# The Prevention of Hereditary Breast and Ovarian Cancer: A Personal View

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## Abstract

Options for the prevention of hereditary breast and ovarian cancer include screening, preventive surgery and chemoprevention. Screening studies with magnetic resonance imaging of the breast are promising but the technology is not widespread and MRI is unlikely to be available as a screening tool in the near future. Prophylactic oophorectomy and mastectomy are effective preventive measures and are gaining in acceptance by patients and physicians. Preventive mastectomy is effective against both primary and contralateral breast cancer. Oophorectomy prevents ovarian cancer, and if done prior to menopause, will prevent breast cancer as well. Tamoxifen has been shown to prevent contralateral breast cancers in BRCA1 and BRCA2 carriers but is not widely accepted as a means of primary prevention. Oral contraceptives and tubal ligation will reduce the risk of hereditary ovarian cancer and should be considered in women who wish to retain ovarian function.

It is nearly ten years since the BRCA1 gene was identified and genetic testing for breast cancer susceptibility is now widespread. During the last ten years we have come to accept that genetic testing can be done outside of research settings, that most women wish to have – and are capable of understanding – personal information about the risks and benefits of genetic testing and that routine pre-test psychological counselling is not mandatory. As a group, women do not suffer unduly from anxiety or depression following the receipt of a positive test result [1] (although we all know of exceptions to this rule). There is still uncertainty about the best estimate to give a carrier for her risks of breast and ovarian cancer. Some argue that different carriers should be given different risks depending on their family history, but this individualized approach to counselling is really too complicated to be practical. But we all agree that the risks are unacceptably high and that something needs to be done to lower them.

It was a relatively straightforward task to establish that prophylactic mastectomy is effective. This has been shown in a small prospective study [2], and in historical cohort studies of primary [3] and contralateral [4] breast cancers. Here the data is consistent. Meijers-Heijboer and colleagues observed no case of breast cancer among 76 women who underwent prophylactic mastectomy after a mean follow-up of three years [2]. Metcalfe and colleagues studied 491 women treated for hereditary breast cancer [4]. Only one contralateral breast cancer was observed among 146 women who had undergone a contralateral mastectomy, versus 42 expected ($p<0.0001$). Some debate remains about the optimal age of prophylactic mastectomy and about the best techniques for mastectomy and for reconstruction,

but there are few who would argue against the effectiveness of the procedure. But our aim is to replace prophylactic mastectomy with something better. This will either come from screening or from finding a less invasive means of primary prevention.

The goal of screening is to identify breast cancer at a stage when a surgical cure is likely. Traditionally this includes small breast cancers (<1 cm) that are node-negative and with no evidence of distant spread. For these women cure can be expected in over 90% of cases. But BRCA1-associated breast cancers are typically high-grade and oestrogen-receptor negative [5] and so prognosis might be worse than average [6, 7]. The majority of physicians will offer adjuvant chemotherapy to women with cancer of this type to boost the cure rate beyond that offered by surgery alone. But there is another problem. Among BRCA1 carriers we see little correlation between tumour size and lymph-node positivity [8]. About one-third of BRCA1 carriers will have lymph node metastases detected at diagnosis, regardless of tumour size (as tumours are being diagnosed at progressively smaller sizes through MRI etc., this may no longer be the case). Therefore it is problematic to predict the benefits of screening using survival data generated from a comparison group of non-carriers.

Currently, screening is done with mammography or with MRI. Although MRI appears to be superior to mammography in early studies [9, 10], access to MRI is rare outside of research settings. The test is costly and time-consuming both for the patient and for the radiologist. Unfortunately mammography does not seem to be a useful alternative to MRI and the exposure to radiation with mammography is worrisome. We have no direct data that ionizing radiation is a carcinogen for BRCA carriers; the data on this topic is derived from cohort studies of Hiroshima survivors and from young women treated for Hodgkin's disease. In both groups younger women were at particularly high risk. It is striking that early menopause mitigated against the carcinogenic effect of therapeutic radiation in women undergoing treatment for Hodgkin's disease [11]. Surgical menopause is also highly effective in preventing BRCA1-related breast cancers [12-14]. The parallels between radiation-induced carcinogenesis and BRCA1-associated carcinogenesis are notable; however, this should not be surprising given that a primary function of BRCA1 is to help in the repair of double strand DNA breaks and these are typical of the type induced by ionizing radiation. It is likely that both radiation-induced and BRCA1-associated breast cancers are initiated by chromosome breakage. Both appear to be advanced by later ovarian hormone exposure. Therefore we might expect other cofactors to be in common and the tumour types to be similar. The incidence of breast cancer in BRCA1 carriers rises from the age of 25 until menopause, after which it plateaus. At the age of 25 radiation (even in small doses) is worrisome.

Currently mammography is almost universally recommended to BRCA1 and BRCA2 carriers. This recommendation is largely based on historical grounds, out of fear of litigation, and wishful thinking. Mammography has not been shown to be effective in reducing mortality from high-grade breast cancers in young women. After 13 years of follow-up there was no reduction in mortality from breast cancer in Canadian women aged 40-49 randomized to mammography versus usual care [15]. 105 deaths occurred in the mammography group and 108 deaths occurred in the unscreened group. In the Swedish two-county trial (which is widely cited by mammography advocates as providing the best evidence in favour) there was no reduction in death from high-grade breast cancers in women aged under 50 [16]. Goffin and colleagues found that only two of eight breast cancers of less than 2 centimetres were detectable by mammogram in BRCA1 carriers aged under 50 at diagnosis, versus 27 of 35 from non-carrier controls ($p=0.01$) [17]. Brekelmans et al followed women at high risk for breast cancer with annual mammography and found that the BRCA carriers were more likely to present with an interval cancer, or with an advanced disease, than a comparable group of non-carriers [18].

MRI appears to be much more effective than mammography in detecting early hereditary breast cancers. In my opinion, breast cancer screening should consist of annual MRI from the age of 25. Also, a bilateral MRI should be conducted in a BRCA carrier with a newly diagnosed breast cancer to assess the extent of disease, in particular if breast-conserving surgery is to be considered.

To date the general approach to prevention of hereditary breast cancer has been anti-hormonal. Although the underlying defect conferred by a BRCA1 mutation is the inability to proficiently repair double strand DNA breaks, prevention has not been aimed at correcting this deficit but rather at reducing the effect of promoting factors. To date the established cofactors for BRCA1-associated breast cancers are hormonally-based [19]. Anti-hormonal approaches include tamoxifen, raloxifene and other SERMS, ovarian ablation (oophorectomy, radiation or chemical ablation) and aromatase inhibition. Of these, only tamoxifen and

oophorectomy have been well studied in the context of BRCA1 and BRCA2 mutations. The rationale for the anti-hormonal approach comes from the observation that oophorectomy prevents against breast cancer in BRCA1 and BRCA2 carriers [12-14]. Cohort studies estimated the reduction in breast cancer risk associated with a pre-menopausal oophorectomy to be about 50%. We are currently analysing a large case-control study of over 1000 cases of hereditary breast cancer and an equal number of matched controls to determine the optimal age of oophorectomy and the duration of protection.

If one anti-hormonal approach is effective, why not all? There is little empirical data on the degree of protection against breast cancer offered by other forms of ovarian ablation (radiation, GNRH agonists). A GNRH agonist may be preferred by a woman who wishes to preserve fertility, but the use of these drugs in BRCA carriers is not yet widespread. Also, there is some concern about the ability of these non-surgical approaches to ovarian ablation to prevent tubal or ovarian cancer.

On theoretical grounds tamoxifen should not reduce the incidence of estrogen-receptor negative breast cancers and most breast cancers which occur in BRCA1 carriers are oestrogen-receptor negative. The NSABP P1 trial attempted to address this issue, but only eight BRCA1 carriers with breast cancer were identified in the follow-up period [20]. Although no protective effect was seen with tamoxifen this number is far too small for the study to be informative. In a large case-control study we found that tamoxifen reduced the incidence of contralateral breast cancer in BRCA1 and BRCA2 carriers by about one-half [21]. To the extent that contralateral cancers in carriers are representative of all new primary breast cancers, the results of this study could be extrapolated to the prevention of first primary breast cancers. But this conclusion might be invalid if the two primary cancers were not independent; for example if tamoxifen was only given to ER-positive patients and if the ER status of bilateral cancers were completely correlated, then results of the case-control study would confirm a protective effect of tamoxifen only against ER-positive breast cancers.

Few physicians are now prescribing tamoxifen to BRCA carriers in the preventive setting [22]. We have recently completed a survey of 100 unaffected BRCA carriers one year after they learned of their mutation status. Most women had undergone oophorectomy (60%) and the side effects of oophorectomy were considered to be acceptable by most. In contrast, 25% had undergone a prophylactic mastectomy and only 10% of the women had ever taken tamoxifen. Many women feared the side effects of tamoxifen sufficiently to avoid the drug. Almost as many women had taken raloxifene; it seems that the presence of, or fear of, reduced bone density was a strong enough incentive for many women to initiate a SERM and most believed raloxifene to have fewer side effects than tamoxifen. It is appealing to offer raloxifene to a BRCA carrier after oophorectomy to protect against the effect of surgical menopause on bone density and to reduce the risk of breast cancer beyond oophorectomy alone, but as yet there is no data on the effectiveness of raloxifene on reducing the incidence of breast cancer in this high risk group.

It is too early to say if the combination of a SERM and oophorectomy offers greater protection against that of oophorectomy alone. However, it is striking that in our recent study the combination of oophorectomy and tamoxifen reduced the incidence of contralateral breast cancer by 82% among premenopausal women [4]. And most of these women had ER-negative tumours.

It is not practical to try to avoid the use of hormonal replacement therapy completely by young women after oophorectomy. There is no study yet which directly addresses this question. However, it is probably best to use hormone replacement sparingly, to attempt to treat the specific symptom of menopause with the appropriate drug and to consider a non-hormonal alternative when possible. Oestrogen use should be limited to five years if possible and progesterone avoided altogether (for this reason it may be prudent to offer hysterectomy with oophorectomy). In any case it is critical that the fallopian tubes be removed at the time of oophorectomy because a large proportion (probably most) gynaecologic cancers in BRCA1 carriers actually arise in the tubes. If a young woman is given oestrogen therapy post-oophorectomy she may benefit from the addition of an aromatase inhibitor. The purpose of the aromatase inhibitor is to prevent the production of local oestrogen in the breast and thereby minimise the concentration of breast oestrogen. On the other hand, the aromatase inhibitor should not eliminate the beneficial effects of the exogenous oestrogen on reducing the acute symptoms of menopause.

Is it possible to counteract the effect of a BRCA1 or BRCA2 mutation on the propensity for DNA damage? Experiments may be done on animal models, on cell cultures or using biological markers in vivo but there is little data yet in this regard. Candidates for chemotherapy include anti-oxidants. In general, anti-oxidants have not

been shown to be effective for preventing breast cancer, but this may not be equally true for BRCA carriers, for whom DNA damage appears to play an initiating role. Oxidative damage appears to be an important factor in prostate cancer aetiology (more so than in breast cancer) and observational studies of selenium and lycopene in prostate cancer prevention have been encouraging [23, 24]. There is little data yet to support the recommendation of anti-oxidants to BRCA1 and BRCA2 carriers, but on the other hand anti-oxidants are considered to be part of what is considered a healthy diet and there are few side effects. Currently I recommended a diet rich in cruciferous vegetables and green tea, supplemented by selenium and lycopene.

What about preventive radiotherapy? In women with breast cancer and a BRCA mutation and who have undergone breast-conserving surgery and radiotherapy, the risk of ipsilateral recurrence at ten years is about 10% [4]. This risk is actually far lower than the risk of contralateral breast cancer in the same patients, which is closer to 40% at ten years [4]. The ipsilateral events include both local recurrences and new ipsilateral primaries, whereas the contralateral cancers are believed to be new primaries only. The effect of radiotherapy is sufficiently strong that it must have an effect on reducing the risk of second ipsilateral primaries as well as local recurrences. One must expect therefore that a similar dose of therapeutic radiation to the contralateral breast would also reduce the risk of new cancer from 40% to 10% or lower. The long-term effect of radiation in these patients is not known but studies to date of atomic bomb survivors and Hodgkin's disease survivors indicate that radiotherapy is a breast carcinogen only when exposure is early and when ovarian function is intact. Preventive contralateral radiotherapy may prove to be beneficial to patients over 40 who wish to conserve their breasts and who undergo ovarian ablation (it is intriguing to think that radiation may be a hazard at low doses but that a high dose may have a protective effect).

The risk of ovarian cancer is also elevated in BRCA1 carriers and when we consider a preventive strategy for breast cancer we must consider the potential impact on ovarian cancer risk, and vice versa. Current strategies for ovarian cancer prevention include oophorectomy [12-14], tubal ligation [25] and oral contraceptives [25, 26]. Two studies have looked at prophylactic oophorectomy and ovarian cancer risk. The first of these was purely prospective but the study population was so small that in order to achieve a significant effect the breast and ovarian cancer endpoints had to be combined [14]. The second study was larger but was based on historical data [13]. The reduction effect of oophorectomy on ovarian cancer risk was large, but it was not clear that affected and unaffected carriers were equally likely to have been ascertained in this study. A large prospective cohort study will be required to resolve this question. It would be ironic if ultimately the protective effect of oophorectomy were found to be greater on breast cancer reduction that on ovarian cancer reduction.

There are two reasons why oophorectomy might fail. Either a latent ovarian or tubal cancer may have spread at the time surgery was performed or a primary cancer may have developed in the peritoneum post-surgery. If failure is due to the presence of a latent cancer then the solution might be earlier surgery. The second scenario is more problematic – we know of no means to prevent primary peritoneal cancer and there is no reason to believe that screening would be effective here. It is important that we study the effects of oral contraceptives, tubal ligation and hormone replacement therapy on peritoneal cancer risk.

In my opinion, the cornerstone for ovarian cancer prevention in BRCA1 and BRCA2 carriers should be oral contraceptives. If taken from the age of 30 to 35 oral contraceptives will reduce the risk of invasive ovarian cancer thereafter by about 60% and will not increase the risk of breast cancer [27]. And there are few side effects. It is probably best to avoid oral contraceptive use before the age of 25. Nor should we ignore the protective effect offered by tubal ligation just because we cannot explain how it works. We observed a 63% reduction in ovarian cancer risk with tubal ligation alone, and in combination with oral contraceptives the risk reduction reached 72%. For women who wish to defer oophorectomy beyond the age of 35 or for those who have finished childbearing tubal ligation is a reasonable temporary measure but should be followed by an oophorectomy at a later date.

Is there any additional benefit to be achieved by ovarian cancer screening? Probably not. In our evaluation of ten years of ovarian cancer screening at the Gilda Radner Center at Cedars-Sinai in Los Angeles, the majority of the incident cancers appeared to be peritoneal, most were detected at stage 3 and few of the screening tests were positive at diagnosis [28]. In studies of incidental tubal and ovarian cancers discovered at prophylactic oophorectomy in asymptomatic women the majority were discovered at stage 3 or 4. This observation implies that an ovarian cancer passes through stage 1 and 2 quickly and that most of the pre-symptomatic

phase is spent at stage 3. It is therefore improbable that annual screening will be found to be effective.

In summary, I believe that there is much that can be done to reduce the risk of cancer in BRCA1 and BRCA2 carriers. Currently I recommend breast MRI annually from the age of 25, an oral contraceptive from the age of 30 to 35, followed by an oophorectomy at the age of 35. Hormone replacement therapy should be transient and oestrogen-based and targeted towards individual acute symptoms. If oophorectomy is postponed then women should consider a tubal ligation as a temporary measure to protect against ovarian cancer. If women wish to undergo a prophylactic mastectomy then no additional measures for breast cancer prevention or screening are recommended. For women who retain their breasts the use of tamoxifen, raloxifene or an aromatase inhibitor (post-oophorectomy) should be encouraged.

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