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Review

Prophylactic mastectomy; evolving perspectives

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Abstract

It is not at all uncommon for surgeons dealing with breast disease to be confronted with the issue of prophylactic mastectomy. Recent advances in understanding the genetic basis of susceptibility to breast cancer and a better identification of the histological factors affecting a woman's lifetime risk of developing breast cancer have contributed to placing prophylactic mastectomy in a proper clinical perspective. Existing data suggest that prophylactic total mastectomy significantly reduces, but does not totally eliminate, the risk of subsequent development of cancer. However, the benefit of prophylactic mastectomy over alternative strategies (surveillance and chemoprevention) remains to be proven. Currently, prophylactic mastectomy may be considered in a few, carefully selected patients. The decision to perform a prophylactic mastectomy should be a multidisciplinary one. Detailed patient' counselling is very important; the patient should understand the limitations of prophylactic mastectomy and the need for post-operative follow-up. Furthermore, she should be well informed about the alternative strategies.

Keywords: Hereditary breast cancer; Familial breast cancer; Total mastectomy; Subcutaneous mastectomy; Surveillance; Chemoprevention; Breast cancer; Surgical prophylaxis

1. Introduction

Clinical breast cancer research has focused on effective methods to detect breast cancer in its earliest stages and standardised treatments to cure the disease after diagnosis. In spite of advances in these areas, almost 175 000 new cases will be diagnosed this year in the USA and approximately one quarter of these patients will die of the disease [1]. Recognition of the limitations of current approaches to breast cancer diagnosis and treatment has resulted in a new focus on breast cancer prevention, including prophylactic mastectomy [2]. The rationale for prophylactic mastectomy is the surgical prevention of this potentially lethal disease in women who are at a substantial risk of developing breast cancer.

The role of surgical prophylaxis has been limited to a few instances, such as colectomy for familial polyposis syndrome. As a measure for prophylaxis against breast cancer, mastectomy remains a highly controversial procedure. As treatment for breast cancer became more conservative during the last two decades, the rationale for an amputative procedure in the name of 'prophylaxis' has been increasingly questioned. Reasons for this may be that the intervention is substantial and its impact on the natural history of the development of disease in the target organ is ill defined. Furthermore, its benefit over surveillance or chemoprevention has not been demonstrated. The controversy over prophylactic mastectomy is highlighted by a recent consensus statement from the *Journal of the American Medical Association*, which stated: "No recommendation is made for or against prophylactic mastectomy; this is an option, but evidence of benefit is lacking and case reports have documented the occurrence of cancer following prophylactic surgery" [3]. This article will critically review the available data on prophylactic mastectomy. Moreover, since patient selection is a critical (and probably the most difficult) issue in the use of prophylactic mastectomy, we will review existing data about the estimation of breast cancer risk and discuss alternative strategies in the management of these women.

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2. Estimation of breast cancer risk

The aetiology of breast cancer appears to be multifactorial. Both endogenous and exogenous factors are known to be involved in breast carcinogenesis and to increase breast cancer risk. The controversy over the merit and application of prophylactic removal of the breast has become heightened with further understanding of the biology of breast cancer, human genetics and the risk of cancer in benign breast disease.

2.1. Familial/hereditary breast cancer

A distinction exists between familial breast cancer, referring to one or more first- or second-degree relatives, and hereditary cancer [4]. Hereditary cancer is a subset of familial breast cancer in which the incidence of breast cancer is related to an autosomal dominant highly penetrant cancer susceptibility such as the hereditary breast–ovarian cancer syndrome.

Family history is probably the most widely recognised risk factor for breast cancer. Most women with a family history of breast cancer do not have the genetically transmitted form of the disease and, therefore, their increase in risk is much less than that seen in women with hereditary breast cancer. The cumulative probability that a 30-year-old woman with a mother or sister with breast cancer will develop breast cancer by the age of 70 years is reported to be between 7 and 18% [5,6]. Whilst this risk increases as the number of relatives with breast cancer increases, the probability of cancer development if both a mother and sister have bilateral breast cancer has been reported to be only 25% [6]. The cumulative risk of breast cancer development in women with a family history of breast cancer rarely exceeds 30% [7].

Approximately 5–10% of breast cancers are thought to be due to a specific inherited mutation that confers an extremely high risk of breast cancer development [8]. According to the American Society of Clinical Oncology, factors that should increase the clinician's index of suspicion that a woman is at risk for genetically transmitted breast cancer include: (a) a family with >2 breast cancer cases and one or more cases of ovarian cancer diagnosed at any age; (b) a family with >3 breast cancer cases diagnosed before 50 years of age; and (c) sister pairs with two of the following cancers diagnosed before age 50 years: two breast cancers, two ovarian cancers, or a breast and ovarian cancer [9]. Although not all women with these factors will have genetically transmitted disease, a referral for genetic counselling will allow the construction of a detailed pedigree to estimate both breast cancer risk and competing causes of death due to increased risk of the development of other types of cancer. Currently, the genetic heterogeneity of familial breast cancer is well recognised. Several specific gene loci involved in hereditary breast carcinogenesis have been identified (such as *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *ataxia-telangiectasia* gene, etc.). However, the majority of hereditary breast cancer can be attributed to the high penetrance genes *BRCA1* and *BRCA2*. With the recent discovery and cloning of *BRCA1* and *BRCA2* enthusiasm as well as concern have been generated regarding their clinical significance. Because identification of *BRCA1* and *BRCA2* is so recent, knowledge about how to translate this powerful genetic knowledge into clinical practice without harming the patient is limited and much more remains to be understood regarding the precise role of these genes in breast cancer. Amongst women who carry germline mutations in these genes, the cumulative risk of breast cancer is estimated to range from 40–85%, and for ovarian cancer from 5–60%, depending on the population from which the data are derived [8,10–12]. The incomplete penetrance of other cancer predisposition genes (CPG) and the presence of modifying genes introduce uncertainty as to whether gene carriers will develop the disease [13]. Moreover, although a family may be likely to carry a CPG as determined by the family structure, the gene may not yet have been located. Estimates of penetrance are therefore based upon epidemiological studies of small numbers of families with the same structure. All these estimates, therefore, have some uncertainty, and the slightly different figures between studies, which can be quoted either in one consultation or by different clinicians, can make patients feel insecure (Table 1) [9].

2.2. Benign breast diseases

The terms 'fibrocystic breast disease' or 'fibrocystic changes or conditions' are not very descriptive and fairly meaningless without a detailed description of the component histological elements [14]. Breast cancer risk can be assessed only when 'fibrocystic disease' is stratified according to its associated histological features. There is agreement that non-proliferative lesions carry

Table 1
Basic elements of informed consent for germline DNA testing

1.	Information on the specific test being performed
2.	Implications of a positive and negative result
3.	Possibility that the test will not be informative
4.	Options for risk estimation without genetic testing
5.	Risk of passing a mutation to children
6.	Technical accuracy of the test
7.	Risks of psychological distress
8.	Risks of insurance or employer discrimination
9.	Confidentiality issues
10.	Options and limitations of medical surveillance and screening following testing

Source: American Society of Clinical Oncology [9] (modified, reproduced with permission).

no increased risk of developing into invasive cancer, in direct contrast to earlier views that a breast biopsy for any reason was associated with an increased risk. This is particularly important, since, as more women undergo breast biopsies for asymptomatic abnormalities found on mammograms, there is the potential of creating a large pool of 'high-risk' women. In contrast, women whose breast tissue is characterised by epithelial proliferative changes are at an increased risk, particularly if these changes are associated with atypia [7,14,15]. Atypical hyperplasia, whether lobular or ductal, is associated with a 4- to 5-fold increase in breast cancer risk; women having atypical breast hyperplasia and a first-degree relative with breast cancer have an 11-fold increase in risk over those without proliferative atypical changes [15]. Proliferative lesions without atypia (moderate or florid hyperplasia, papilloma with fibrovascular core) are associated with a modest increase in risk, approximating 1.5- to 2-fold [7,13–15]. It should be emphasised that atypical hyperplasia is uncommon when strict diagnostic criteria are used. Indeed, although non-proliferative lesions account for 70% of breast biopsies carried out for palpable masses, atypical hyperplasia is found in less than 5% of biopsies carried out for clinical abnormalities [15].

2.3. *Lobular/ductal carcinoma* in situ *(LCIS/DCIS)*

Premalignant lesions, such as LCIS and DCIS, have been shown to be associated with an increased risk of subsequent invasive cancer [16–19]. Current data suggest that LCIS is a risk factor rather than the anatomical precursor of invasive carcinoma [16–18] and for this reason mastectomies performed for LCIS should be considered prophylactic rather than therapeutic. Estimates of the relative risk of developing invasive breast cancer in patients with LCIS range from 6.9 to 12 [16–18]. Of note, the incidence of multicentricity is high and invasive cancer can develop in either breast [18,20]. Furthermore, Rosen and colleagues reported an incidence of 4% of invasive carcinoma in mastectomy specimens from patients with LCIS [21].

Whilst LCIS is considered as a 'marker' for the development of invasive breast cancer, DCIS is more likely to be a 'precursor' of the disease and establish a higher risk of invasive disease for the same but not for the opposite breast [22]. Currently, the controversial issues in the treatment of DCIS have for the most part abated. There is general agreement that in most patients with non-multicentric DCIS, lumpectomy with breast irradiation is a treatment as effective as mastectomy [22–24]. Thus, prophylactic contralateral mastectomy is difficult to justify for women with low risk DCIS and no additional risk factors [25].

2.4. *Prior history of breast cancer*

The patient with a prior history of breast cancer is at increased risk for cancer developing in the contralateral breast. The risk has been estimated to be approximately 1% per year of survival, with a cumulative lifetime risk increasing to five times beyond that of the general population [26–28]. Not all patients with previous breast cancer are at equal risk for cancer developing in the contralateral breast. Factors increasing the risk of developing contralateral breast cancer include hereditary [29,30] and familial [31,32] breast cancer, radiation exposure at a young age [33], LCIS [34], lobular invasive carcinoma [35], proliferative changes in the remaining breast and especially when associated with atypia and multicentric cancer [34,35]. Young age at primary breast cancer diagnosis may be associated with an increased susceptibility for bilateral breast cancer, probably because of the increased likelihood of living long enough to develop a metachronous breast cancer [36]. Furthermore, development of breast cancer at a young age may be indicative of an underlying predisposition of breast parenchyma to malignant transformation and this may explain the development of a metachronous contralateral breast cancer.

2.5. *Occult breast cancer*

Occult breast cancer is defined as clinically or mammographically undetected, but histologically proven invasive and/or non-invasive cancer. Occult synchronous cancers, mostly *in situ* lesions, are found in as many as 50% of contralateral mastectomy specimens removed prophylactically from patients with primary breast cancer [35,37–39]. However, when LCIS and DCIS are excluded from these studies, the incidence of invasive contralateral breast cancer was reduced to 0–10% [40,41]. In accordance with these findings, autopsy reports have found the incidence of asymptomatic contralateral breast cancer, again mostly *in situ* lesions, to be 21–68% amongst women with a history of breast cancer [42,43]. However, these data are difficult to interpret because the selection of patients and the sampling of specimens were not uniform; moreover, mammographic information was lacking or not considered. It is possible that many of the occult carcinomas described in some older series, would be detected today with the use of dedicated high-quality mammographic equipment and localisation of non-palpable lesions.

3. Technical considerations

Two different procedures have been used to achieve surgical prophylaxis against breast cancer, subcutaneous

and total mastectomy, usually with breast reconstruction. The selection of the surgical procedure should be based mainly on the truly prophylactic nature of either operation, and secondarily on the cosmetic results.

Total mastectomy removes the mammary gland mass with the nipple/areola complex and a variable amount of overlying skin. An ellipse of skin including the nipple/areola complex is removed to allow excision of the breast tissue. This incision provides equal surgical access to all parts of the breast, including the axillary tail of Spence, and can easily be covered by any sort of clothing that the patient wishes to wear. Moreover, it does not diminish a subsequent satisfactory cosmetic result. In order to excise as much breast parenchyma as possible and to offer the best oncological protection, the skin flaps must be made thin (no thicker than those resulting from mastectomies for carcinoma) [44]; some authors have even proposed the *en bloc* excision of the pectoralis fascia [45], whilst others suggested frozen biopsy of the periphery of the resection, and especially of the axillary tail and of the lower skin flap, to determine that all the breast tissue has been removed [44,46]. Breast reconstruction can be performed either primarily or secondarily. Immediate reconstruction is preferable, if possible, since it eliminates the need for a second operation and has obvious psychological advantages. However, this depends on the indication for prophylactic mastectomy. Women undergoing prophylactic mastectomy are excellent candidates for immediate breast reconstruction because a large part of the skin of the breast can usually be preserved and postoperative chemotherapy and radiation therapy are only considered if occult invasive carcinoma is identified. Similarly, for women with breast cancer stage 0, I, or II undergoing contralateral prophylactic mastectomy, immediate reconstruction is an attractive and reasonable option. In contrast, for women with stage III disease undergoing contralateral prophylactic total mastectomy, reconstruction is typically delayed until after all multimodality therapy is complete [47]. In patients who have adequate skin and subcutaneous tissue following prophylactic mastectomy, a subpectoral prosthesis is a good reconstructive option [48]. The reconstruction problems resulting from thin skin flaps are largely overcome by subcutaneous placement of the prosthesis (silicone implants). Submuscular placement of the prosthesis not only overcomes the reconstruction problems resulting from thin skin flaps, but also facilitates palpation of any remaining breast tissue, which allows for early detection of any problem in the future. However, for women with deficient local skin and soft tissue on the anterior chest wall, a transverse rectus abdominis myocutaneous (TRAM) flap is an alternative technique. A new nipple/areola complex can be reconstructed if desired some 6–12 weeks after the initial reconstruction to allow the breast to settle and assume its final shape [48].

Subcutaneous mastectomy removes as much as possible of the breast tissue, but the overlying skin and the nipple/areola complex are preserved [49]. Therefore, subcutanous mastectomy is different from total mastectomy, in which both the nipple/areola complex and a varying amount of overlying skin are removed. Subcutaneous mastectomy is usually performed through an inframammary incision [49]. Access to all of the breast tissue, and particularly the axillary tail, may be difficult through this incision. Moreover, during subcutaneous mastectomy, breast tissue must be left behind under the nipple and the areola to prevent devascularisation of these structures. Advocates of subcutaneous mastectomy argue that the cosmetic results achieved with this procedure are superior to total mastectomy. However, the appearance of the nipple following subcutaneous mastectomy is often distorted without the underlying breast tissue, resulting in poor cosmetic outcome. Moreover, advances in reconstructive surgery and the use of skin-sparing mastectomy incisions (radial incision toward the axilla, encircling the nipple/areola complex, which is removed together with the breast parenchyma) have eliminated many of these differences and, therefore, preservation of the nipple/areola complex appears to be of questionable cosmetic benefit.

A careful histological examination is required following prophylactic mastectomy (either total or subcutaneous) to rule out the presence of occult invasive cancer.

When performing prophylactic mastectomy, the surgeon should take care to ensure that the resection of breast parenchyma is as complete as possible. The Achilles heel of prophylactic mastectomy is the difficulty in achieving a total glandular extirpation of the breast parenchyma. Breast tissue is known to extend superiorly to the clavicle, medially past the midline of the sternum, inferiorly below the costal margin into the rectus abdominal fascia, along Cooper's ligament up to the dermis of the skin and on the pectoralis muscle deep to the fascia, laterally into the axilla as the axillary tail of Spence and sometimes past the border of the latissimus dorsi [50,51]. No form of mastectomy can completely eliminate all breast tissue. The amount of residual tissue varies up to 25% of the breast after subcutaneous mastectomy to microscopic foci at the resection margins after modified radical mastectomy [44]. Even after radical mastectomy, histological studies have demonstrated the presence of residual breast tissue across the thoracic midline and onto the abdominal wall [25].

Whilst prophylactic mastectomy, performed not only by surgical oncologists but also by plastic surgeons, is not primarily a cosmetic operation, the contour and

consistency of the reconstructed breast are of great importance. However, to improve the cosmetic result and to minimise the complications, there has been a tendency to leave thicker skin flaps, especially in the subareolar lesion [47]. Preservation of the nipple/areola complex and thicker skin flaps (needed to preserve circulation to the skin by protecting the subdermal plexus), whilst facilitating a more aesthetic reconstruction, also leaves a substantial amount of breast tissue behind [52]. Indeed, it should be emphasised that following subcutaneous mastectomy a significant amount (up to 25%) of breast tissue remains, mainly in the nipple/areola complex, in the axillary tail of the breast, on the skin flaps (particularly the inferior), and the infra-clavicular area [44,52]. This reduces the prophylactic effect of the procedure since a significant amount of breast tissue remains in place in a high risk woman. In contrast, total mastectomy may remove 95% or even higher of the breast parenchyma [44,46]. It should be noted that, in today's environment of reconstructive operations, there are many possibilities of excellent cosmetic appearance following total mastectomy [48]. For these reasons, the appropriate procedure for surgical prophylaxis from breast cancer should be total mastectomy [46,53–57]. During total mastectomy, every attempt should be made to achieve resection of as much as possible of the breast parenchyma. Breast tissue may be in areas either not suspected or not realised previously [44]. It is not easy to identify the edge of the breast tissue grossly during surgery, especially in the axillary tail. To ensure 'complete' breast tissue removal, the boundaries of dissection should be carefully identified at surgery. These borders are the clavicle superiorly, the superior border of the rectus abdominis inferiorly, the sternum medially, and the anterior border of the latissimus dorsi laterally. Posteriorly, excision of the fascia of the pectoralis major aids in breast removal [7]. Laterally, the excision should extend into the axilla through the clavico-pectoral fascia, excising if needed some of the lower axillary lymph nodes with the tail of Spence [44]. However, since axillary node dissection is not a part of prophylactic mastectomy, damage to any of the axillary structures (for example, the intercostobrachial nerve) is not justified. Thin skin flaps similar to those used for a therapeutic mastectomy should be employed in an effort to ensure that the maximum amount of breast tissue is removed. The thickness of the skin flaps will vary with the amount of subcutaneous fat present and if there are questions regarding the adequacy of the removal of all the breast tissue, frozen sections of the area in question may be used [44]. To offer a lesser, inadequate and non-prophylactic operation (such as subcutaneous mastectomy) where there is a need for true surgical prophylaxis is not desirable. For these reasons some authors have even proposed that subcutaneous mastectomy should not be considered as 'prophylactic' [58,59].

4. Effectiveness of prophylactic mastectomy

The literature of prophylactic mastectomy is fraught with many problems. Most important, there are no prospective, controlled trials of the reduction in the risk of breast cancer associated with bilateral prophylactic mastectomy. The ideal study would be a randomised clinical trial comparing prophylactic mastectomy with surveillance or chemoprevention (alternative strategies, see below) in women of high risk. However, it is unlikely that high risk women would agree to participate in such a study, given the substantial differences in management in the two groups. Moreover, the number of patients and many years (approximately 10–20 years) for adequate accrual and follow-up required make such a study unfeasible.

The historical indications for prophylactic mastectomy have been broad, ranging from painful breasts (mastodynia) and cancerophobia to a 'strong family history' and probably included conditions that were not associated with a significantly increased risk of breast cancer. Since most of these studies were done when the ability to predict the risk of breast cancer was less precise, even the group of women who were considered to have a strong family history was heterogeneous. This group most likely included women with little if any increased risk, because both women and their physicians tend to overestimate a patient's risk of breast cancer on the basis of family history. However, the ability to predict risk on the basis of both hereditary and non-hereditary factors has improved in recent years [60–62] and now the ability to identify women at high risk on the basis of family history or genetic analysis should help to ensure that this procedure is considered for the population at highest risk. In addition to inadequately described or controversial indications, the data that are published in the literature suffer from many other methodological problems, including non-standardisation of surgical techniques, and variable and often inadequate length of follow-up. Thus, for such a controversial area, surprisingly few data are available and therefore women contemplating prophylactic mastectomy must rely on expert opinions or decision analysis studies that use assumptions of the procedure's efficacy.

A recent decision analysis by Schrag and colleagues from the Dana-Farber Cancer Institute in Boston, USA used a statistical model designed to predict the protective value of prophylactic mastectomy (and oophorectomy) on life expectancy amongst *BRCA1*/*BRCA2* mutation carriers [63]. They concluded that prophylactic mastectomy in a 30-year-old mutation carrier leads to 2.9–5.3 years of additional life expectancy. The gains in life expectancy declined with increasing age and were minimal for women greater than 60 years of age.

Grann and colleagues [64] in another decision analysis showed that for a 30-year-old *BRCA1*- or *BRCA2*-positive woman, prophylactic mastectomy improved survival by 2.8–3.4 years; oophorectomy, by 0.4–2.6 years; and mastectomy and oophorectomy, by 3.3–6 years over surveillance. They assumed a 90% reduction in risk and concluded that amongst women who test positive for a *BRCA1* or *BRCA2* gene mutation, prophylactic surgery at a young age substantially improves survival, but unless genetic risk of cancer is high, provides no benefit for quality of life.

Hartmann and coworkers from the Mayo Clinic in Rochester, MN, USA, reviewed that institution's extensive experience with prophylactic mastectomy and published recently probably the best study currently available in this area [65]. Between 1960 and 1993, 639 women with a family history of breast cancer had bilateral prophylactic mastectomies (214 at high risk and 425 at moderate risk). A control study of the sisters of the high-risk probands and the Gail biostatistical model were used to predict the number of breast cancers expected in these two groups in the absence of prophylactic mastectomy. They showed that, in this group of patients, prophylactic mastectomy was associated with a reduction in the incidence of breast cancer of at least 90%. As a result of prophylactic mastectomy, instead of the 20 deaths related to breast cancer that were expected during the period of observation there were only 2. However, none of these patients were tested for *BRCA1* or *BRCA2* mutations.

There are no data evaluating the efficacy of contralateral prophylactic mastectomy in primary breast cancer patients. Breast cancer patients have a decreased life expectancy and, thus, the results of the decision analysis of primary preventive mastectomy in *BRCA1*/*BRCA2* mutation carriers is not applicable to contralateral preventive mastectomy. There is no current evidence to support routine contralateral prophylactic mastectomy in women with primary breast cancer. However, selected patients with a risk of developing contralateral breast cancer greater than the risk of developing metastatic recurrence would potentially benefit from contralateral prophylactic mastectomy [56]. This group consists mainly of women with hereditary breast cancer diagnosed with good prognosis breast cancer at a young age, with a long life expectancy. In contrast, patients with advanced primary breast cancer and substantial risk of distant disease relapse will be less likely to benefit from preventive mastectomy.

The concept of surgical prophylaxis is challenged by the reported instances of carcinoma developing in residual breast tissue after prophylactic mastectomy [46,66,67]. However, the incidence of breast cancer after prophylactic mastectomy is low. Pennisi and Capozzi [67] accumulated data from 1500 patients treated with prophylactic subcutaneous mastectomy. They were able to follow-up 1046 (70%) of these patients for an average period of 9 years. 6 patients (0.6%) developed a primary breast cancer. Ziegler and Kroll concluded that the rate of cancer occurring in high-risk patients is 1.2% [68]. Woods reported 3 cases of breast carcinoma in residual breast tissue in over 1700 contralateral mastectomies after treatment for breast carcinoma [58]. In one series of 500 patients who underwent prophylactic mastectomy, none developed cancer during the mean follow-up period of 5 years [45]. Issues of concern with these studies include the possibility of selection bias toward the inclusion of patients with a favourable outcome (i.e. women with non-proliferative breast disease), a high rate of loss to follow-up (approximately 30%) with the remaining 70% followed for only 10 years, the inclusion of women with cancer in the surgically treated breast, the lack of definition of the underlying risks of breast cancer, and the lack of a central review of the pathological specimens.

Although it seems intuitively correct that the risk decreases in direct proportion to the amount of breast parenchyma removed, this has not been firmly established [69]; the lack of correlation is also suggested by laboratory studies [70,71]. Clearly, in high-risk patients even microscopic amounts of residual breast tissue remain at risk for cancer development. Of note, Petrakis and associates [72,73] suggested that it is possible that a reduction in the amount of remaining breast parenchyma may result in an increased risk for the development of breast cancer, due to a higher concentration of potential carcinogens in the residual breast tissue, thus providing a stronger stimulus for neoplastic transformation. However, these suggestions are based on animal studies and — since no correlation between these animal studies and humans is available — extrapolation of these results is not possible.

Despite the methodological problems of many published series, there is evidence that in carefully selected patients prophylactic mastectomy results in a significant decrease in breast cancer incidence [65]. However, the risk of subsequent breast cancer development is not totally eliminated, due to the incomplete excision of breast parenchyma. This underscores the importance of careful and long-term follow-up of these high-risk patients. After prophylactic mastectomy, patients should still practise routine breast self-examination to look for any abnormalities in or under the skin or at the periphery of the breast region, including the axilla. Patients should also have annual examinations by their physician for the rest of their lives to check for any evidence of breast cancer. When examining a breast mass or an anterior chest wall mass in a patient who had a prophylactic mastectomy the physician should not fail to include breast cancer in the differential diagnosis. It should be acknowledged that after prophylactic mastectomy, the patient's anxiety and fear of

developing breast cancer diminishes, leading her to forego regular self-examination and periodical examination by her physician [66]. Furthermore, the level of suspicion on the part of the patient as well as on the part of her physician may decrease because of a false sense of security that results from the operation. This can explain why the cancers that appear in these women are often advanced.

5. Complications and sequelae

Prophylactic mastectomy is associated with a significant morbidity [74]. Technical complications can be divided into peri-operative (or immediate) and delayed (or chronic). Overall complications occur in 10–60% of patients, mostly caused by necrosis of the skin or nipple/areola complex (if preserved, as in subcutaneous mastectomy), haematoma, or infection [75,76]. Skin necrosis alone accounts for up to 10% of major complications [76]. Skin ischaemia is more commonly observed following subcutaneous mastectomy. The area between the areola and inframammary incision is most sensitive to ischaemia. Moreover, scars from previous biopsies are sensitive to ischaemic insult and can become weak points leading to the formation of cutaneous fistulas or skin necrosis [77]. Diminished or lost sensitivity and erogenous response occurred in 10–25% of patients in some series [78]. Other problems, such as unsatisfactory cosmetic results (asymmetry, unnatural contour whilst lying supine), capsular contraction, pain, coolness of the overlying skin, inability to sleep prone, are complaints that may become worrisome and surely impact on lifestyle and perhaps even on self-imaging [74].

Prophylactic mastectomy may also be associated with severe psychological and psycho-emotional morbidity. Existing data suggest increased somatic distress, anxiety, severe depression, anger, guilt, fear, sense of loss of sexuality and femininity, self-depreciation, psycho-emotional impairment and irritability, and denial [79]. Moreover, the acceptance of the implants as part of the woman's body may be difficult [13]. It is interesting that this psychological morbidity may approximate that recorded for patients who sustained mastectomy for treatment of carcinoma [79]. Should prophylactic mastectomy be considered as an option for selected patients, the psychological issues must be more rigorously addressed. A working alliance between surgeons and mental health professionals trained in psychometrics would seem a most necessary collaboration [74]. The psychological sequelae of irreversible prophylactic surgery should not be underestimated by the clinician and must be considered before advising reluctant women to undergo mastectomy, particularly because the surgery is not an absolute guarantee of freedom from breast cancer.

6. Potential indications

Selecting a target population at high risk for developing breast cancer is the first essential step in ensuring appropriate surgical prophylaxis. It should be emphasised that there are no 'absolute' indications for prophylactic mastectomy and, therefore, an absolute recommendation cannot be made. The procedure should be considered only in carefully selected women who have a significant risk of breast cancer development. During the last three decades, the indications for prophylactic mastectomy have often changed. Appropriate indications and actual benefit to the patient are areas of continued controversy, with both advocates and detractors offering conflicting opinions, often without the support of acceptable data. However, as the accuracy of predicting the risk of breast cancer improves, prophylactic mastectomy may become a more useful option. Hereditary/familial breast cancer, specific proliferative lesions (and especially when associated with atypia), and a history of carcinoma of the breast are the commonly accepted indicants of potential risk today (see above, risk estimation).

Recent progress in understanding the genetic basis of susceptibility to breast cancer has simultaneously allowed the identification of women at increased risk using molecular methods [8]. Prophylactic mastectomy and/or oophorectomy have been proposed as methods for surgical prophylaxis in those women. The role of prophylactic mastectomy in *BRCA1*/*BRCA2* mutation carriers remains controversial. However, prophylactic mastectomy should only be done amongst these women under strict research guidelines [80]. Similarly, recommendations for prophylactic mastectomy based on a familial history remain tenuous; indeed, there is a different impact on the risk of carcinoma of the breast based on whether the relative was a first- or a second-degree relative and whether that person was pre- or postmenopausal at the time of diagnosis [15]. For example, the level of risk of a woman with a single relative with bilateral premenopausal breast cancer is less than 30% [7]. However, in the presence of a pedigree suggestive of genetically inherited breast cancer, the level of risk rises considerably and these women may be considered for prophylactic mastectomy.

The level of risk associated with atypical hyperplasia is generally too low (×4–5) to justify recommending radical prophylactic surgery for the management of these women. However, the presence of bilateral atypical hyperplasia may indicate an even higher risk for breast cancer, especially when associated with other risk factors and in these cases prophylactic mastectomy may be considered. For example, prophylactic mastectomy may be an option in the management of women with bilateral atypical hyperplasia with a first-degree relative with premenopausal breast cancer, bilateral hyperplasia

with two or more first-degree relatives with premenopausal or bilateral breast cancer and bilateral atypical hyperplasia in a premenopausal woman; women with bilateral multifocal DCIS, unilateral DCIS or LCIS with contralateral atypical hyperplasia may also be considered as potential candidates for prophylactic mastectomy [25].

Amongst women with a history of previous breast cancer, prophylactic mastectomy may be considered in the presence of other established risk factors, such as DCIS, LCIS, or atypical hyperplasia in the contralateral (remaining) breast or in the presence of a strong family history of breast cancer (see familial/hereditary breast cancer) [47]. Some women who are undergoing mastectomy for invasive breast cancer may choose to undergo contralateral mastectomy in order to have both breasts reconstructed simultaneously. This not only reduces the risk of subsequent cancer in the opposite breast (albeit small in the absence of other associated risk factors), but also produces a better symmetry. In this case, the indications for surgery are largely aesthetic rather than for oncological reasons. It should be emphasised that in women with a history of breast cancer a prophylactic mastectomy should be considered only when the prognosis is good for the first tumour [68]. For example, the poor prognosis of a carcinoma that has metastasised to 10 lymph nodes would in itself outweigh any potential benefit from a prophylactic contralateral mastectomy. This is also true for women with larger, high-grade, node-negative cancers. Under these circumstances, prophylactic mastectomy does nothing to reduce the risk of breast cancer death and is best avoided. For the same reasons, it has been proposed that candidates would include those who have been followed up for some years to ensure disease-free survival from the initial breast cancer [81].

Prophylactic mastectomy may also be considered in women with fibronodular, dense breasts that are mammographically and/or clinically difficult to evaluate [82]. However, breast nodularity, and in many cases density, decrease when a woman becomes postmenopausal and the glandular elements of the breast atrophy, making examination easier over time. In women with multiple previous biopsies, resulting again in difficulties performing or interpreting diagnostic breast examinations, prophylactic mastectomy may facilitate subsequent examination and results in a better cosmetic appearance [83]. However, this is highly controversial. The combination of multiple risk factors and cancerophobia in a woman who is difficult to examine is a more compelling argument for considering prophylactic mastectomy [74]. Obviously, prophylactic mastectomy is contraindicated when the patient's life expectancy is significantly reduced due to the presence of another pathology.

In the discussion about indications of prophylactic mastectomy, it is important to recognise the impact of different cancer risks on all the outcomes. For example, in a *BRCA1* mutation carrier, where the risk of having breast and ovarian cancer by age 70 years is 85% and 50–65%, prophylactic surgery will not only increase her likelihood of survival, but also improve her quality of life (63–65). Indeed, living with cancer may have serious physical, emotional and economic effects that treatment may alleviate or cure and that surgical prophylaxis may prevent. In contrast, women with less risk may only derive a marginal improvement in survival and an adverse impact on quality of life because of possible long-term surgical morbidity, including adverse psychological sequelae.

Finally, when considering such radical preventive surgery, it is important to acknowledge that approximately 70–80% of women with invasive breast cancer are candidates for conservative surgery [84,85], making prevention more radical than the treatment of established disease. Of note, the role of conservative surgery for the management of breast cancer in high-risk patients remains to be defined. Concerns about this type of surgery relate to the fact that the remaining breast parenchyma continues to be at high risk; moreover, sensitivity to breast irradiation, which is a part of breast conservation therapy, may be higher in this group of patients [86]. Today, it appears that this procedure may have a role in the management of a minority of carefully selected women at high risk, until other effective preventive strategies, including gene therapy after accurate identification of genetic mutations, are thoroughly understood and firmly established in clinical practice.

7. Patient counselling

Breast surgeons will be faced with an increasing number of women, many of whom will be mutation carriers in specific genes predisposing to breast cancer. Most women who are at an increased risk for breast cancer will choose to be followed closely and are reluctant to undergo prophylactic mastectomy. However, some will want to resort to the desperate and drastic measure of prophylactic mastectomy, believing that this will save their lives. These women tend to be young, highly educated and well informed, and usually they have a personal experience with breast cancer in their family and also have undergone genetic testing and counselling. These consultations are as difficult for the doctor as for the patient, since no consensus about an optimal preventive approach exists. Though options such as prophylactic mastectomy or chemoprevention using tamoxifen (see below) will probably reduce the incidence of breast cancer, none will totally obliterate the risk. Intensive surveillance is another option, but without proof of benefit [80].

Many factors contribute to a high risk woman's choice of course of action: her objective risk of breast

cancer; clinical features, such as the consistency of breast parenchyma and the resultant ease of examination; breast density on mammography; personal characteristics, including her experience with cancer within her family; her role and responsibilities in her own family; her values; her experiences with the medical systems; and her subjective assessment of risk. Before a high risk woman undergoes prophylactic mastectomy, efforts must be made to correct any overestimates of risk and to allay excessive anxiety; the significant reduction of risk of breast cancer and of death from breast cancer must be weighed against other factors, including the need for breast reconstruction (usually at the time of prophylactic mastectomy, but occasionally as a separate delayed procedure), the irreversibility of the decision, the realisation that breast cancer would not have developed in all the women who undergo the procedure, and of course the morbidity of the procedure, including the effect of surgery on a woman's body image and sexuality.

It is of crucial importance that a woman who is considering prophylactic mastectomy understands the issues concerning prophylactic mastectomy and especially that this procedure will substantially reduce, but not totally eliminate the risk of subsequent breast cancer development. Therefore, the need and importance of a life-long, careful postoperative follow-up, including periodical self examination and routine physical examination, supplemented with periodical mammographic examinations, should be emphasised.

Prophylactic mastectomy is not an emergency procedure. The patient must be unhurried in her decision making and should be encouraged to take her time to consider a decision of this magnitude [47]. A 6-month period of reflection is necessary before proceeding with the operation [87]. Multiple visits and consultations with patient and spouse allow the physician to understand the potential impact of this procedure on the patient's self-image, marital relationship and other potentially important issues. A consultation with a psychologist should be proposed prior to surgery, because of the psychological problems liable to ensue. Moreover, a plastic surgeon with experience in all forms of breast reconstruction should be consulted; the woman must have the opportunity for an immediate breast reconstruction. This is especially important, since most women considering prophylactic mastectomy are relatively young, and the cosmetic result is a significant consideration. These considerations emphasise the importance of a multidisciplinary approach [87].

8. Alternative strategies

Recommending mastectomy for cancer prevention represents a paradox in the era of breast conservation therapy, which preserves a breast (albeit irradiated) with prior cancer. Currently, there are no data to suggest that surgical prophylaxis is superior to the alternative options of surveillance and/or chemoprevention.

8.1. Surveillance

Since breast cancer mortality in women with occult malignancy is small, periodic surveillance is an acceptable alternative [80,88]. Especially for *BRCA1*/*BRCA2* mutation carriers, the recommended surveillance include breast self-examination (monthly, beginning at age 20–25 years), clinical examination (annually or semi-annually, beginning at age 25–35 years), mammography (annually, beginning at age 25–35 years) and/or breast ultrasonography (annually, beginning at age 25 years) [3]. In selecting the breast imaging modality for the surveillance of those patients, the surgeon should acknowledge the relatively limited sensitivity of screening mammography amongst very young women (due to increased density of breast parenchyma) and the potentially increased risk of breast cancer from repeated radiation exposure when periodic mammography is initiated at an early age [89]. This risk may be even higher amongst individuals with some inherited cancer predisposition; for example, mutation carriers of the *ataxia telangiectasia* gene are known to demonstrate increased radiosensitivity [90]. Because of these concerns, annual breast ultrasonography may be a valuable alternative. Since carriers of *BRCA1*/*BRCA2* also have a predisposition for the development of other cancers (including ovary, colon, and — in male carriers — prostate cancer), targeted screening for these tumours should also be considered [3].

8.2. Chemoprevention

Potential primary prevention medications, such as tamoxifen [91] and raloxifene [92], have been found to reduce breast cancer risk. For women who have already had one primary breast cancer, the risk of a second primary in the contralateral breast has been shown to be reduced by as much as 40% with the use of adjuvant tamoxifen [93]. The NSABP P-1 project compared prophylactic tamoxifen with placebo and found that tamoxifen reduced the risk of invasive cancer by 49% during a median follow-up of 55 months [94]. Conversely, recent interim reports of two European trials showed that tamoxifen prophylaxis did not reduce the incidence of breast cancer significantly [95,96]. Possible explanations for those conflicting data include the use of different numbers of patients, differences in the age and risk levels of the study participants, differences in the lengths of follow-up, and the allowance of the use of hormone-replacement therapy in the European studies (used by 41% of women in the British trial [95] and 14%

in the Italian study [96]). The larger number of patients in the NSABP P-1 trial and its prohibition of hormone-replacement therapy add to the strength of its findings. However, unanswered questions about tamoxifen as a chemopreventive agent include the durability of its effect, its effect on *BRCA1*/*BRCA2* mutation carriers, and its effect on the risk of death. Of note, in a recent study the risk of invasive breast cancer was decreased by 76% during 3 years of treatment with raloxifene amongst postmenopausal women with osteoporosis [97]. Interestingly, in this study the use of raloxifene has not been associated with an increased risk of uterine cancer.

References

1. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics. *CA Cancer J Clin* 1999, **49**, 8–31.
2. Jordan VG, Morrow M. An appraisal of strategies to reduce the incidence of breast cancer. *Stem Cells* 1993, **11**, 252–262.
3. Burke W, Daly M, Garber J, *et al*. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. *BRCA1* and *BRCA2*. *J Am Med Assoc* 1997, **277**, 997–1003.
4. Marcus JN, Watson P, Page DL, Lynch HT. Pathology and heredity of breast cancer in younger women. *Monogr Natl Cancer Inst* 1994, **16**, 23–34.
5. Henderson IC. What can a woman do about her risk of dying from breast cancer? *Curr Probl Cancer* 1990, **14**, 161–230.
6. Anderson DE, Badzioch MD. Risk of familial breast cancer. *Cancer* 1985, **56**, 383–387.
7. Bilimoria MM, Morrow M. The woman at increased risk for breast cancer: evaluation and management strategies. *CA Cancer J Clin* 1995, **45**, 263–278.
8. Bowcock AM. Breast cancer genes. *Breast J* 1997, **3**(Suppl.), 1–6.
9. Statement of the American Society of Clinical Oncology. Genetic testing for cancer susceptibility. *J Clin Oncol* 1996, **14**, 1730–1736.
10. Easton DF, Bishop DT, Ford D, *et al*. Breast and ovarian cancer incidence in *BRCA1* mutation carriers. *Am J Hum Genet* 1995, **56**, 267–271.
11. Struewing JP, Hartge P, Wacholder S, *et al*. The risk of cancer associated with specific mutations of *BRCA1* and *BRCA2* among Ashkenazi Jews. *N Engl J Med* 1997, **336**, 1401–1408.
12. Whittemore AS, Gong G, Itnyre J. Prevalence and contribution of *BRCA1* mutations in breast cancer and ovarian cancer. *Am J Hum Genet* 1997, **60**, 496–504.
13. Eeles R, Cole T, Taylor R, *et al*. Prophylactic mastectomy for genetic predisposition to breast cancer: the proband's story. *Clin Oncol* 1996, **8**, 222–225.
14. Hutter RVP, Albores-Saavedra J, Anderson E, *et al*. Is "fibrocystic disease" of the breast pre-cancerous? *Arch Pathol Lab Med* 1986, **110**, 171–173.
15. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 1985, **312**, 146–151.
16. Page DL, Kidd Jr TE, DuPont WD, *et al*. Lobular neoplasia of the breast: higher risk for subsequent invasive cancer predicted by more extensive disease. *Hum Pathol* 1991, **22**, 1232–1239.
17. Salvadori B, Bartoli C, Zurrida S, *et al*. Risk of invasive cancer in women with lobular carcinoma *in situ* of the breast. *Eur J Cancer* 1991, **27A**, 35–37.
18. Ottesen GL, Graversen HP, Blihert-Toft M, *et al*. Lobular carcinoma *in situ* of the female breast: The Danish Breast Cancer Cooperative Group: short term results of a prospective nationwide study. *Am J Surg Pathol* 1993, **17**, 14–21.
19. Rosai J. Borderline epithelial lesions of the breast. *Am J Surg Pathol* 1991, **15**, 209–221.
20. Haagensen CD, Lane N, Lattes R, *et al*. Lobular neoplasia (so-called lobular carcinoma *in situ*) of the breast. *Cancer* 1978, **42**, 737–769.
21. Rosen PP, Braun DW, Kinne DW. The clinical significance of pre-invasive breast carcinoma. *Cancer* 1980, **46**, 919–923.
22. Talamonti MS. Management of ductal carcinoma *in situ*. *Semin Surg Oncol* 1996, **12**, 300–313.
23. Lagios MD, Silverstein MJ. Ductal carcinoma *in situ*. A shared experience of two single institutional nonrandomized prospective studies. *Surg Oncol Clin North Am* 1997, **6**, 385–392.
24. Soran A, Vogel VG. Optimal management of primary breast cancer. *Breast J* 1999, **5**, 81–93.
25. Lopez MJ, Porter KA. The current role of prophylactic mastectomy. *Surg Clin North Am* 1996, **76**, 231–242.
26. Healey EA, Cook EF, Orav EJ, *et al*. Contralateral breast cancer: clinical characteristics and impact on prognosis. *J Clin Oncol* 1993, **11**, 1545–1552.
27. Rosen PP, Groshen S, Kinne DW, Hellman S. Contralateral breast carcinoma: an assessment of risk and prognosis in stage I (T1N0M0) and stage II (T1N1M0) patients with 20 year follow-up. *Surgery* 1989, **106**, 904–910.
28. Fracchia AA, Borgen PI. Bilateral breast cancer. *Semin Surg Oncol* 1991, **7**, 300–305.
29. Easton DF, Bishop DT, Ford D, *et al*. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. The Breast Cancer Linkage Consortium. *Am J Hum Genet* 1993, **52**, 678–701.
30. Ford D, Easton DF, Bishop DT, *et al*. Risk of cancer in *BRCA1* mutation carriers. *Lancet* 1994, **343**, 692–695.
31. Bernstein JL, Thompson WD, Risch N, Holford TR. The genetic epidemiology of second primary cancer. *Am J Epidemiol* 1992, **136**, 937–948.
32. Anderson DE, Badzioch MD. Bilaterality in familial breast cancer patients. *Cancer* 1985, **56**, 2092–2098.
33. Boice Jr JD, Harvey EB, Blettner M, *et al*. Cancer in the contralateral breast after radiotherapy for breast cancer. *N Engl J Med* 1992, **326**, 781–785.
34. Lesser ML, Rosen PP, Kinne DW. Multicentricity and bilaterality in invasive breast carcinoma. *Surgery* 1982, **91**, 234–240.
35. Lee JSY, Grant CS, Donohue JH, *et al*. Arguments against routine contralateral mastectomy or undirected biopsy for invasive lobular breast cancer. *Surgery* 1995, **118**, 640–648.
36. Robbins GF, Berg JW. Bilateral primary breast cancers. A prospective clinicopathologic study. *Cancer* 1964, **17**, 1501–1527.
37. Smith BL, Bertagnolli M, Klein BB. Evaluation of the contralateral breast. *Ann Surg* 1992, **216**, 17–21.
38. Staren ED, Robinson DA, Wit TR, *et al*. Synchronous, bilateral mastectomy. *J Surg Oncol* 1995, **59**, 75–79.
39. Ringberg A, Palmer B, Linell F, *et al*. Bilateral and multifocal breast carcinoma. *Eur J Surg Oncol* 1991, **17**, 20–29.
40. Pennisi VR, Capozzi A, Perez FM. Subcutaneous mastectomy data: an interim report. *Breast* 1979, **5**, 18–22.
41. Barton Jr FE. Breast cancer, subcutaneous mastectomy, breast reconstruction. *Select Readings Plast Surg* 1986, **3**, 1–23.
42. Nielsen M, Christensen L, Anderson J. Contralateral cancerous breast lesions in women with clinically invasive breast carcinoma. *Cancer* 1986, **57**, 897–903.
43. Lawson R. Mammary cancer: the other breast. *Can Med Assoc J* 1955, **73**, 676–677.
44. Temple WJ, Lindsay RL, Magi E, *et al*. Technical considerations for prophylactic mastectomy in patients at high risk for breast cancer. *Am J Surg* 1991, **161**, 413–415.
45. Nemecek JR, Young VL, Lopez MJ. Indications for prophylactic mastectomy. *Missouri Med* 1993, **90**, 136–140.

46. Goodnight JE, Quagliana JM, Morton DL. Failure of subcutaneous mastectomy to prevent the development of breast cancer. *J Surg Oncol* 1984, **26**, 198–201.
47. Ames FC. Prophylactic mastectomy. In Singletary ES, ed. *Breast Cancer*. New York, Springer, 1999, 149–154.
48. Hang-Fu L, Snyderman RK. State-of-the art; breast reconstruction. *Cancer* 1991, **68**, 1148–1156.
49. Jarrett JR. Prophylactic subcutaneous mastectomy and reconstruction. In Cohen M, Goldwin RM, eds. *Mastery of Plastic and Reconstructive Surgery*. Little, Brown and Company, Boston, 1994, Vol. II, 1276–1282.
50. Haagensen CD. *Diseases of the Breast*. 2nd edn. Philadelphia, WB Saunders, 1971, 16–17.
51. Davies DV, Coupland RE. *Gray's Anatomy*. London, Longmans, 1967, 1585.
52. Goldman LD, Goldwyn RM. Some anatomical considerations of subcutaneous mastectomy. *Plast Reconstr Surg* 1973, **51**, 501–505.
53. Eisen A, Weber BL. Prophylactic mastectomy — the price of fear. *N Engl J Med* 1999, **340**, 137–138.
54. Hoffman S, Pressman PI. Prophylactic mastectomy. *Mount Sinai J Med* 1982, **49**, 102–109.
55. Horton CE, Dascombe WH. Total mastectomy: indications and techniques. *Clin Plast Surg* 1988, **15**, 677–687.
56. Dawson LA, Chow E, Goss PE. Evolving perspectives in contralateral breast cancer. *Eur J Cancer* 1998, **34**, 2000–2009.
57. Humphrey LJ. Subcutaneous mastectomy is not a prophylaxis against carcinoma of the breast: opinion or knowledge? *Am J Surg* 1983, **145**, 311–312.
58. Woods JE. Prophylactic partial mastectomy. *Surgery* 1987, **101**, 120–121.
59. Snyderman RK. Prophylactic mastectomy. *Plast Reconst Surg* 1984, **73**, 704–705.
60. Couch FJ, DeShano ML, Blackwood MA, *et al*. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. *N Engl J Med* 1997, **336**, 1409–1415.
61. Berry DA, Parmiagiani G, Sanchez J, *et al*. Probability of carrying a mutation of breast–ovarian cancer gene *BRCA1* based on family history. *J Natl Cancer Inst* 1997, **89**, 227–238.
62. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer: implications for risk prediction. *Cancer* 1994, **73**, 643–651.
63. Schrag D, Kuntz KM, Garber JE, *et al*. Decision analysis — effects of prophylactic mastectomy and oophorectomy on life expectancy among women with *BRCA1* or *BRCA2* mutations. *N Engl J Med* 1997, **336**, 1465–1471.
64. Grann VR, Panageas KS, Whang W, *et al*. Decision analysis of prophylactic mastectomy and oophorectomy in *BRCA1*-positive or *BRCA2*-positive patients. *J Clin Oncol* 1998, **16**, 979–985.
65. Hartmann LC, Schaid DJ, Woods JE, *et al*. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med* 1999, **340**, 77–84.
66. Eldar S, Meguid MM, Beattu JD. Cancer of the breast after prophylactic subcutaneous mastectomy. *Am J Surg* 1984, **148**, 692–695.
67. Pennisi VR, Capozzi A. Subcutaneous mastectomy data: a final statistical analysis of 1500 patients. *Aesth Plast Surg* 1989, **13**, 15–21.
68. Ziegler LD, Kroll SS. Primary breast cancer after prophylactic mastectomy. *Am J Clin Oncol* 1991, **14**, 451–454.
69. Shone AR, Press BHJ. Subcutaneous mastectomy. *Arch Surg* 1983, **118**, 844–850.
70. Wong JH, Jackson CF, Swanson JS, *et al*. Analysis of the risk reduction of prophylactic partial mastectomy in Sprague–Dawley rats with 7,12,dimethylbenzantracene-induced breast cancer. *Surgery* 1986, **99**, 67–71.
71. Nelson H, Miller SH, Buck D, *et al*. Effectiveness of prophylactic mastectomy in the prevention of breast tumors in C3H mice. *Plast Reconst Surg* 1989, **83**, 662–669.
72. Petrakis NL. Breast secretory activity in nonlactating women, postpartum breast involution, and the epidemiology of breast cancer. *Natl Cancer Inst Monogr* 1977, **47**, 161–164.
73. Petrakis NL, Gruenke LD, Beelen TC. Nicotine in breast fluid of nonlactating women. *Science* 1978, **199**, 303–304.
74. Wapnir IL, Rabinovitz B, Greco RS. A reappraisal of prophylactic mastectomy. *Surg Gynecol Obstet* 1990, **171**, 171–184.
75. Slade LC. Subcutaneous mastectomy: acute complications and long-term follow-up. *Plast Reconstr Surg* 1984, **73**, 84–88.
76. Woods JE. Subcutaneous mastectomy. *Plast Reconstr Surg* 1984, **74**, 151–152.
77. Holzgreve W, Beller FK. Surgical complications and follow-up evaluation of 163 patients with subcutaneous mastectomy. *Aesth Plast Surg* 1987, **11**, 45–48.
78. Glaumann B. Investigation of 72 patients following subcutaneous mastectomy. *Scand J Plast Reconstr Surg* 1985, **19**, 273–281.
79. Meyer L, Ringberg A. A prospective study of psychiatric and psychosocial sequelae of bilateral subcutaneous mastectomy. *Scand J Plast Reconstr Surg* 1986, **20**, 101–107.
80. Bennett IC, Gattas M, Tean The B. The genetic basis of breast cancer and its clinical implications. *Aust N Z J Surg* 1999, **69**, 95–105.
81. Temple WJ. Surgical management of the patient at high risk for breast cancer. *Can J Surg* 1985, **28**, 256–261.
82. Society of Surgical Oncology. SSO develops position statement on prophylactic mastectomies. *SSO News* 1993, **1**, 10.
83. Scarfi A, Ordemann K, Huter J. Subcutaneous mastectomy: indications, histologic results. *Eur J Gynaecol Oncol* 1986, **7**, 130–132.
84. Sakorafas GH. *Breast Cancer, Monograph*. Athens, Lagos Medical Publications, 1999. 105
85. Sakorafas GH, Farley DR. *Conservative Surgery in Breast Cancer. An Atlas*. Athens, Lagos Medical Publications, 2000, in press.
86. Vasen HFA, Haites NE, Evans DGR, *et al*. Current policies for surveillance and management in women at risk of breast and ovarian cancer: a survey among 16 European Family Cancer Clinics. *Eur J Cancer* 1998, **34**, 1922–1926.
87. Eisinger F, Alby N, Bremond A, *et al*. Recommendations for medical management of hereditary breast and ovarian cancer: the French National Ad Hoc Committee. *Ann Oncol* 1998, **9**, 939–950.
88. Lopez MJ, Blackwell CW. Breast cancer detected by screening: the importance of long-term follow-up. *Surgery* 1989, **106**, 590–595.
89. Law J. Cancers detected and induced in mammographic screening: new screening schedules and younger women with family history. *Br J Radiol* 1997, **70**, 62–69.
90. Gatti RA, Boder E, Vinters HV, *et al*. Ataxia-telangiectasia: an interdisciplinary approach to pathogenesis. *Medicine* 1991, **70**, 99–117.
91. Powles TJ, Jones AC, Ashley SE, *et al*. The Royal Marsden Hospital pilot tamoxifen chemoprevention trial. *Breast Cancer Res Treat* 1994, **31**, 73–82.
92. Cummings S, Norton L, Eckert S, *et al*. Raloxifene reduces the risk of breast cancer and may decrease the risk of endometrial cancer in postmenopausal women: two-year findings from the Multiple Outcomes of Raloxifene Evaluation Trial. *Proc ASCO* 1998, **17**, 3 (abstract).
93. Iornander T, Rutquist LE, Cedermark B, *et al*. Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. *Lancet* 1989, **1**, 117–120.
94. Fisher B, Costantino JP, Wickerham DL, *et al*. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998, **90**, 1371–1388.
95. Powles T, Eeles R, Ashley S, *et al*. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomized chemoprevention trial. *Lancet* 1998, **352**, 98–101.

96. Veronesi U, Maisonneuve P, Costa A, *et al*. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomized trial among hysterectomized women. *Lancet* 1998, **352**, 93–97.

97. Cummings SR, Eckert S, Krueger KA, *et al*. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple outcomes of raloxifene evaluation. *J Am Med Assoc* 1999, **281**, 2189–2197.