Familial breast cancer, whether associated or not with particular other breast cancer features (male, early onset, bilateral breast cancer), determines a wide and variable risk of developing breast cancer in the ‘unpatients’ (unaffected individuals) of these families, particularly in those harboring a genetic predisposition. The antiestrogen tamoxifen has been proposed in different trials to prevent breast cancer in women at risk. The NSABP-P1 study demonstrated that tamoxifen drastically reduced (by $\sim 50\%$) the incidence of breast cancer in women at risk selected according to the Gail score. The preventive effect was particularly consistent in postmenopausal women and in those showing familial breast cancer (three or more affected patients). \textit{BRCA1/2} gene analysis in women accrued in the NSABP-P1 trial who developed breast cancer showed that tamoxifen chemoprevention reduced breast cancer incidence in \textit{BRCA2} carriers. Different chemoprevention trials are ongoing to compare different selective estrogen receptor modulators and aromatase inhibitors with tamoxifen. The Italian Consortium of Hereditary Breast Ovarian Cancer recently developed the Aromasin$^\text{®}$ Prevention Study, a multicenter, double-blind, randomized, placebo-controlled phase III study evaluating the effect of the aromatase inhibitor exemestane for chemoprevention in postmenopausal women carriers of \textit{BRCA1/2} genetic predisposition. Women who are postmenopausal unaffected carriers of \textit{BRCA1/2} mutations will be selected by participating institutions and randomly assigned to receive either oral exemestane or oral placebo every day for 3 years in order to reduce the incidence of breast cancer. Genetic counseling and the detection of predisposing \textit{BRCA1/2} mutations are mandatory before accrual into the study. Signed informed consents for the performing of \textit{BRCA1} and \textit{BRCA2} genetic analysis and for enrollment into the study are required. Eligible women will be followed thereafter in order to evaluate the efficacy of exemestane in reducing the incidental rate of breast cancer in unaffected postmenopausal carriers of \textit{BRCA1/2} mutations.

Key words: breast cancer, drugs, prevention

Introduction

During the past 20 years, clinical observations concerning the presence of ‘cancer clustering’ in certain families have led to the identification of an increasing number of hereditary breast cancer syndromes [1–3]. These syndromes are now better elucidated thanks to the identification of culprit germline mutations within specific genes [4, 5]. In particular, mutations of the \textit{p53}, \textit{PTEN}, \textit{ATM} and \textit{BRCA} genes are the sine qua non for the diagnosis of Li–Fraumeni syndrome, Cowden’s disease, ataxia-telangiectasia syndrome and hereditary breast/ovarian cancer syndrome, respectively [6].

Overall, diagnosed breast cancer cases can be classified as follows: hereditary (5–10%), i.e. correlated to a mutated phenotype of a specific gene segregating with a Mendelian inheritance pattern in families; familial (15–20%), i.e. one or more first- and/or second-degree relatives of the proband affected by breast cancer, in the absence of Mendelian inheritance and/or of an identified cancer-causing germline mutation of a specific gene; or sporadic (70–80%), namely the lack of breast cancer among a patient’s first- and/or second-degree relatives [6].

Yearly, between 60 000 and 120 000 of newly diagnosed breast cancers are of the hereditary type, implying that efforts must be made to identify these individuals to reduce the incidence of breast cancer.

\textit{BRCA1/2} and familial breast cancer

A proportion of hereditary breast cancer has been attributed to germline mutations of either \textit{BRCA1} or \textit{BRCA2}, and since the identification of these genes [7, 8], the hereditary breast
and/or ovarian cancer syndrome has been recognized as a clinical entity.

Women carrying a pathologic germline mutation of either gene have a markedly increased lifetime risk of developing breast and/or ovarian cancer, typically at early ages [9, 10]. The lifetime risk of breast cancer conferred by BRCA1/BRCA2 (BRCA1/2) mutations ranges from 56% [11] to 85% [9], the lifetime risk of contralateral breast cancer lies between 50% and 60%, and may exceed 5% per year [12]. In reality, two studies have described lifetime risks of breast cancer approaching 100% for BRCA1 mutation carriers [13, 14], although <2% of breast cancer cases are diagnosed before 70 years of age and nearly 8% before 30 years [15]. The estimated lifetime breast cancer risk in males with BRCA2 mutations is 6% by age 70 years [16].

While BRCA1 mutations confer a lifetime ovarian cancer risk of between 20% and 40% [11, 14], for BRCA2 mutations this approaches 20% [11]. BRCA1/2 mutations also confer an increased risk of developing colon, prostate, pancreas, stomach and gall bladder cancers, as well as melanoma, with relative risks (RRs) ranging between 2.06% and 4.14% depending on the gene involved and the cancer considered [9, 17, 18].

Hence, genetic testing for BRCA1/2 mutations identifies a high-risk population with increased susceptibility to different types of cancer, especially breast cancer and/or ovarian cancer. Medical oncologists therefore face the challenges of identifying this high-risk group among the normal population and of reducing morbidity and mortality in BRCA1/2 mutation carriers.

To this end, several avenues are currently being explored: (i) genetic counseling and cancer risk assessment to understand who should undergo genetic testing to identify BRCA1/2 mutation carriers; and (ii) increased surveillance [19–21], prophylactic mastectomy [22–24] and/or prophylactic ovariectomy [25–29], chemoprevention [29], or combinations of these, for breast cancer risk reduction in high-risk women, especially in BRCA1/2 mutation carriers.

**Lifetime breast cancer risk assessment**

After BRCA1/2 analysis and genetic testing, the ultimate duty of the oncologist is to personalize breast cancer risk reduction strategies in both BRCA1/2 carriers and non-carriers, with the aim of increasing survival in high-risk women and decreasing costs and needless anxiety in low-risk women.

The Gail and Claus models, currently the most widely used, are helpful risk assessment tools that quickly estimate the absolute lifetime risk a woman has of developing breast cancer [30–32]. The Gail model underestimates risk assessment in 50% of families with cancer in the paternal lineage [31, 33]. The Claus model assesses breast cancer risk solely on the basis of family history, but includes maternal and paternal breast/ovarian cancer history, first- and second-degree relatives and age at breast cancer diagnosis [30, 34]. Since both models were developed before the birth of BRCA1/2 genetic testing, breast cancer risk assessment is not of utmost accuracy in genetically predisposed women.

Briefly, early probability models may be of help in deciding whom to subject to BRCA1/2 testing. Once genetic disclosure has been faced, the Gail and/or Claus model may further help the physician decide which breast cancer risk reduction strategy to adopt, especially in non-carriers.

**Increased surveillance**

Today, routine breast cancer screening is recommended in women of 50–70 years of age, at average risk for the disease, since it is in this category of women that breast cancer screening has proven to be cost-effective [35–38]. Some advantages of breast cancer screening have been seen in younger women [39], but the lower incidence of breast cancer and the greater screening risks in women <50 years old render routine screening less efficient [40] unless women are at high breast cancer risk (i.e. positive family history and/or BRCA1/2 carriers) [41]. Hence, women at high risk for breast cancer may opt for increased surveillance, irrespective of their age, even if a clear favorable effect on survival has not been demonstrated.

Current breast cancer surveillance guidelines in high-risk women, or in BRCA1/2 carriers, are breast self-examination, clinical examination twice a year and mammography once a year [42]. Magnetic resonance imaging (MRI) seems to be promising [43–45], but is presently used only in the research setting. Screening should begin at 30 years of age, or 5–10 years prior to the age of the youngest affected relative in the family if early onset cases are present [42].

Unfortunately, the limited preliminary results on increased surveillance are not promising [20, 42, 43, 46–48], especially in young BRCA1/2 mutation carriers [42]. This is partially explained by the fact that the cancer growth rate is greater [49, 50] in BRCA1/2 mutation carriers [42]. In BRCA1/2 carriers, mammographic cancer detection is lower in young women [51–53] because of greater breast tissue density.

Overall, BRCA1/2 carriers show the highest cancer detection rate (33/1000 yearly) compared with moderate (3.3/1000 yearly) and high-risk (8.4/1000 yearly) women or compared with women from the normal population of comparable age [42]. Thus, in young BRCA1/2 carriers, screening programs might have to be intensified with respect to the above-mentioned guidelines, and many countries are currently evaluating the efficacy of MRI for early breast cancer detection in high-risk women [54, 55].

In short, since increased surveillance does not reduce breast cancer mortality, or, obviously, incidence, but only gives the possibility of early breast cancer detection, it is probably justified in women over 50 years of age at high risk of developing breast cancer, especially if they are BRCA1/2 carriers.

**Prophylactic surgery**

Owing to the limitations of increased surveillance programs, some clinicians opt for prophylactic bilateral mastectomy and/or oophorectomy as a cancer reduction strategy, although prophylactic mastectomy remains controversial for
the paradox of performing more extensive surgery for breast cancer prevention than for the actual disease [56].

Two clinical decision-making models based on the assumed efficacy of prophylactic mastectomy and prophylactic oophorectomy [57, 58] have shown prophylactic surgery to be cost-effective in increasing life expectancy in BRCA1/2 carriers [57], without, however, abrogating cancer risk completely.

**Prophylactic mastectomy**

One of the drawbacks of prophylactic mastectomy is the uncertainty that all glandular tissue has been removed and, in genetically predisposed women, any amount of residual breast tissue has significant neoplastic potential [59]. Not surprisingly then, cases of breast cancer occurrence after prophylactic mastectomy have been reported in the literature [60–65].

The efficacy of prophylactic mastectomy in preventing breast cancer in women with hereditary susceptibility to the disease has not been addressed in prospective clinical trials, but two large case series [20, 66] have shown prophylactic mastectomy to reduce breast cancer mortality and incidence (90%) [20]. Since the effects of prophylactic mastectomy on risk reduction in BRCA1/2 carriers has not been investigated, the analytical models of Grann et al. [57] and Schrag et al. [58] are the only decision-making tools available to the physician. Both these analytical models report that gain in life expectancy is greatest (between 2.8 and 5.3 years) if mastectomy is performed in 30-year-old carriers in whom the estimated lifetime risk of breast cancer is greatest. A lower gain in life expectancy is obtained in 40-year-olds (5.3 versus 2.6 years), while for a 50-year-old carrier such a delay results in a modest life expectancy gain (2.3 versus 0.1 years).

The few studies that have investigated the psychiatric and psychosocial consequences of prophylactic mastectomy in high-risk women confirmed that most women surveyed after surgery were highly satisfied and only a small proportion reported feelings of depression and/or some impact on their sexuality [67–69].

**Prophylactic oophorectomy**

Oophorectomy has been used as adjuvant treatment in premenopausal breast cancer patients to reduce breast cancer recurrences [70].

With the advent of BRCA1/2 testing, prophylactic oophorectomy can now be recommended in mutation carriers as a strategy to reduce both breast [71, 72] and ovarian cancer risks. Although prophylactic oophorectomy almost entirely abrogates ovarian cancer risk in BRCA1/2 carriers, a 4% risk of developing peritoneal cancer remains [26, 27], and has been described [72–77]. No prospective study has investigated the efficacy of prophylactic oophorectomy in reducing ovarian cancer incidence or mortality from ovarian cancer in BRCA1 mutation carriers, even though prophylactic oophorectomy has shown to reduce breast cancer risk by ~50% [28]. However, the potential risks of causing premature menopause in a young woman must be carefully balanced against the age-related risk of developing ovarian cancer. In hereditary ovarian cancer, the mean age at diagnosis is 48–51 years in BRCA1 carriers [78–81], and this cancer is rarely seen at or before 30 years [78]. Hence, prophylactic oophorectomy can be deferred to older age groups [82] or can be considered after 35 years of age or once childbearing has been completed, whichever comes first [83]. After all, delaying prophylactic oophorectomy by 10 years in a 30-year-old BRCA1 carrier, with a 40% risk of ovarian cancer, decreases the gain in life expectancy only from 1.7 to 1.2 years [58].

**Chemoprevention**

Oophorectomy performed early in reproductive life is effective in reducing breast cancer risk in BRCA1/2 carriers [28], thus suggesting a potential role for preventive hormone therapy. The role of estrogen in the proliferation of breast cells is well documented: high estrogen levels and local estrogen synthesis, through aromatase activity, are important in the development of breast cancer [84–86].

Historically, the evidence that estrogen was a proliferation stimulus for breast cells and could ultimately induce breast cancer provided the basis for using tamoxifen in the treatment of breast cancer. In fact, over the years, many studies have proven the effectiveness of adjuvant tamoxifen therapy in reducing contralateral breast cancer incidence in breast cancer patients, independently of BRCA1/2 status [29, 87–90]. Today, the enhancement of our knowledge of breast cancer and of the role of estrogen in the pathogenesis of breast cancer, together with the extraordinary results provided by tamoxifen therapy in breast cancer patients, have led to conceiving chemoprevention as a strategy to counteract the development of breast cancer in high-risk women.

**Tamoxifen and chemoprevention**

The rationale for the use of selective estrogen receptor modifiers (SERM), such as tamoxifen, in breast cancer prevention is based on the inhibition of hormonal stimulation of breast cell proliferation by antagonizing estrogen receptor (ER) activity. However, the encouraging results recently observed with the use of tamoxifen in reducing breast cancer incidence in healthy, at-risk women, remain controversial [91–93], and the efficacy of tamoxifen in specifically reducing the incidence of breast cancer in healthy BRCA1/2 mutation carriers has not been fully elucidated.

Recently, an updated meta-analysis of the four randomized tamoxifen trials identified an overall 38% reduction in breast cancer incidence, slightly less than that seen in the P1 trial alone [94]. An interim analysis of the Royal Marsden Hospital chemoprevention trial indicated no benefit of tamoxifen treatment in healthy women at high breast cancer risk [92], while the NSABP-P1 trial demonstrated a nearly 50% reduction with tamoxifen prevention therapy in high-risk women [91]. This discrepancy may be due to the different patient...
The demonstrated role of estrogen in promoting breast cancer also supports the idea that suppression of estrogen production could be used as a chemoprevention strategy [84, 85, 102]. This can be accomplished by inhibition of aromatase, the rate-limiting enzyme in estrogen biosynthesis [103]. Irreversible aromatase inhibition decreases both estrogen production and cell proliferation, and irreversible aromatase inhibitors, such as exemestane, may be more effective in preventing the initiation of breast cancer than antiestrogens. Therefore, use of aromatase inhibitors may be an alternative prevention strategy in BRCA1/2 carriers.

Exemestane prevention in BRCA1/2 carriers

Exemestane irreversibly binds to aromatase, almost completely inhibiting enzyme activity (>97.9%) [104] and reducing circulating estrogen to 6–11% of baseline levels [97]. The proven efficacy of this agent in metastatic disease [105, 106] and neo-adjuvant therapy [107] supported its use in early-stage disease. Now, preclinical models suggest it may have a role in breast cancer prevention [86, 108]. Moreover, the better tolerability of this agent compared with tamoxifen makes it appropriate for the chemoprevention setting [104] (Table 2).

The Aromasin® Prevention Study (APreS) trial has been proposed by the Italian Consortium of Hereditary Breast/Ovarian Cancer to assess the role of exemestane in preventing breast cancer in healthy postmenopausal BRCA1/2 carriers. The primary end point of this randomized phase III trial is to determine the magnitude of the reduction in breast cancer incidence in the group treated with exemestane compared with a placebo group. Secondary end points include the efficacy of exemestane in reducing the incidence of ductal carcinoma in situ and lobular carcinoma in situ, safety of exemestane, changes in bone and breast density, and quality of life. The trial will enroll 400 BRCA1/2 carriers who are unaffected relatives of patients with breast cancer. Participants will be randomized to receive either exemestane or placebo, every day, for 3 years. Key eligibility criteria are summarized in Table 3.

**BRCA1/2 mutations and hormone receptor status**

Reports suggest that BRCA1/2 mutations relate to hormone receptor (HR) status: BRCA1 tumors are mostly ER/progestrone receptor (PgR)-negative, and BRCA2 tumors more commonly ER/PgR-positive [47, 97–101]. The lack of HR positivity in BRCA1 tumors suggests that treatment with tamoxifen, or other hormonal therapy, may be less effective in this patient population [97]. In contrast, the hypothesis that hormones may influence the development of BRCA1 tumors implies that hormonal therapy may have a role in prevention [97, 99]. In addition, BRCA1/2 tumors have both favorable and unfavorable prognostic associations, so that examining outcome in BRCA1/2 mutation carriers separately is of paramount importance [100].

Presently, no trial has been designed to study chemoprevention in BRCA1/2 carriers, and the mixed results seen in this limited number of subjects preclude reliable assessment of tamoxifen effects in this specific subgroup [96].
MI, myocardial infarction; TIA, transient ischemic attack; DVT, deep venous thrombosis; PE, pulmonary embolism.

Table 3. Aromasin® Prevention Study key eligibility criteria

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<th>BRCA1/2 carrier</th>
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<td>Postmenopausal women</td>
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<td>Unaffected by cancer (specifically, no evidence of breast cancer or suspicious breast lesions and no prior breast malignancy)</td>
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<td>No prior mastectomy (unilateral or bilateral)</td>
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<tr>
<td>No prior hormonal therapy in previous 3 months</td>
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<td>Age 30–70 years</td>
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<td>Adequate liver and renal function</td>
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<td>No prior MI, stroke, TIA, DVT or PE</td>
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Conclusions

During the last decade, the overwhelming amount of information that has been acquired in cancer genetics has brought about a quickly advancing cascade of parallel and intertwining discoveries, both in the clinical and biological research fields. From a clinical point of view, the identification of individuals with genetic breast cancer predisposition is becoming ever more important in terms of cancer prevention. However, both the clinical and biological fields need to improve certain aspects to ensure breast cancer prevention.

Most of the available probability models underestimate an individual’s risk of being a BRCA1/2 mutation carrier, thus preventing some women from being tested. Furthermore, some of the women tested will prove to be negative for BRCA1/2 mutations, probably due to inadequate sensitivity of presently used diagnostic techniques or to the existence of other predisposing genes that have not yet been identified.

Therefore, in order to maximize identification of these genetically predisposed individuals, the following points must be addressed: (i) the improvement and/or better interpretation of probability models to calculate an individual’s risk of being a BRCA1/2 mutation carrier [109]; (ii) the development of more sensitive molecular diagnostic techniques [110, 111]; and (iii) the identification of new breast cancer predisposing genes, other than BRCA1 and BRCA2.

Secondly, in order to better advise a woman towards more targeted screening and management strategies, improvements must be made in her lifetime risk assessment and in breast cancer prevention.

To maximize breast cancer risk assessment, models should be updated to include BRCA1/2 mutation status and other cancers or specific features (early onset age, individuals with multiple cancers). Women at high breast cancer risk, but not carrying a BRCA1/2 mutation, should always be considered as belonging to a familial breast cancer syndrome in which the BRCA1/2 germline mutation or predisposing gene remains to be identified and should, therefore, at least be considered for increased surveillance. Increased surveillance seems to be best suited to high-risk women, especially BRCA1/2 mutation carriers who are 50 years of age and over. For young BRCA1/2 carriers, the present surveillance guidelines do not seem to be sufficient, and in the future they might have to be further intensified and/or enhanced by including MRI. An optimal surveillance program is of utmost importance, as this ‘prevention’ strategy will supplement other available prevention options more frequently (i.e. after prophylactic surgery, during chemoprevention).

As of today, the best preventive strategy for women at high risk of breast cancer has yet to be established. So far, evidence of the efficacy of secondary cancer prevention strategies in women with BRCA1/2 mutations demonstrates that prophylactic mastectomy may yield the highest gain in prevention for young women with these mutations [58], reducing the breast cancer risk (by ~90–95%) and mortality [23]. Prospective data are limited but suggest similar results [24]. Despite the substantial disadvantages of this procedure, including loss of body integrity and unknown effects of the surgery on long-term quality of life, BRCA1/2 mutation carriers may choose this option. Prophylactic oophorectomy also reduces breast cancer risk in BRCA1 mutation carriers (RR 0.53) [25, 26] and remains another viable option. However, the unknown and known systemic effects of premature menopause represent a substantial drawback to this strategy, and must be further elucidated.

Prophylactic surgery remains controversial since its exact efficacy for cancer risk reduction and mortality is unknown, and because chemoprevention is a practical option. In fact, reversibly counteracting the effects of circulating estrogens with safe drugs may represent the best and primary prevention strategy in high-risk women, especially BRCA1/2 mutation carriers.

Recent analyses of the NSABP P-1 results suggest that tamoxifen therapy may not be appropriate for BRCA1 carriers [95]. However, hormone deprivation through oophorectomy remains an effective preventive therapy in BRCA1/2 carriers [25, 26], suggesting a plausible role for hormonal manipulation in these patients.

The effects of chemoprevention on breast cancer risk reduction in this particular group of patients have yet to be evaluated, and placebo controls are appropriate since no intervention has been established to have a favorable impact on overall well-being and survival [96]. An ongoing trial is evaluating the efficacy of exemestane in the prevention of breast cancer in healthy BRCA1/2 carriers.

Nonetheless, results from breast cancer prevention trials leave several unanswered questions: what is the optimal preventive therapy, how long should therapy last, how durable is the preventive effect, and who benefits the most?

Progress in our understanding of the underlying causes of breast cancer and the potential for introducing chemoprevention into clinical practice suggest that over time, primary prevention strategies will contribute more directly to breast cancer control. Today, despite accelerating discoveries, the magnitude and complexity of hereditary cancer problems far exceeds our resources. Therefore, while awaiting the answers to unresolved dilemmas, fine clinical judgement and keen medical decision-making remain the mainstays of the management of women at high risk of developing breast cancer.
References