Impact of MRI surveillance and breast cancer detection in young women with BRCA mutations

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Based on several observational studies that have yielded consistent results, the combination of annual magnetic resonance imaging (MRI) plus mammography is now the standard of care for screening women with BRCA mutations who decline risk-reducing mastectomy. However, many of these women will develop breast cancer at a young age and, while most of these cancers will be very early stage, oncologists need to be aware of the unique issues faced by women in this age group due to the diagnosis and treatment. Fear of death, loss of fertility, premature menopause, relationship stress, career disruption and financial losses are only some of the problems that are either unique to young women or much more pronounced in this age group. Urgent referral to a fertility specialist of any woman who has not yet completed her family should be made as soon as the possible need for systemic treatment is recognized. The oncologist should also have a low threshold for referring young women to professionals experienced in navigating young women and their families through the psychosocial trauma of a breast cancer diagnosis.

Introduction

Women with inherited BRCA1 or BRCA2 gene mutations have a 56%–83% risk of breast cancer by age 70, with substantial risk beginning at age 30 [1, 2]. Although risk-reducing mastectomy decreases the probability of developing breast cancer by >90%, the majority of women with BRCA mutations opt instead for breast screening in the hope that if cancer develops it will be detected at a curable stage. In an international survey, Metcalfe et al. [3] found that only 18% of unaffected BRCA mutation carriers had undergone mastectomy. There were large differences according to country of residence with the highest rate of mastectomy in the United States (36%) and the lowest in Poland (3%). Of the women who elected to keep their breasts >93% (in all countries except Poland) had undergone breast screening.

Screening for hereditary breast cancer

Until recently, screening recommendations, based on expert opinion, for women with BRCA mutations were to undergo annual mammography and biannual clinical breast examination (CBE) starting at age 25. However, the interval cancer rate was 50% and the percentage of large and/or node-positive breast cancers detected in women screened in this manner was unacceptably high [4–7]. Multiple prospective observational screening studies have now demonstrated significantly improved sensitivity of breast magnetic resonance imaging (MRI) when added to mammography in women at very high risk for breast cancer based on genetic mutations or family history. Despite considerable heterogeneity in patient population, sample size, number of screening examinations and MRI technique, the results of these studies have been remarkably consistent with sensitivity of 71%–100% for MRI alone and 89%–100% when combined with mammography, compared with 25%–59% for mammography alone. It is particularly reassuring that the results of studies carried out in a single highly experienced centre are not significantly different from the results of studies in which multiple centres participated, the latter a much better predictor of the performance of MRI in the ‘real world’. For example, in the the High Breast Cancer Risk Italian Trial (HIBCRIT) [8] 278 women from 17 centres underwent annual mammography, MRI, ultrasound and CBE for 2 years with a 1-year follow-up period. Eighteen invasive and four intraductal cancers were detected. The sensitivity of MRI was 94% compared with 59% for mammography and 65% for ultrasound with no interval cancers. Of the six cancers detected with MRI alone, three were purely intraductal, one was microinvasive and the other two invasive cancers were both 6 mm in size.

A meta-analysis of 11 studies found a sensitivity of 77% [95% confidence interval (CI) 70% to 84%] for MRI alone and 94% (95% CI 90% to 97%) when combined with mammography, compared with 39% (95% CI 37% to 41%) for mammography alone [9]. Although the specificity of the combination (77%) was significantly lower than that of mammography (95%), specificity was better on subsequent
reproductive issues in the management of young women with breast cancer

premature ovarian failure

infertility. Until relatively recently, women with a diagnosis of breast cancer were told that pregnancy after breast cancer was contraindicated due to the very high levels of estrogen and progesterone, which would undoubtedly activate latent micrometastases, particularly in women with hormone-responsive cancers. In addition, because of the relatively poor prognosis of breast cancer in younger women, even disregarding the theoretical risks of precipitating cancer recurrence, a young woman was advised against bringing a baby into the world whom she would be unable to care for once her cancer recurred, and she would ultimately leave orphaned.

That situation has markedly changed. The combination of earlier diagnosis due to greater breast cancer awareness, and more effective systemic therapies, has significantly improved the prognosis of breast cancer in younger women. Moreover, there is mounting evidence that pregnancy after a diagnosis of breast cancer is safe. While initial reports showing a lack of any detrimental effects of pregnancy were passed off as a ‘healthy mother effect’, i.e. that only women with the best prognosis would decide and/or be encouraged to try to get pregnant, studies that have carefully corrected for these factors have shown that pregnancy after a breast cancer diagnosis may actually reduce recurrence rates [24–26]. This observation has been attributed to a possible anti-tumor effect of the high circulating hormone levels. These reassuring findings, together with the progressive delay in childbearing in western societies, means that an increasing number of young women faced with a diagnosis of breast cancer will want to either start or continue childbearing after treatment.

Ironically, the very same effective systemic therapies that have made pregnancy after breast cancer a realistic goal have significantly increased the probability of infertility after treatment has been completed. Infertility is functionally defined as the inability to conceive after 1 year of intercourse without contraception. Certain chemotherapeutic drugs, particularly alkylating agents such as cyclophosphamide, which are included in almost all current adjuvant regimens, are toxic to the ovaries and produce premature ovarian failure by decreasing the number of primordial follicles. Resumption of regular menstruation does not ensure fertility. Even if women are initially fertile after treatment, the duration of fertility may be shortened. The probability of infertility depends not only on the drugs used but also on the dose and schedule, method of administration, age and pre-treatment fertility of the patient [27]. Since most BRCA1-related cancers are ‘triple negative’, all but the smallest invasive cancers will require chemotherapy. Fortunately, standard adjuvant chemotherapies have been shown to be particularly effective in this population. Most women with BRCA2 mutations and ~20% of women with BRCA1 mutations have estrogen-receptor-positive cancers and will be offered hormonal therapy. Hormonal therapies such as tamoxifen or gonadotropin-releasing hormone (GnRH) analogues, while not in themselves toxic to the ovaries, are
generally given for 5 years. Since fertility declines rapidly after age 35, a women diagnosed in her mid- to late 30s may no longer be fertile by the time she has completed her adjuvant hormonal therapy.

The American Society of Clinical Oncology (ASCO) has recommended that oncologists discuss fertility issues with young breast cancer patients who have not completed their families as soon as the possibility of a need for systemic adjuvant therapy becomes apparent [27]. A similar recommendation has been made in the most recent St Gallen guidelines [28]. In some cases a particular systemic therapy regimen may have a borderline indication, and fertility issues may sway the patient’s decision against treatment. Molecular assays such as Oncotype DX or MammaPrint may be particularly helpful. In cases where systemic therapy is clearly necessary, referral should be made for a fertility preservation consultation. Unfortunately, many patients are not made aware of the fact that their treatment may compromise their fertility until treatment is completed. For example, in a survey of young breast cancer survivors only 17% had received a referral to a fertility specialist [29]. Despite clear guidelines released in 2006 by ASCO emphasizing the need for fertility discussion and appropriate referral of young cancer patients [27], in a survey of 516 American oncologists conducted 2 years later only 47% of physicians reported that they always or often referred patients who had questions about fertility to an infertility specialist, with male physicians half as likely as females to refer patients [30].

Today there are several effective fertility preservation options available for patients about to begin systemic therapy. While this process might delay treatment by up to 6 weeks, this is generally not an issue as delaying adjuvant chemotherapy up to 12 weeks after breast surgery has not been found to have a detrimental impact on survival [31]. Embryo cryopreservation after in vitro fertilization is the most established and effective method with live birth rates of ≥60% depending on the age of the patient at the time of egg harvest and the number of eggs retrieved and fertilized. There are several disadvantages to this method, however. It requires ~2 weeks of ovarian stimulation resulting in very high hormone levels, which are of theoretical concern to women with hormone-receptor-positive cancers. Alternative hormone stimulation protocols using tamoxifen or letrozole have been developed which result in lower estrogen levels. To date there has been no evidence that breast cancer recurrence rates in women who have undergone this procedure are higher than in matched controls but follow-up is short [32]. Oocyte collection can be carried out without ovarian stimulation but the embryo yield is very low. Additional disadvantages are the very high cost (approximately $10 000 in the USA) which is often not covered by insurance plans, and the need for a partner or sperm donor [27].

Cryopreservation of unfertilized eggs after ovarian stimulation is generally the procedure of choice for women who do not have an appropriate partner or will not undergo embryo freezing for religious reasons. With recent improvements in freezing and thawing techniques pregnancy rates now approach those of embryo cryopreservation [33]. However, this technique otherwise involves the same concerns as embryo freezing. One caveat about both techniques is a recent observation that the number of oocytes retrieved from BRCA1 mutation carriers over age 33 after ovarian stimulation may be lower than the number retrieved from age-matched non-carriers [34].

Ovarian tissue cryopreservation is a newer technique that is still considered highly experimental. Although it has the advantage of not requiring ovarian stimulation or a sperm donor, it does require a laparoscopic operation for removal of the ovarian tissue and very few live births have been reported after this technique to date. Moreover, if breast cancer cells have spread to the ovary there is a theoretical risk of inducing recurrence when the ovarian tissue is returned to the patient [27]. The presence of occult cancer in the ovaries may be of particular concern in the BRCA population.

It has been hypothesized that ovarian suppression during chemotherapy with a GnRH analogue might reduce toxicity to the ovary but evidence has been conflicting. The results of several randomized trials should soon be available to definitively settle this issue [35].

Premature menopause. Premature menopause, either permanent or temporary, is a frequent consequence of either chemotherapy or hormonal therapy. Symptoms such as hot flashes, insomnia, mood swings, vaginal dryness, loss of libido and weight gain may have a significantly detrimental effect on patient quality of life. From a medical point of view, perhaps the most important effect is the rapid loss of bone mass observed after only 4 months of amenorrhea, which may be irreversible even if menses eventually resume. The average drop in bone mineral density (BMD) after 1 year of amenorrhea is 5% and after 3 years the average decrease in BMD is 14% [36]. Although tamoxifen has a bone-sparing effect in postmenopausal women, in premenopausal women estrogen antagonist effects predominate and bone loss ensues. Studies have shown that oral clodronate partially attenuates this bone loss [37] while risedronate has no effect [38]. Very encouraging results have been reported from the use of intravenous zoledronic acid every 6 months [36]. Since there is some evidence that bisphosphonates in general and zoledronic acid in particular may also reduce breast cancer recurrence rates, use of these agents to prevent bone loss before it occurs should be strongly considered. RANK ligand inhibitors such as denosumab are also being studied in this setting and may even prove superior to bisphosphonates. One important caveat is that an increased risk of osteonecrosis of the jaw has been reported with both classes of agent [39, 40]. However, there are no reports to date of this complication in premenopausal women receiving adjuvant zoledronic acid every 6 months.

Hereditary breast cancer during pregnancy

Although breast cancer in pregnancy is a relatively rare occurrence (~1 in 3000 pregnancies) [41], one would expect it to be more common among women with BRCA mutations. In a population-based study in Sweden the odds ratio for pregnancy-associated breast cancer was 3.9 (95% CI 1.4–10.8) for BRCA1 mutation carriers and 1.9 (95% CI 0.5–7.0) for BRCA2 mutation carriers [42]. Since these relative risks are actually lower than the relative risk of breast cancer for non-pregnant BRCA mutation carriers of reproductive age, this is...
months after the baby is weaned and the interval from the last
more than 6 months, as screening cannot resume until 3–6
women every 3 months for CBE. Ultrasound is carried out for
until right after undergoing a normal MRI scan, when
MRI screening and wish to get pregnant to delay such efforts
diagnosis of breast cancer, had been unaware of their mutation
regular MRI screening than in carriers who, until their
status and thus were not getting optimal screening, if any. We
psychosocial issues specific to young
women with breast cancer

Multiple studies have shown that younger women have greater
psychological morbidity and poorer quality of life after a breast
cancer diagnosis than older women, both initially and long
term [23]. Causes of this morbidity include the diagnosis itself,
the treatment and its toxicities, and the untimeliness of both in
relation to the woman’s stage in life.

A breast cancer diagnosis is devastating for any young
woman as it leads to a premature confrontation with mortality.
For the woman with young children concerns for their future
welfare are paramount but, at the same time, there is the
natural more ‘selfish’ focus on whether she will live to celebrate
future milestones such as graduations, weddings and the birth
of grandchildren. It is often difficult for these young women to
share their concerns with their spouses, siblings or parents, who
are experiencing their own tremendous psychological
difficulties, or with peers who are busy ‘getting on with their
lives’ and have little or no personal experience with life-
threatening diseases. This leads to tremendous social isolation.

It is generally far more disruptive for young women to have
to take time off for diagnostic tests, surgery, chemotherapy
treatments and their toxicities, and radiation treatments, than it
is for older women. Younger women may be at a critical time in
their education, working in relatively new jobs, struggling to
keep fledging businesses afloat, or looking after very young
children. Young breast cancer patients also experience greater
morbidity from treatment ranging from more chemotherapy-
related nausea and vomiting [49] to the problems of infertility
and premature menopause described above. The negative
effects of breast cancer and its treatment on the physical and
psychological aspects of sexuality are particularly marked in
younger women [50]. Furthermore, younger women are more
likely to be single and these issues may paralyze their desire
and/or efforts to date. For those young women in relatively new
relationships, sexuality issues put a further strain on the couple,
compounding the numerous other stresses such as fear of
infertility, renegotiation of family roles [51], reduced social
activity [52] and financial strain [53]. Research has shown that
younger couples with relationships of shorter duration may
lack the relationship resiliency of longer married couples [54].
Financial issues may be overwhelming for many younger
women and include career/job disruption to the woman herself,
the need for her partner to limit work in order to care for
children or take on other household tasks, and the costs of
treatments including fertility preservation. A recent study by
the Canadian Breast Cancer Network found that the financial
implications of a breast cancer diagnosis often persisted long
after active treatment was completed, as many women were
unable to return to their previous job either because the job no
longer existed or because they were no longer able to do the
work.

While all the issues mentioned above are relevant to young
women with a BRCA-related breast cancer, these women face
additional sources of psychosocial morbidity. Distress over the
diagnosis is often magnified tremendously by identification
with close relatives who died of cancer, and from guilt over
likely having transmitted their ‘cancer gene’ to their children. In
our experience ~50% of these women will opt for bilateral
mastectomy, usually with delayed reconstruction, even if they
are candidates for breast conservation. This further aggravates
the logistical stresses and body image issues. It is critical that
the oncologist initiates timely referral to a psychologist, social
worker or other appropriate professional for the many young
women who will need such help.

At our centre we have a unique clinical and research program
for women aged ≤40 with breast cancer, inspired in part by our
many young BRCA mutation carriers diagnosed with breast
cancer during screening. This program (PYNK: Breast Cancer
Program for Young Women), developed in collaboration with
several breast cancer survivors, provides the continuum of care
for patients and their families from diagnosis through
treatment and long-term follow-up, and conducts research to
develop specific therapeutic and supportive care for this
understudied group. We currently have two very promising psychosocial studies focused on younger women. For young couples in a long-term heterosexual relationship within 1 year of a breast cancer diagnosis in the female partner, we are studying an online intervention consisting of sets of exercises that the couple completes sometimes as individuals and sometimes together, covering topics such as communication, intimacy and sexuality. For women who finished active treatment at least 1 year earlier and still have significant body image problems, we are studying a group intervention consisting of eight weekly sessions led by a facilitator trained in group therapy and guided imagery. Feedback from both interventions has been extremely positive so far and randomized controlled trials are underway.

**Conclusion**

Annual breast screening with the combination of MRI and mammography started by age 30 has proved to be an effective management option for women with BRCA mutations. However, a fairly high proportion of these women will develop breast cancer at a young age during screening, and oncologists need to be aware of the unique medical and psychosocial needs of this subpopulation of breast cancer patients.

**Disclosures**

Honorarium from Bayer for an advisory board meeting.

**References**


