Review article

Chemoprevention or mastectomy for women at high risk of developing breast cancer

Piero Sismondi *, Marta D’Alonzo, Silvia Pecchio, Valentina Elisabetta Bounous, Elisabetta Robba, Nicoletta Biglia

Unit of Obstetrics and Gynaecology, Mauriziano Umberto I Hospital, Department of Surgical Sciences, University of Turin, Turin, Italy

A R T I C L E   I N F O

Article history:
Received 12 June 2015
Received in revised form 1 July 2015
Accepted 2 July 2015

Keywords:
Breast cancer risk assessment
High-risk breast cancer women
Risk-reduction strategies
Chemoprevention
Risk-reduction mastectomy

A B S T R A C T

Breast cancer (BC) is the most commonly diagnosed invasive cancer among women; in developed countries, BC occurs in one out of eight women during her lifetime. Many factors, both genetic and non-genetic, determine a woman’s risk of breast cancer and several mathematical models have been proposed that determine the risk. It is important to identify those at high risk, as there are now effective preventive strategies, such as chemoprevention therapy and risk-reduction surgery. Risk-reduction agents are recommended for women aged 35 years or more who are at high risk of breast cancer. Tamoxifen is presently deemed to be the agent of choice. However, raloxifene may be preferable, at least for some postmenopausal women, because of its lack of effect on the endometrium and the reduced incidence of venous thromboembolic events compared with tamoxifen. Prophylactic surgery has been widely investigated. Bilateral mastectomy decreases the risk of developing breast cancer by approximately 90% in women at moderate or high risk and in known BRCA1/2 mutation carriers. This review summarizes the recent advances in the identification of women at high risk of developing breast cancer and reports on the strategies used to prevent breast cancer; the risk–benefit balance of such preventive choices is also briefly analyzed.

© 2015 Elsevier Ireland Ltd. All rights reserved.

Contents

1. Introduction .......................................................................................................................................................... 271
2. Risk-reduction agents ......................................................................................................................................... 272
3. Risk-reduction mastectomy (RRM) .................................................................................................................... 273
4. Conclusions ....................................................................................................................................................... 273

Contributors ............................................................................................................................................................. 273
Conflict of interest .................................................................................................................................................. 273
Funding .................................................................................................................................................................... 273
Provenance and peer review ................................................................................................................................. 273
References ............................................................................................................................................................... 273

1. Introduction

In developed countries, one in eight women will develop breast cancer (BC) at some point during her lifetime, given an estimated life expectancy of 85 years. The majority of cases are sporadic but about 10% of BCs are associated with genetic risk factors, principally mutations of BRCA1 and BRCA2. Risk factors for BC are primarily related to age and estrogen exposure (early menarche, late menopause, nulliparity, use of exogenous hormones); in addition, the population at high risk includes women with atypical hyperplasia, women with ductal or lobular carcinoma in situ and women with a history of thoracic radiotherapy before the age of 30 years. High risk has been defined as a 5-year breast cancer risk of at least 1.7% [1]. Several mathematical models to estimate this risk have been proposed; currently the most widely used is the National Cancer Institute (NCI) Breast Cancer Risk Assessment Tool, which

* Corresponding author at: University of Turin, School of Medicine, Turin, Italy.
Fax: +39 11 5082683.
E-mail address: piero.sismondi@unito.it (P. Sismondi).

http://dx.doi.org/10.1016/j.maturitas.2015.07.002
0378-5122/© 2015 Elsevier Ireland Ltd. All rights reserved.
is a modified version of the Gail model. It incorporates age, ethnicity, age at first pregnancy, family history and history of atypical hyperplasia. Individuals with a 5-year risk of 1.66% or greater are considered to be at high risk [2]. A recent report in the New England Journal of Medicine [3] underscored the importance of atypical hyperplasia as an independent factor, and recommended that it be used as a criterion for the inclusion of women in chemoprevention programs. In studies with long-term follow-up, atypical hyperplasia has been shown to confer a relative risk for future breast cancer of 4. A large cohort study at the Mayo Clinic [4] similarly reported a cumulative high risk of breast cancer among women with atypical hyperplasia. Specifically, 25 years after a biopsy confirmed the atypical hyperplasia, breast cancer (either in situ or invasive) had developed in 30% of the women, with a greater number of foci of the hyperplasia associated with a higher risk of breast cancer. The authors suggested that guidelines for high-risk women be updated to include women with atypical hyperplasia.

Women who are considered to be at increased risk of breast cancer on the basis of any of the above factors, and who have a life expectancy of at least 10 years and no diagnosis or history of breast cancer, should receive individualized counseling on how they might decrease their risk of breast cancer. **There are three principal strategies to prevent breast cancer:** modification of lifestyle factors (the avoidance of obesity, physical inactivity, and high alcohol intake), chemoprevention therapy with risk-reduction agents, and risk-reduction surgery [1].

### 2. Risk-reduction agents

**Chemoprevention** relies on the use of pharmacologic or natural agents to inhibit the development of invasive cancer. Risk-reduction agents are recommended for women deemed to be at high risk of breast cancer who are at least 35 years old [1].

**Tamoxifen** was one of the earliest drugs to be used for this purpose and is therefore one of the most studied. Four large trials with long-term follow-up have been published: a Royal Marsden study, NSABP P-1, an Italian study, and IBIS I. A meta-analysis by Cuzick et al. [5] has shown an overall risk reduction of 33% (p < 0.0001) compared with placebo. This reduction is mainly due to a large effect on estrogen receptor (ER) positive invasive breast cancer, for which the reduction is 44% (p < 0.0001), and a significant reduction in ductal carcinoma in situ (DCIS) (p = 0.009). Women receiving tamoxifen had a higher rate of endometrial cancer than did those given placebo (OR 2.18, CI 1.39–3.42; p = 0.001); venous thromboembolic events were increased as well (OR 1.60, CI 1.21–2.12; p = 0.001). The NSABP P-1 [6] study stratified adverse events according to patient age and found that they occurred mainly in women aged 50 years or more.

**Raloxifene**, like tamoxifen, is a selective ER modulator (SERM). It was initially studied in women with osteoporosis and coronary heart disease in the MORE [7], CORE [8] and RUTH [9] trials, which found a lower incidence of breast cancers compared with placebo. These promising results encouraged investigators to design the National Surgical Adjuvant Breast and Bowel Project (NSABP) Study of Raloxifene and Tamoxifen (STAR or P-2 study) [10]. The first report, after a follow-up of 4 years, demonstrated that raloxifene was as effective as tamoxifen in preventing invasive BC, with a reduction of about 50% of the incidence of invasive BC in the treated population compared with the placebo group. The toxicity and side-effects favored raloxifene, as the women taking it had a lower incidence of deep-vein thrombosis, pulmonary embolism and hysterectomies for benign uterine conditions, and a non-significant reduction in endometrial cancer. On the basis of these results, the US FDA approved raloxifene for BC prevention in 2007. An updated analysis of the STAR trial at 81-month median follow-up [11] showed that the preventive effect of raloxifene was not as persistent as that of tamoxifen, however: raloxifene was less effective than tamoxifen for the prevention of invasive breast cancer in the long term, retaining only 76% of its effect compared with tamoxifen.

Another family of chemoprevention drugs are the aromatase inhibitors (AIs). Two large clinical trials have compared AIs with placebo in the prevention of primary breast cancer. The Mammary Protocol 3 (MAP.3) trial [12] was a randomized, placebo-controlled, double-blind trial of exemestane 25 mg administered to postmenopausal women at high risk of BC. The study showed a 65% relative reduction in the annual incidence of invasive BC (HR 0.35, 95% CI 0.18 – 0.70; p = 0.002). In the International Breast Cancer Intervention Study-II (IBIS-II) [13] Prevention trial, 1920 women were randomly allocated to receive anastrozole 1 mg daily and 1944 were allocated to placebo. Significantly more BCS (including ductal carcinoma in situ) were observed during the follow-up in the placebo group than in the anastrozole group (HR 0.47, 95% CI 0.32–0.68; p < 0.0001).

**Estrogen receptor negative tumors**, which account for about 30% of BC, remain a challenge for prevention. Current approaches to BC prevention mainly target ER-alpha. Several classes of drugs have been shown to prevent ER negative BC in animal models, including retinoids (Fenretinide), COX inhibitors and tyrosine kinase inhibitors, such as lapatinib and gefitinib.

### 3. Risk-reduction mastectomy (RRM)

Retrospective analyses with median follow-up periods of 13–14 years have indicated that bilateral risk-reducing mastectomy (RRM) decreases the risk of developing breast cancer by approximately 90% in women at moderate or high risk and in known BRCA1/2 mutation carriers [14]. Further results from smaller prospective studies with shorter follow-up periods have provided support for the conclusion that RRM provides a high degree of protection against BC in women with a BRCA1/2 mutation. The 2015 NCCN Breast Cancer Risk Reduction Panel supports the use of RRM for carefully selected women at high risk of BC who desire this intervention, taking into consideration exclusively BRCA1/2 or other genetic mutation carriers and women with a previous history of lobular carcinoma in situ (LCIS) 1. There are not enough data to support a recommendation that women with prior mantle radiation exposure should have RRM, but it must be remembered that women surviving pediatric Hodgkin’s disease have a 37-fold increase in the risk of BC and a high likelihood of rapidly developing bilateral disease.

As regards atypical hyperplasia, the Society of Surgical Oncology recognizes it can be a possible but not a routine indication for bilateral prophylactic mastectomy [15]. A recent report on atypical hyperplasia and surgical risk-reduction interventions concluded that, in current practice, with minimal data available on this topic and with chemopreventive agents for risk-reduction available, atypical hyperplasia is generally not an indication for prophylactic mastectomy [3].

Women considering RRM **should first have appropriate multidisciplinary consultations**, a clinical breast examination and bilateral mammograms (if these have not been performed within the past 6 months). If the results are normal, women who choose RRM may undergo the procedure with or without immediate breast reconstruction. **Axillary node assessment** has no indication at the time of RRM, and neither has axillary lymph node dissection, unless BC is identified on pathologic evaluation of the mastectomy specimen. **Following RRM,** women should continue with annual exams of the chest and the reconstructed breast, as there is still a small risk of developing BC. Mammograms are not recommended, however [1].
4. Conclusions

Although the potential benefits of preventive strategies in women at increased risk of BC were first demonstrated more than a decade ago, both chemopreventive agents and prophylactic surgery are rarely used, even by those women with a favorable risk–benefit profile. The effectiveness of all the preventive options must be evaluated in each individual case. Studies are needed to understand the level of interest of patients and their physicians in endorsing these options.

Contributors

All authors declare that have participated in this work and that have seen and approved the final version.

Piero Sismondi: scientific responsible, manuscript preparation, manuscript supervision.

Marta D’Alonzo: manuscript preparation.

Valentina Elisabetta Bounous: manuscript supervision.

Elisabetta Robba: manuscript preparation.

Nicoletta Biglia: manuscript supervision.

Conflict of interest

P. Sismondi and N. Biglia had a financial relationship (member of advisory boards and/or consultant) with Gedeon Richter, Italfamarco and Shionogi Ltd. The other authors declare that they have no conflict of interest.

Funding

The authors have received no funding for this article.

Provenance and peer review

Commissioned: externally peer reviewed.

References