Breast cancer prevention in women with a *BRCA1* or *BRCA2* mutation

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Counselling women about the resources that are available to them to assess their risk of breast cancer and providing advice on appropriate screening and risk-reduction strategies can be challenging for clinicians. This article discusses genetic risk factors for breast cancer, how to take a family history, and how to counsel and organize appropriate referrals for patients who may be at an increased risk of breast cancer because of a mutation in the *BRCA1* or *BRCA2* gene. In addition, it provides information on counselling women who have been identified as having a mutation in *BRCA1* or *BRCA2*.

Case

A 40-year-old patient informs you that her sister has been diagnosed with breast cancer at the age of 38. The patient's mother, at age 65, is healthy and has never had a cancer diagnosis. The patient knows of no other family history of breast cancer on her mother's side of the family; her father's grandmother possibly had breast cancer, but she died before the patient was born. The patient also mentions a paternal aunt who died of ovarian cancer. She is of Ashkenazi Jewish descent. The patient inquires whether she should be concerned about her sister's breast cancer diagnosis and if she is too young to begin breast screening. How would you advise her?

Assessing breast cancer risk

Several models are available to help assess a woman's risk of breast cancer. The Gail Model calculates a woman's breast cancer risk over the next five years, in addition to her lifetime risk (www.cancer.gov/bcrisktool/). The model considers age, ethnicity, history of breast cancer in first-degree relatives, age of menarche, and previous history of breast biopsies and benign breast disease.

Clinicians should be familiar with the process of taking a detailed family history (pedigree) to assess cancer risk. This involves collecting information with regard to types of cancer, the ages at which cancer diagnoses were made, and the vital status of three generations of relatives within a family. In addition, family ethnicities should be recorded. There are many resources available to help clinicians assess genetic family histories, including a detailed list on the University of Kansas Medical Center website.

Genetic testing for *BRCA1* and *BRCA2* mutations helps physicians identify women who are at significantly increased risk of developing breast and ovarian cancer. 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% lifetime risk of developing breast cancer and a 1.5% risk of developing ovarian cancer (Table 1). After the initial diagnosis of breast cancer in a *BRCA1* or *BRCA2* carrier, the risk of cancer in the opposite breast (a new primary cancer) increases by approximately 3% per year.[2–4]

Table 1: Lifetime breast cancer risk

	Lifetime breast cancer risk	Median age of breast cancer onset (y)
General population	11%	61
BRCA1	65%	43
BRCA2	45%	41

About 1 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 1 in 50.[7,8] Other groups with high frequencies of mutations include women from Iceland[9] and Poland.[10] These high prevalence rates are explained by the presence of

founder mutations. (Founder mutations are one or more specific mutations in a population that have been inherited from a common ancestor, and that have become amplified through chance effects, often aided by geographic isolation of the population.)

Patients identified as being at increased risk for any familial cancers should be referred for genetic counselling. The *Ontario Medical Review* published guidelines for the referral of patients with a family history of cancer to cancer genetics clinics (www.oma.org/pcomm/OMR/nov/01genetics.htm).[11] These guidlines identify risk factors for inherited breast and ovarian cancer (Textbox 1). The presence of one or more of these factors in an individual's personal or family history may suggest an increased risk for hereditary cancer and warrants a referral for genetic counselling. Information on genetic counselling centres within Canada can be found at www.cagc-accg.ca.

Case revisited

The patient's family history suggests a possible *BRCA1* or *BRCA2* mutation. She has a sister with premenopausal breast cancer, a paternal grandmother with breast cancer who died at a young age, and a paternal aunt with ovarian cancer. Her Ashkenazi Jewish descent may also increase her risk of a mutation. Information is collected on 3 generations within the family and presented in a genetic pedigree (Figure 1), which proves to be suggestive of hereditary breast cancer. You refer your patient for genetic counselling and testing, and also suggest that her sister with breast cancer seek genetic counselling. Models are available to assess an individual's risk of having a mutation in the *BRCA1* or *BRCA2* genes (www4.utsouthwestern.edu/breasthealth/cagene/). Your patient's genetic counseller, using the BRCAPRO model, determines that she has a 30% lifetime risk of breast cancer and a 42% chance of having a *BRCA1* or *BRCA2* mutation. She then receives genetic testing and is found to have a *BRCA1* mutation. Your patient returns to consult you and wants to know what she can do to prevent the development of breast cancer. What would you tell her?

Cancer prevention options

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 who die of the disease. 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 routine screening (secondary prevention) with the goal of detecting any cancers at an early, treatable stage.

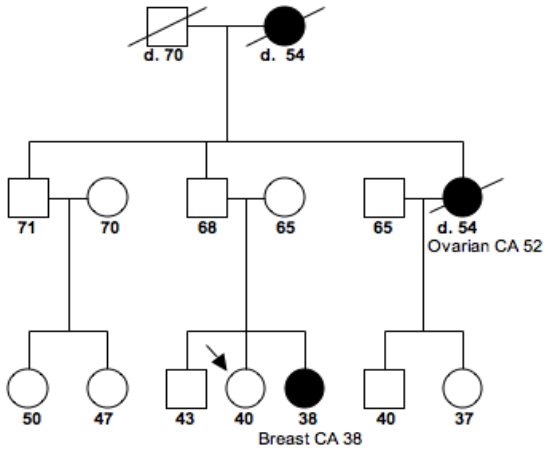

Figure 1: A family history of cancer. The patient (arrow) is considered the proband.

Prophylactic mastectomy. The goal of prophylactic mastectomy is to prevent breast cancer, thereby eliminating the potential for metastatic spread and death from the disease. The effectiveness of prophylactic mastectomy in preventing breast cancer in *BRCA1* and *BRCA2* mutation carriers has been established in a small prospective study and in historical cohort studies of primary and contralateral breast cancers. In the small prospective study of 26 women with a *BRCA1* or *BRCA2* mutation, observed numbers of cancer were compared to expected numbers of breast cancer based on penetrance estimates. Statistical analysis demonstrated that prophylactic mastectomy offered at least an 89% risk reduction of breast cancer in *BRCA1* and *BRCA2* carriers.[12] Meijers-Heijboer and colleagues observed no cases of breast cancer over 3 years among 76 women who underwent prophylactic mastectomy.[13] Rebbeck and colleagues observed 2 cases of breast cancer among 191 women after mastectomy, compared to 184 cases among 378 women who did not choose mastectomy ($p < 0.0001$).[14] Metcalfe and colleagues studied the development of contralateral breast cancer in 491 women treated for hereditary breast cancer using various stand-

ard surgical and adjuvant therapies.[2] Only one contralateral breast cancer was observed among 146 women who had undergone a contralateral mastectomy, versus 33 expected with no contralateral mastectomy ($p < 0.0001$). These studies suggest that the residual breast cancer risk after mastectomy is minimal (less than 5%), and much less than the risk of breast cancer in the general population.

Total mastectomy is currently recommended over subcutaneous or nipple-sparing mastectomy; in the latter procedure, some breast tissue must remain below the nipple-areola complex to maintain the blood and nerve supply, and therefore there is the potential for breast cancer to develop in this residual tissue. However, one systematic review previously reported that in all of the case studies in the literature reporting a failure of a subcutaneous mastectomy in the prevention of breast cancer, the majority of cancers did not occur in this residual tissue.[15] As such, the risks and benefits of both surgical options should be discussed with patients.

Although prophylactic mastectomy offers the best protection against developing breast cancer, it is known that the majority of women in Canada are unwilling to exercise this option.[16]

Prophylactic oophorectomy. It has been shown that *BRCA1*-associated breast cancers are hormonally associated.[17] The purpose of an anti-hormonal therapy is to eliminate or block the effect of ovarian estrogen, and probably progesterone, or to prevent aromatization of androgen to estrogen. Anti-hormonal approaches include therapy with tamoxifen, raloxifene and other selective estrogen receptor modulators (SERMs), ovarian ablation (oophorectomy, radiation or chemical ablation with gonadotropin-releasing hormone [GNRH] agonists) and aromatase inhibition (with an agent such as anastrozole or letrozole). Of these, only tamoxifen and oophorectomy have been well studied in women with *BRCA1* or *BRCA2* mutations.

The rationale for an 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 premenopausal oophorectomy to be about 50%.[18–20] A recent case-control study reported that this risk reduction may be greater if oophorectomy is performed before age 40 and that the duration of protection is approximately 15 years.[21] Short-term use of estrogen for menopausal symptom relief in young women after oophorectomy might abrogate some of the breast cancer protection associated with oophorectomy but may be important to a woman's quality of life. In one study the effectiveness of prophylactic oophorectomy was not reduced by the addition of hormone replacement therapy.[20] Women who elect for prophylactic mastectomy should receive routine screening for osteoporosis associated with low estrogen.

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. GNRH agonists are a reversible form of ovarian suppression and thus 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 the risk for ovarian or fallopian tube cancers, which are also elevated in *BRCA1* and *BRCA2* carriers.

Selective estrogen receptor modulators. 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 tumours.[22] On theoretical grounds, tamoxifen should not reduce the incidence of estrogen-receptor (ER) negative breast cancers, and most breast cancers that occur in *BRCA1* (but not *BRCA2*) carriers are ER negative. An attempt to understand the preventative role of tamoxifen was made in the National Surgical Adjuvant Breast and Bowel Project — P1 trial.[23] In this study, the authors compared the incidence of breast cancer among women who took tamoxifen with the incidence among those who took a placebo. In the cohort of 288 women who developed breast cancer during the study, 8 women were found to have a *BRCA1* mutation and 11 were found to have a *BRCA2* mutation. When cancer incidence was examined in this group of women with *BRCA1* and *BRCA2* mutations, it was concluded that tamoxifen was protective against breast cancer in women with a *BRCA2* mutation, but not in those with a *BRCA1* mutation. 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 (odds ratio = 0.5; 95% confidence interval 0.30–0.85).[24] If we assume 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 2 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 and colleagues, the majority of contralateral breast cancers after ER-positive breast cancer were in fact, estrogen-receptor negative, suggesting that tamoxifen prevents ER-negative contralateral breast cancers.[25]

There are risks associated with taking tamoxifen: for every 10,000 women who take tamoxifen there are 15 endometrial cancers, 2 uterine sarcomas, 4 cerebrovascular events, and 5 pulmonary emboli per year above that expected in those not on tamoxifen.[26]

Screening. The goal of screening is to identify breast cancer at a stage when surgical cure is likely. For women in the general population, this outcome would pertain to small (< 1 cm) node-negative tumours with no evidence of distant spread. However, *BRCA1*-associated breast tumours are typically high grade and are estrogen-receptor negative,[2] which may impart higher risk even when they are detected early. Although several small studies have been done of breast-cancer-specific survival in women with a *BRCA1* or *BRCA2* mutation,[27] there is little consensus on survival outcomes in this group of women. In one study involving *BRCA1* carriers, little correlation was found between tumour size and lymph-node positivity, as would be expected with sporadic breast cancer. About one-third of *BRCA1* carriers had lymph node metastases detected at diagnosis, regardless of tumour size,[28] making it difficult to predict the benefit of screening using survival data generated from a comparison group of non-carriers.

A number of advisory groups in the United States and Europe have published recommendations for surveillance for women at hereditary risk for breast cancer and ovarian cancer.[29–31] 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.

Certain histological features of *BRCA1*-associated breast cancer (e.g., the appearance of pushing margins) and high breast density (characteristic of young women) in women with a *BRCA1* or *BRCA2* mutation[32] may make *BRCA*-associated tumours difficult to detect mammographically. Studies conducted in the US and in the United Kingdom of women under 50 with a family history of breast cancer reported mammography sensitivities of 63%–70%[33] and 44%,[34] respectively. Goffin and colleagues[35] found that only 2 of 8 breast cancers (25%) in *BRCA1* carriers were detectable by mammogram at diagnosis, versus 27 of 35 (77%) among non-carrier controls (p = 0.01). In a large cohort at a single centre (n = 251), of 12 breast tumours diagnosed in *BRCA* mutation carriers, fewer than half were detected by mammogram.[36] 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 that included ductal carcinoma in situ (DCIS) reported lower sensitivities.[36–43] In the largest series reported to date, the sensitivity of MRI was 83% for invasive disease but was only 71% overall.[44] 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 9 breast tumours that were missed by the other screening modalities.[45] Of note, only 2 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.

Case revisited

Your patient is *BRCA1* positive, and women with a *BRCA1* or *BRCA2* mutation represent the group at highest risk for breast cancer. She should be made aware of her options to reduce her cancer risk. Prophylactic mastectomy has the greatest likelihood of preventing cancer but is not acceptable to many women. The risk reductions resulting from tamoxifen and prophylactic oophorectomy are lower (approximately 50% risk reduction for each) and are associated with the side effects of hormone withdrawal and infertility. For these reasons, for many women screening is the preferred option.

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 Apr 03. 72(5):1117–30. [Full Text] [PubMed]
2. Metcalfe K *et al.* Contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers. *J Clin Oncol* 2004 22(12):2328–35. [CrossRef] [PubMed]
3. Verhoog LC, Brekelmans CT, Seynaeve C, Meijers-Heijboer EJ, Klijn JG. Contralateral breast cancer risk is influenced by the age at onset in *BRCA1*-associated breast cancer. *Br J Cancer* 2000 83(3):384–6. [CrossRef] [PubMed]
4. Robson M *et al.* BRCA-associated breast cancer in young women. *J Clin Oncol* 1998 16(5):1642–9. [PubMed]
5. Claus EB, Risch N, Thompson WD. Genetic analysis of breast cancer in the cancer and steroid hormone study. *Am J Hum Genet* 1991 48(2):232–42. [Full Text] [PubMed]
6. Whittemore AS, Gong G, Itnyre J. 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):496–504. [Full Text] [PubMed]
7. Struewing JP *et al.* The risk of cancer associated with specific mutations of *BRCA1* and *BRCA2* among Ashkenazi Jews. *N Engl J Med* 1997 336(20):1401–8. [Full Text] [PubMed]
8. Oddoux C *et al.* The carrier frequency of the *BRCA2* 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%. *Nat Genet* 1996 14(2):188–90. [CrossRef] [PubMed]
9. Thorlacius S *et al.* Population-based study of risk of breast cancer in carriers of *BRCA2* mutation. *Lancet* 1998 352(9137):1337–9. [PubMed]
10. Górski B *et al.* A high proportion of founder *BRCA1* mutations in Polish breast cancer families. *Int J Cancer* 2004 110(5):683–6. [CrossRef] [PubMed]
11. Predictive Cancer Genetics Screening Committee. Ontario physicians' guide to referral of patients with family history of cancer to a familial cancer genetics clinic or genetics clinic. *Ont Med Rev* 2001 Nov:24–30. [Full Text]
12. Hartmann LC *et al.* Efficacy of bilateral prophylactic mastectomy in *BRCA1* and *BRCA2* gene mutation carriers. *J Natl Cancer Inst* 2001 93(21):1633–7. [Full Text] [PubMed]
13. Meijers-Heijboer H *et al.* Breast cancer after prophylactic bilateral mastectomy in women with a *BRCA1* or *BRCA2* mutation. *N Engl J Med* 2001 345(3):159–64. [Full Text] [PubMed]
14. Rebbeck TR *et al.* Bilateral prophylactic mastectomy reduces breast cancer risk in *BRCA1* and *BRCA2* mutation carriers: the PROSE Study Group. *J Clin Oncol* 2004 Feb 23. 22(6):1055–62. [CrossRef] [PubMed]
15. Metcalfe KA, Semple JL, Narod SA. Time to reconsider subcutaneous mastectomy for breast-cancer prevention?. *Lancet Oncol* 2005 6(6):431–4. [CrossRef] [PubMed]
16. Metcalfe KA, Ghadirian P, Rosen B, Foulkes W, Kim-Sing C, Eisen A. Variation in rates of uptake of preventive options by Canadian women carrying the *BRCA1* or *BRCA2* genetic mutation. *Open Med* 2007. 1(2):e92–98. [Full Text]
17. Narod SA. Modifiers of risk of hereditary breast and ovarian cancer. *Nat Rev Cancer* 2002 2(2):113–23. [PubMed]
18. Kauff ND *et al.* Risk-reducing salpingo-oophorectomy in women with a *BRCA1* or *BRCA2* mutation. *N Engl J Med* 2002 May 20. 346(21):1609–15. [Full Text] [CrossRef] [PubMed]
19. Rebbeck TR *et al.* Breast cancer risk after bilateral prophylactic oophorectomy in *BRCA1* mutation carriers. *J Natl Cancer Inst* 1999 91(17):1475–9. [Full Text] [PubMed]
20. Rebbeck TR *et al.* Prophylactic oophorectomy in carriers of *BRCA1* or *BRCA2* mutations. *N Engl J Med* 2002 May 20. 346(21):1616–22. [Full Text] [CrossRef] [PubMed]
21. 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):7491–6. [CrossRef] [PubMed]
22. Pritchard KI. Breast cancer prevention with selective estrogen receptor modulators: a perspective. *Ann N Y Acad Sci* 2001 949:89–98. [PubMed]
23. King MC *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):2251–6. [Full Text] [PubMed]
24. Gronwald J *et al.* Tamoxifen and contralateral breast cancer in *BRCA1* and *BRCA2* carriers: an update. *Int J Cancer* 2006 118(9): 2281–4. [CrossRef] [PubMed]
25. Weitzel JN *et al.* A comparison of bilateral breast cancers in BRCA carriers. *Cancer Epidemiol Biomarkers Prev* 2005 14(6):1534–8. [Full Text] [CrossRef] [PubMed]
26. Wooltorton E. Tamoxifen for breast cancer prevention: safety warning. *CMAJ* 2002 167(4):378–9. [Full Text] [PubMed]
27. Liebens FP, Carly B, Pastijn A, Rozenberg S. Management of *BRCA1/2* associated breast cancer: a systematic qualitative review of the state of knowledge in 2006. *Eur J Cancer* 2006 Nov 13. 43(2):238–57. [CrossRef] [PubMed]
28. Foulkes WD *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):1569–77. [Full Text] [CrossRef] [PubMed]
29. Burke W *et al.* Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. *BRCA1* and *BRCA2*. Cancer Genetics Studies Consortium. *JAMA* 1997 277(12):997–1003. [PubMed]
30. 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):939–50. [Full Text] [PubMed]
31. Pichert G *et al.* Evidence-based management options for women at increased breast/ovarian cancer risk. *Ann Oncol* 2003 14(1):9–19. [Full Text] [PubMed]
32. 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):91–5. [CrossRef] [PubMed]
33. 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):855–63. [Full Text] [PubMed]
34. Kollias J *et al.* Screening women aged less than 50 years with a family history of breast cancer. *Eur J Cancer* 1998 34(6):878–83. [Full Text] [PubMed]
35. Goffin J, Chappuis PO, Wong N, Foulkes WD. Re: Magnetic resonance imaging and mammography in women with a hereditary risk of breast cancer. *J Natl Cancer Inst* 2001 93(22): 1754–5. [Full Text] [PubMed]
36. 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):1260–8. [PubMed]
37. Brekelmans CT *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):924–30. [PubMed]
38. Tilanus-Linthorst MM, Obdeijn IM, Bartels KC, *et al.* First experiences in screening women at high risk for breast cancer with MR imaging. *Breast Cancer Res Treat* 2000 63(1):53–60. [PubMed]
39. Stoutjesdijk MJ *et al.* Magnetic resonance imaging and mammography in women with a hereditary risk of breast cancer. *J Natl Cancer Inst* 2001 93(14):1095–102. [Full Text] [PubMed]

40. Morris EA *et al.* MRI of occult breast carcinoma in a high-risk population. *AJR Am J Roentgenol* 2003 181(3):619–26. [Full Text] [PubMed]

41. 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):427–37. [Full Text] [CrossRef] [PubMed]

42. Liberman L, Morris EA, Benton CL, Abramson AF, Dershaw DD. Probably benign lesions at breast magnetic resonance imaging: preliminary experience in high-risk women. *Cancer* 2003 98(2): 377–88. [Full Text] [CrossRef] [PubMed]

43. Robson ME, Offit K. Breast MRI for women with hereditary cancer risk. *JAMA* 2004 292(11):1368–70. [CrossRef] [PubMed]

44. Gui GP, Hogben RK, Walsh G, A'Hern R, Eeles R. 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):1668–73. [PubMed]

45. 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):1317–25. [Full Text] [CrossRef] [PubMed]

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