprevention may become an option for post-menopausal women with a BRCA1 or BRCA2 mutation.

*Screening*

The goal of screening is to identify a breast cancer at a stage when surgical cure is likely. Traditionally, this includes small breast cancers (<1 cm) that are node-negative and with no evidence of distant spread. Cure can be expected for the great majority of these cases. But *BRCA1*-associated breast cancers are typically of high grade and are estrogen-receptor negative and so prognosis might be expected to be worse than average. Among *BRCA1* carriers there was little correlation between tumor size and lymph-node positivity in one study; about one-third of *BRCA1* carriers had lymph node metastases detected at diagnosis, regardless of tumor size [24]. Therefore it may be problematic to predict the benefits of screening using survival data generated from a comparison group of non-carriers.

A number of advisory groups in the U.S. and Europe have published recommendations for surveillance for women at hereditary risk for breast cancer and ovarian cancer [25-27]. In general, these

guidelines called for annual mammography beginning around age 25, as well as monthly breast self-examinations (BSE) and clinical breast examination (CBE) once to twice a year.

*BRCA*-associated tumors may be particularly hard to detect mammographically. Pushing margins, breast density, and mutation status contribute independently to false-negative mammograms in *BRCA* heterozygotes [28]. U.S and U.K studies of women under 50 with a family history of breast cancer reported sensitivities of 63-70% [29] and 44% [30], respectively. Goffin and colleagues [31] found that only 2 of 8 breast cancers (25%) in *BRCA1* carriers were detectable by mammogram at diagnosis, versus 27 of 35 (77%) from non-carrier controls ( $p = 0.01$). In a large cohort at a single center, of 12 breast tumors diagnosed in *BRCA* mutation carriers, less than half were found by mammogram [32]. Breast magnetic resonance imaging (MRI) offers the promise of a greatly improved sensitivity of detection of breast cancers in those at high risk. Early studies reported sensitivities in the range of 100% for invasive breast cancer, but later studies which included DCIS reported lower sensitivities [32-39]. In the largest series reported to date, the sensitivity of MRI was 83% for invasive disease, but was only 71% overall [40]. However, the benefit attributable to finding cases of DCIS (versus early invasive cancers) has not been established. In a study with longitudinal follow-up, MRI detected nine breast tumors that were missed by the other screening modalities [41] . Of note, only two of the 22 women with breast cancer (9%) detected in this Canadian trial had lymph node metastases. Thus, we feel that MRI has a role in screening *BRCA* mutations carriers. It is not clear if the addition of mammography to MRI improves the sensitivity of screening.

## Conclusions

Women with a BRCA1 or BRCA2 mutation represent the highest risks group for the development of breast cancer. Fortunately, several options are available for women - each option has varying levels of breast cancer risk reduction, in addition to various risks. Prophylactic mastectomy offers the best protection against developing breast cancer, but the majority of women in Canada are

unwilling to exercise this option. The extent of risk reduction associated with tamoxifen and prophylactic oophorectomy are less (approximately 50% risk reduction for each) and are associated with the side effects of hormone withdrawal. For these reasons, for many women screening is the preferred option. Screening will not prevent breast cancer from developing; the intention is to detect a tumour at a treatable stage. Women identified as having a BRCA1 or BRCA2 mutation should be made aware of all of their breast cancer prevention options. Ultimately, the goal of genetic testing for BRCA1 and BRCA2 is to identify high-risk women so that cancer can be prevented.

References


1. Antoniou, A., et al., *Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies.* Am J Hum Genet, 2003. **72**(5): p. 1117-30.
2. Metcalfe, K., et al., *Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers.* J Clin Oncol, 2004. **22**(12): p. 2328-35.
3. Verhoog, L.C., et al., *Contralateral breast cancer risk is influenced by the age at onset in BRCA1-associated breast cancer.* Br J Cancer, 2000. **83**(3): p. 384-6.
4. Robson, M., et al., *BRCA-associated breast cancer in young women.* J Clin Oncol, 1998. **16**(5): p. 1642-9.
5. Claus, E.B., N. Risch, and W.D. Thompson, *Genetic analysis of breast cancer in the cancer and steroid hormone study.* Am J Hum Genet, 1991. **48**(2): p. 232-42.
6. Whittemore, A.S., G. Gong, and J. Itnyre, *Prevalence and contribution of BRCA1 mutations in breast cancer and ovarian cancer: results from three U.S. population-based case-control studies of ovarian cancer.* Am J Hum Genet, 1997. **60**(3): p. 496-504.
7. Struewing, J.P., et al., *The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews.* New England Journal of Medicine, 1997. **336**(20): p. 1401-1408.
8. Oddoux, C., et al., *The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%.* Nature Genetics, 1996. **14**: p. 188-190.
9. Thorlacius, S., et al., *Population-based study of risk of breast cancer in carriers of BRCA2 mutation.* Lancet, 1998. **352**(9137): p. 1337-9.
10. Gorski, B., et al., *A high proportion of founder BRCA1 mutations in Polish breast cancer families.* Int J Cancer, 2004. **110**(5): p. 683-6.
11. Meijers-Heijboer, M., et al., *Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation.* The New England Journal of Medicine, 2001. **345**(3): p. 158-164.
12. Rebbeck, T.R., et al., *Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group.* J Clin Oncol, 2004. **22**(6): p. 1055-62.
13. Metcalfe, K.A., J.L. Semple, and S.A. Narod, *Time to reconsider subcutaneous mastectomy for breast-cancer prevention?* Lancet Oncol, 2005. **6**(6): p. 431-4.
14. Levine, D.A. and M.L. Gemignani, *Prophylactic surgery in hereditary breast/ovarian cancer syndrome.* Oncology (Williston Park), 2003. **17**(7): p. 932-41; discussion 946-8, 950-2.
15. Narod, S.A., *Modifiers of risk of hereditary breast and ovarian cancer.* Nat Rev Cancer, 2002. **2**(2): p. 113-23.
16. Kauff, N.D., et al., *Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation.* N Engl J Med, 2002. **346**(21): p. 1609-15.
17. Rebbeck, T.R., et al., *Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers.* J Natl Cancer Inst, 1999. **91**(17): p. 1475-9.
18. Rebbeck, T.R., et al., *Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations.* N Engl J Med, 2002. **346**(21): p. 1616-22.
19. Eisen, A., et al., *Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study.* J Clin Oncol, 2005. **23**(30): p. 7491-6.
20. Pritchard, K.I., *Breast cancer prevention with selective estrogen receptor modulators: a perspective.* Ann N Y Acad Sci, 2001. **949**: p. 89-98.

21. King, M.C., et al., *Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial.* Jama, 2001. **286**(18): p. 2251-6.
22. Gronwald, J., et al., *Tamoxifen and contralateral breast cancer in BRCA1 and BRCA2 carriers: an update.* Int J Cancer, 2006. **118**(9): p. 2281-4.
23. Weitzel, J.N., et al., *A comparison of bilateral breast cancers in BRCA carriers.* Cancer Epidemiol Biomarkers Prev, 2005. **14**(6): p. 1534-8.
24. Foulkes, W.D., et al., *Disruption of the expected positive correlation between breast tumor size and lymph node status in BRCA1-related breast carcinoma.* Cancer, 2003. **98**(8): p. 1569-1577.
25. Burke, W., et al., *Recommendations for follow-up care of individuals with an inherited predisposition to cancer.* JAMA, 1997. **277**(12): p. 997-1003.
26. Eisinger, F., et al., *Recommendations for medical management of hereditary breast and ovarian cancer: the French National Ad Hoc Committee.* Ann Oncol, 1998. **9**(9): p. 939-50.
27. Pichert, G., et al., *Evidence-based management options for women at increased breast/ovarian cancer risk.* Ann Oncol, 2003. **14**(1): p. 9-19.
28. Tilanus-Linthorst, M., et al., *A BRCA1/2 mutation, high breast density and prominent pushing margins of a tumor independently contribute to a frequent false-negative mammography.* Int J Cancer, 2002. **102**(1): p. 91-5.
29. Kerlikowske, K., et al., *Performance of screening mammography among women with and without a first-degree relative with breast cancer.* Ann Intern Med, 2000. **133**(11): p. 855-63.
30. Kollias, J., et al., *Screening women aged less than 50 years with a family history of breast cancer.* Eur J Cancer, 1998. **34**(6): p. 878-83.
31. Goffin, J., et al., *Re: Magnetic resonance imaging and mammography in women with a hereditary risk of breast cancer.* J Natl Cancer Inst, 2001. **93**(22): p. 1754-5.
32. Scheuer, L., et al., *Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers.* J Clin Oncol, 2002. **20**(5): p. 1260-8.
33. Brekelmans, C.T., et al., *Effectiveness of breast cancer surveillance in BRCA1/2 gene mutation carriers and women with high familial risk.* J Clin Oncol, 2001. **19**(4): p. 924-30.
34. Tilanus-Linthorst, M.M., et al., *First experiences in screening women at high risk for breast cancer with MR imaging.* Breast Cancer Res Treat, 2000. **63**(1): p. 53-60.
35. Stoutjesdijk, M.J., et al., *Magnetic resonance imaging and mammography in women with a hereditary risk of breast cancer.* J Natl Cancer Inst, 2001. **93**(14): p. 1095-102.
36. Morris, E.A., et al., *MRI of occult breast carcinoma in a high-risk population.* AJR Am J Roentgenol, 2003. **181**(3): p. 619-26.
37. Kriege, M., et al., *Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition.* N Engl J Med, 2004. **351**(5): p. 427-37.
38. Liberman, L., et al., *Probably benign lesions at breast magnetic resonance imaging: preliminary experience in high-risk women.* Cancer, 2003. **98**(2): p. 377-88.
39. Robson, M.E. and K. Offit, *Breast MRI for women with hereditary cancer risk.* Jama, 2004. **292**(11): p. 1368-70.
40. Gui, G.P., et al., *The incidence of breast cancer from screening women according to predicted family history risk: Does annual clinical examination add to mammography?* Eur J Cancer, 2001. **37**(13): p. 1668-73.
41. Warner, E., et al., *Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination.* Jama, 2004. **292**(11): p. 1317-25.