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The curability of breast cancer: present and future

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Abstract

The clinical course of breast cancer is more of a chronic nature, as compared to other, highly curable malignancies, such as testicular cancer, acute leukemia and Hodgkin's disease. Therefore, five-year and ten-year relapse-free survival is not equivalent to cure. Patients with operable breast cancer can be cured with combined modality therapies. The probability of cure is inversely proportional to initial stage. The hazard rate of relapse is highest during the first three to five years and decreases gradually thereafter. Survival curves for operable breast cancer start to parallel the survival of the general population 15 to 25 years after diagnosis. Between a quarter to a third of patients with locally advanced and/or inflammatory breast cancer are curable with combined modality strategies and a small fraction of highly selected patients with overt metastatic breast cancer have lengthy complete remissions after chemotherapy or combined modality therapy. In recent years proof of principle was obtained for chemoprevention with selective estrogen receptor modulators in several multicenter trials. Additional studies are ongoing to determine the optimal preventive intervention.

Whether you believe you can, or whether you believe you can't, you're absolutely right.
Henry Ford

1. Introduction

Breast cancer remains the most common malignancy in women in the USA and Western Europe [1,2]. Its incidence is increasing in the rest of the world, where it is usually second in importance after cervical uterine cancer. It is calculated that approximately 800 000 to 1 million new cases of breast cancer will be diagnosed in the world this year [2].

Breast cancer represents the second most common cause of cancer mortality in women in the industrialized western world, second only to lung cancer [1,2]. Over the past decade, national statistics from the USA, the UK, Italy, Switzerland and other countries show a significant gradual decrease in breast cancer mortality; this trend has persisted for almost 10 years now [2–5]. Whether the significant reduction in breast cancer mortality is due to earlier diagnosis secondary to systematic use of screening mammography or the improvement in combined modality management of all stages of breast cancer is difficult to determine [6–9]. It is likely that both have contributed to this trend.

2. The concept of curability

Whether breast cancer is curable or not has been hotly debated for many years [10–15]. Therefore, before we review the evidence, it is critical to define our terms. Clearly, breast cancer is often an indolent disease. Therefore, arbitrary definitions of cure (such as 5-year disease-free survival) are irrelevant for all but a small minority of elderly patients with limited life expectancy [13,16–18]. Other malignancies, especially those considered to run an acute course, are more appropriately considered cured if no relapses occur 2 or 5 years following completion of curative treatment. In those malignancies, late relapses occur infrequently, so patients who reach the landmark date are very likely to be cured.

Numerous publications have demonstrated that breast cancer does not belong in this category. Long-term follow-up of untreated breast cancer clearly shows that, essentially, all patients will die of the disease [19–21]. However, it must be realised that comorbid conditions present competing causes of mortality, even for patients

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with metastatic breast cancer [22–26]. Comorbid conditions increase in frequency with age, so older patients with breast cancer have a higher probability of dying of causes different from breast cancer. On the basis of these observations, the concept of personal cure arose. A patient with breast cancer achieves a personal cure if, following completion of curative treatment she eventually dies from a different cause (e.g. cardiovascular disease, chronic obstructive lung disease, stroke, etc.) before a relapse from breast cancer can be documented. Certainly, for individual patients, this is a perfectly satisfactory definition of cure. However, from the biological and statistical perspective, this definition is still inadequate and provides insufficient support for the worth of a specific treatment.

Statistical cure has been defined on the basis of population survival figures [13,17,18]. Thus, it is considered that a group of patients with breast cancer has achieved cure in statistical terms if its survival curve becomes parallel to the survival curve of the general population. For additional precision, these comparisons are made on age-matched populations.

The mortality rate of breast cancer increases with clinical and pathological stage [27,28]. In fact, correlations of clinical characteristics with mortality after treatment defined clinical stages in the first place [29,30]. Hazard rates of mortality show that there is an initial peak of several years in hazard rates, followed by a gradual decline over subsequent years [15,17]. The initial peak is higher and narrower for more advanced stages (stages III and IV); most relapses and deaths occur within the first 3–5 years in these groups. In contrast, patients diagnosed with stages I and II evidence a lower peak that tends to occur later. Thus, the survival curves of patients with more advanced or higher-risk breast cancer start to parallel the survival curves of the general population earlier than the survival curves of the earlier breast cancers. Stated in a different way, higher-risk breast cancer groups achieve statistical cure earlier (10–15 years after diagnosis) than lower-risk groups (20–25 years after diagnosis). Because such lengthy follow-up is necessary for complete evaluation of treatment results, some have stated that breast cancer is, in essence, incurable. This argument states that, if follow-up is long enough, relapses will occur. The systematic application of combined modality therapies and mammographic screening has shown this position to be mistaken [31]. Clearly, mammographically diagnosed early breast cancer (stages 0 and I) is associated with excellent survival rates, exceeding 90% at 20 years following surgical resection alone or breast conserving therapies; as shown below, 25 years after diagnosis, the survival curves of patients with stages II, III and even IV breast cancer suggest relapse-free survival plateaux that parallel the survival curves of the general population [13].

3. Curative interventions

The efficacy of all anticancer treatments is inversely proportional to the stage of disease. Thus, patients with stage I breast cancer have higher 5-, 10-, 20- and 30-year survival rates than patients with stage II breast cancer [13]. Each group with more advanced stage has lower survival rates than the group with earlier stage at all points of follow-up. This is true whether treatment is surgery only, surgery with radiotherapy, or combined modality therapy that incorporates surgery, chemotherapy, endocrine therapy and radiotherapy [7–9,13,32]. There is extensive documentation of these statements with follow-ups of 5 and 10 years. The Early Breast Cancer Trialists Collaborative Group has developed prospective databases that now reach 15 years of follow-up; it is hoped that such prospective data collection will continue to enable us to address the issues of long-term curability with the highest levels of evidence. In addition, a few, mostly single-institution databases provide additional, long-term information.

4. The curability of early breast cancer

Perhaps the best source for this information is derived from long-term, prospective follow-up of the clinical trials of screening mammography [31]. With follow-up now exceeding 20 years, the Two County Trial reports very high survival rates, in the range of 96–98%. Similarly, patients with T1a + b N0 primary breast cancers diagnosed and followed as part of the same study had a 20-year survival that exceeded 85%. Quiet and colleagues reported for this same group of patients a 40-year disease-specific survival rate of 80% or more [33]. Clearly, in both Stage 0 and Stage I, patients die of multiple other causes, but breast cancer is a cause of death for only a minority of patients. Personal cure is achieved for the great majority, and statistical cure is accomplished after 20 years or so.

5. The curability of lymph node-positive operable breast cancer

Over the past three decades, more than 200 prospective randomised trials have been completed to determine the role and efficacy of adjuvant chemotherapy, endocrine therapy and radiotherapy [7–9]. Most patients included in such trials had lymph node-positive breast cancer. Most published trials have follow-up ranging from 5 to 10 years, with a handful providing follow-ups exceeding 20 years. The world overview of randomised trials, performed and updated every 5 years since 1985, pools individual patient data and provides answers to clinically relevant questions based on

thousands of patients. On the basis of large, individual randomised clinical trials and on the basis of the overview, we know that the effects of systemic adjuvant therapy are long term, and that these beneficial effects now exceed 15 years without any indication that the magnitude of the effects diminishes (2000 World Overview, unpublished results). This is a remarkable observation, since treatment in most adjuvant chemotherapy trials was administered for 1 year or less, and for adjuvant tamoxifen, 5 years or less. Therefore, our systemic interventions produce long-term and apparently irreversible changes in the clinical course of primary breast cancer. Since the follow-up of a very large number of patients included in these trials is now reaching or exceeding the time period when the survival of breast cancer patients starts to parallel that of the general population, it is increasingly likely that the reduction in odds of recurrence and death is equivalent to an increase in cure rate. Single-institution reports of the results of combined-modality treatment of patients with node-positive or stage III disease show that even for the highest risk category of patients (i.e. those with more than 10 positive lymph nodes) 20–40% of patients remain disease-free 15–20 years after diagnosis [13,34–37].

6. Locally advanced and inflammatory breast cancer

Other reports have documented that patients with Stage IIIB disease can be rendered disease-free with combined modality therapy and about one-third of them remain disease-free more than 20 years later [35,38–40] (Table 1). This is particularly dramatic in the case of inflammatory breast cancer, previously considered the most aggressive and lethal form of breast cancer. Before the introduction of chemotherapy into the management of this type of breast cancer, more than 90% of patients treated with surgery and/or radiotherapy developed metastases within the first 24 months, and the 5-year survival rate was consistently under 5% [41,42]. In contrast, these same patients treated with combined modality treatments that include neoadjuvant anthracycline-containing chemotherapy now routinely achieve 5-year survival rates that exceed 40%, and almost one-third of them remain relapse-free 20 years after diagnosis [38,43–46]. Since the hazard rate associated with inflammatory breast cancer shows a sharp peak within the first 2 years and a rapid reduction in risk in subsequent years, it is highly likely that the great majority of patients alive 20 years after diagnosis are cured. Another group of patients that deserves comment is that with supraclavicular lymph node involvement at presentation. In the current AJCC/UICC clinical staging system, these patients are considered to have overt distant metastases and, therefore, are considered incurable. However, our experience with this group of patients treated with combined modality therapy indicates that the great majority can be rendered free of active disease, and that about one-third of them remain progression-free (disease-free) 5 and 10 years after completion of all therapy [39] (Fig. 1). This experience would also indicate that this group of patients does not belong in the incurable category of the staging classification, and should be approached aggressively, with curative intent.

Table 1
Five-year survival rates of patients with inflammatory breast cancer according to treatment

Treatment	No. of patients	Percent alive
Surgery only	398	2
Radiotherapy	334	3
Both	142	5
Chemotherapy + local treatment(s)	708	47

7. Metastatic breast cancer

It is generally believed that metastatic breast cancer is incurable with currently available treatment modalities [47,48]. In fact, and contrary to the experience reported from metastatic colorectal cancer or soft-tissue and osteogenic sarcoma, it is generally believed that surgical resection of metastatic breast cancer is a futile exercise and does not alter the natural history of the disease. However, there are a few reports of surgical resection of pulmonary metastases followed by lengthy relapse-free periods, and anecdotal cases of successful resection of liver, soft-tissue and brain metastases have been observed [49–56]. At the M. D. Anderson Cancer Center, we have approached patients with a single metastatic lesion with combined modality therapy and curative intent since 1974 [56–59]. Our strategy includes surgical resection (which automatically provides histological confirmation of metastases), radiotherapy and systemic adjuvant chemotherapy and, when appropriate, endocrine therapy. Three consecutive, prospective clinical trials included 321 patients, including 62 historical controls (Fig. 2). While we have attempted to perform a randomised trial to assess the value of adjuvant chemotherapy in this strategy, we were unsuccessful in completing the targeted accrual. We understand that several other groups have also failed in their attempt to complete a randomised trial of adjuvant chemotherapy in this setting. We have identified a historical control group of patients with solitary metastases treated at our institution between 1967 and 1976 with surgical resection with or without radiotherapy, but without systemic treatment [56,58]. While many of the patients treated with our combined modality approach presented with chest-wall recurrence or

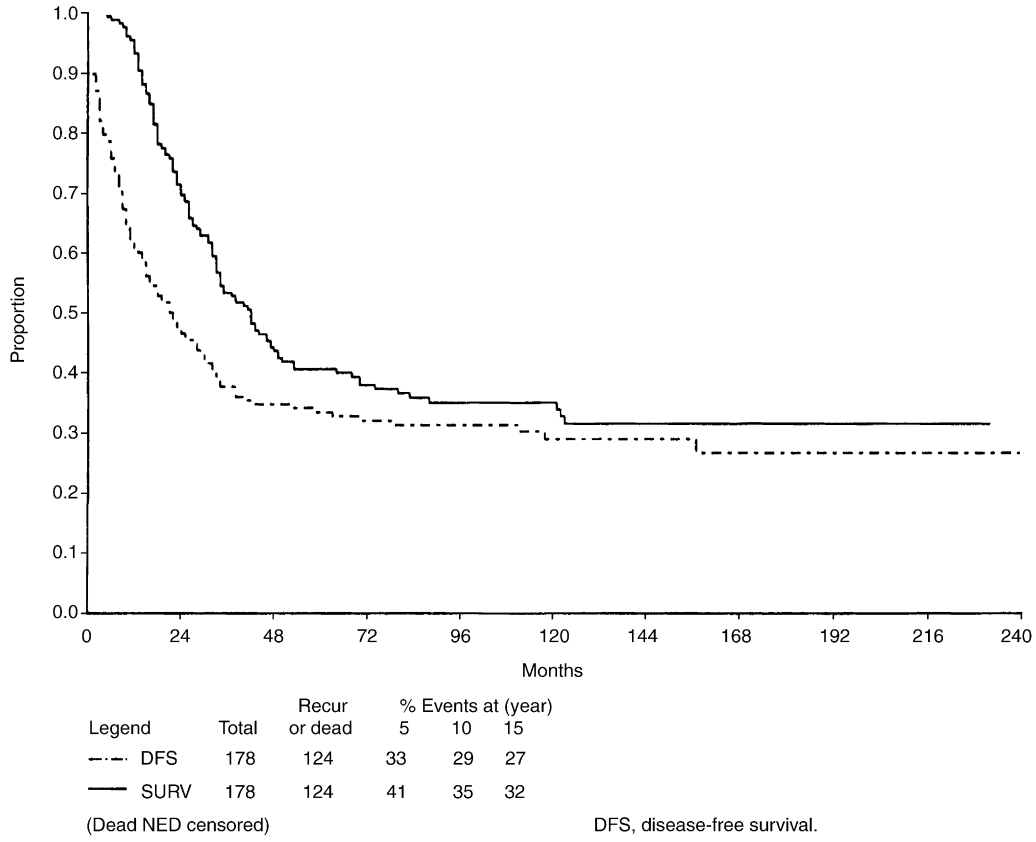

Fig. 1. Disease-free and overall survival of 178 patients with inflammatory breast cancer treated with neoadjuvant chemotherapy, radiotherapy with or without mastectomy at the University of Texas M. D. Anderson Cancer Center (from Ref. [38], reprinted with permission from BC Decker Inc.).

distant soft-tissue metastases, up to 25% had bone or visceral metastases (lungs, liver, or brain). With a median follow-up of 13 years and a maximal follow-up approaching 27 years, the 15- and 20-year relapse-free survival rates for this group of patients are 30 and 25%, respectively. There have been only two second recurrences after 15 years, suggesting that the hazard rate drops substantially after the initial decade of follow-up. In contrast, the 15- and 20-year relapse-free survival rates for the historical control patients were 3 and 3%, respectively, indicating that in the absence of systemic therapy, additional metastases or recurrences occur in practically all patients once an initial recurrence or metastasis has been detected.

A second group of patients with metastases is also relevant to the discussion of cure. Between 1974 and 1982, we treated 1581 patients with clinical evidence of metastatic breast cancer with first-line, anthracycline-containing chemotherapy (FAC, and related regimens) [60–62]. All these patients were treated in prospective clinical trials with anthracycline-based first-line chemotherapy regimens. Their pretreatment evaluation was similar across trials, and the definitions of response followed in the assessment of efficacy were also similar. Since the outcome of the various treatments used in these trials was similar in all trials, the results were pooled for an analysis of prognostic factors. Updates of this same database with median follow-up times of 15 and 20 years demonstrated that a small percentage of patients (3%) remained alive and disease-free in the absence of maintenance therapy [63] (Fig. 3). Further analysis indicated that all long-term disease-free survivors had achieved a clinical complete remission with first-line therapy. Their characteristics included younger age, excellent performance status and limited amount of metastatic disease. This latter characteristic makes this group similar to patients included in the Stage IV NED category.

So where do we draw the line in terms of curability? While quantitatively different, some patients in Stages 0, I, II, III and IV breast cancer can achieve a very long period of disease-free survival with combined modality therapy. Whether the percentage is 1 or 99%, the practical implications are the same: if there is a possibility of cure (however remote), initial treatment should have curative and not only palliative intent. In fact, whether a 20-year long disease-free survival represents a cure or not, it is a very substantial therapeutic achievement that for many patients represents 'personal' cure.

The assumption that cure of breast cancer is not feasible, except for the very early stages leads to a circular argument: patients considered 'incurable' are offered

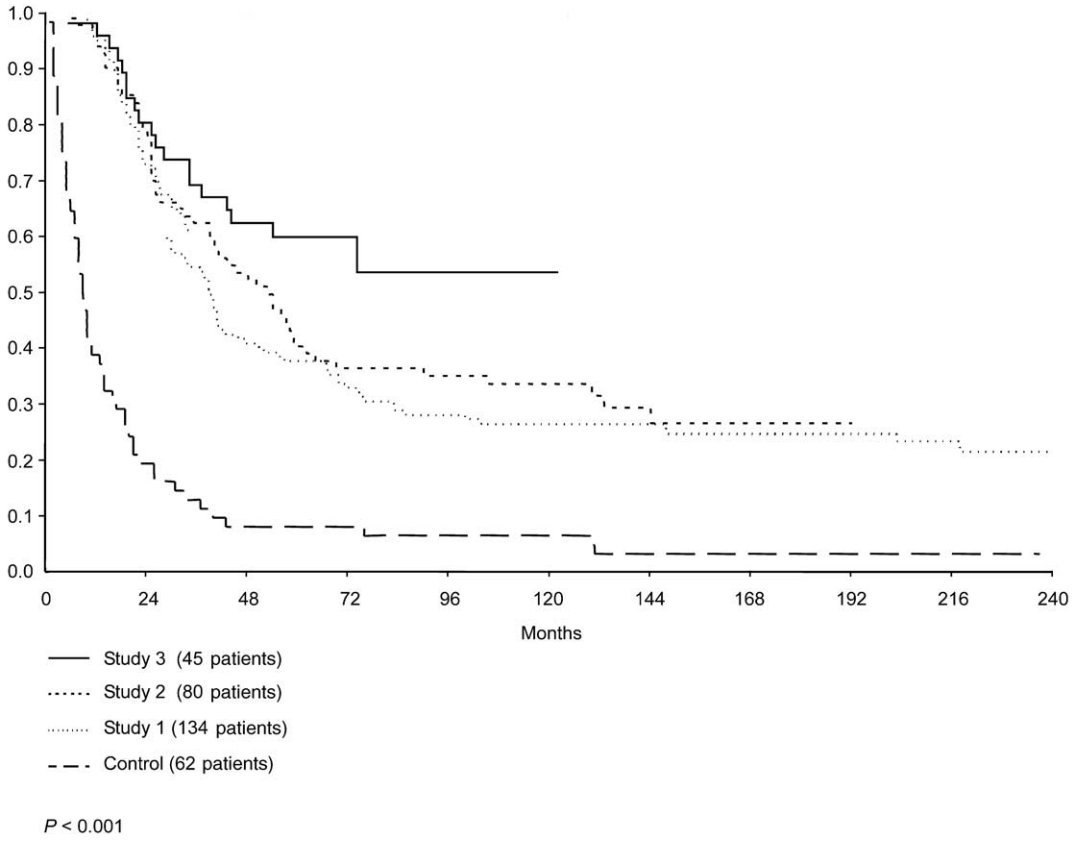

Fig. 2. Disease-free survival of patients with stage IV-NED breast cancer according to study group (from Ref. [56], reprinted with permission from Blackwells Publishing Ltd.).

only palliative treatments, thus missing any possibility to achieve a cure. While this is often justified by stating that, in the absence of cure, offering the least toxic treatment is the most ethical treatment policy, it is the wrong approach.

Over the past decade, several new and effective anticancer agents have been added to our treatment armamentarium [64–66]. Several of these (the taxanes, capecitabine, trastuzumab, the third-generation aromatase inhibitors) have been shown to prolong survival of patients with metastatic breast cancer in the context of randomised trials. These agents must be incorporated rapidly into first-line therapy of patients with high-risk primary or metastatic breast cancer. We must do similarly with the host of new agents under development today, once their efficacy is determined, and their contribution into the overall management of breast cancer is defined. Only such therapeutic attitude will provide the maximum possibility of cure for patients with breast cancer.

8. Preventive strategies

The past decade witnessed the emergence of several cancer-prevention strategies, with preliminary documentation of effectiveness in reducing risk of developing breast cancer. I will briefly review and summarise this experience, focusing mostly on reports of immediate clinical relevance. It is intuitive that the best cure is prevention, and this summary should complement the former segment about curative strategies for various stages of breast cancer.

A combination of environmental factors (e.g. exposure to carcinogens, lifestyle and hormonal factors) and genetic factors plays a role in the development of breast cancer and affects both incidence and mortality rates. Increased understanding of the mechanisms of malignant transformation, as well as the identification of potential markers of increased risk of developing breast cancer, facilitated the appearance of chemoprevention as a potentially useful early intervention. The quantification of risk of developing cancer is usually estimated from epidemiologic models, which consider a variety of risk factors and project a cumulative risk for the development of disease over a finite period of time [67–69]. Among the various models proposed, the one developed by Gail and colleagues is probably the most widely accepted [70]. Proposed in 1989 and subsequently modified, this model attempted to define the contributions of multiple risk factors combined in a multivariate logistic regression model. The variables identified were patient's age, number of first-degree

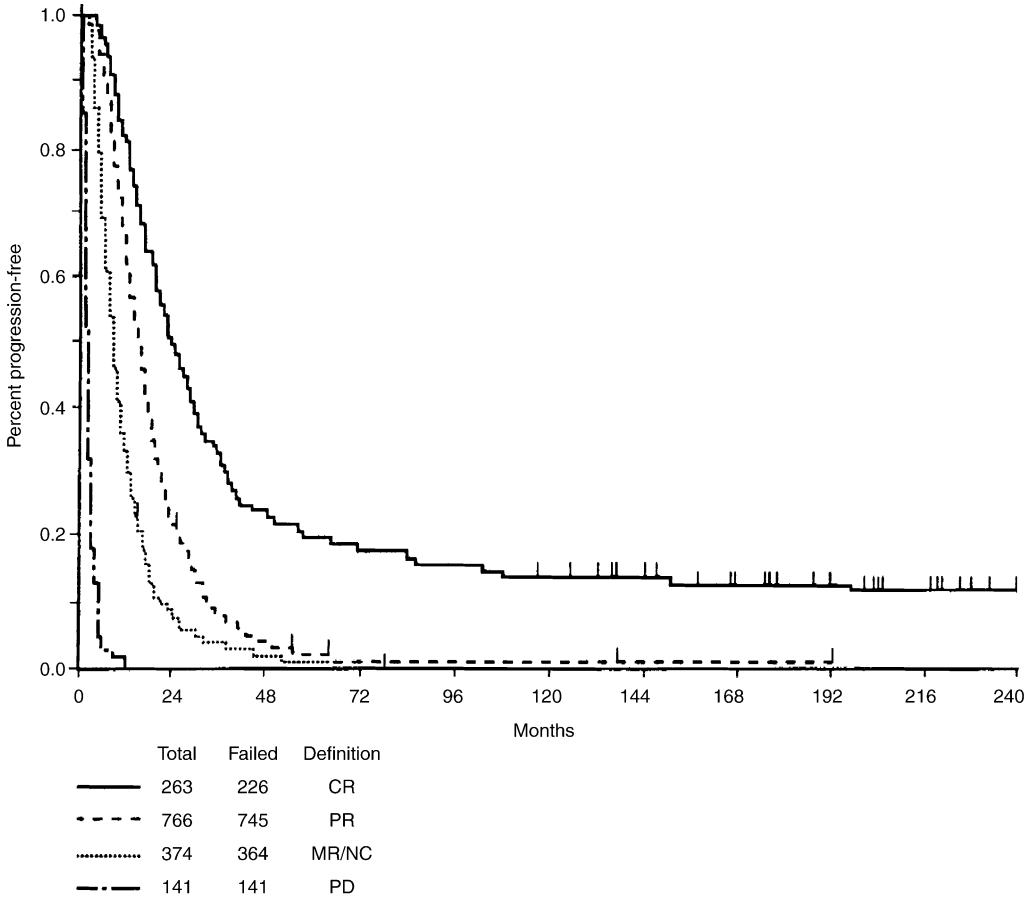

Fig. 3. Long-term follow-up of 1581 chemotherapy-naïve patients with metastatic breast cancer treated with anthracycline-containing first-line chemotherapy regimens. Progression-free survival (from Ref. [63], reprinted with permission of the American Society of Clinical Oncology).

relatives with breast cancer, nulliparity or age at first live birth, number of breast biopsies, presence or absence of atypical hyperplasia, and age at menarche. In particular, women with a strong family history of breast cancer or of breast and ovarian cancers have a lifetime risk of developing breast cancer 25% or greater. The 'Gail model' is the most widely used and validated to date, but it has several weaknesses. The model does not clearly quantify the risk for women with a hereditary predisposition (e.g. a BRCA1 or BRCA2 mutation) and, although the personal menstrual and reproductive histories are included, other factors, such as the use of hormonal replacement therapy, are not considered. It is hoped that the inclusion of other significant risk factors will allow future models to more precisely define personal risk.

Risk-reduction attempts have followed diverse strategies: chemoprevention, surgical ablation of the breast or the ovaries, and dietary and behavioural modification.

9. Chemopreventive agents for breast cancer

Chemoprevention is the inhibition or reversal of carcinogenesis before the onset of overt malignancy. This intervention employs chemical agents that have demonstrated efficacy and safety in preclinical and animal models, with the hope that these agents will be safe and effective in prospective clinical trials.

9.1. Anti-oestrogens or selective oestrogen receptor modulators (SERMs)

Tamoxifen is a non-steroidal triphenylethylene derivative that is generally classified as an anti-oestrogen with partial oestrogen-agonist activity in some tissues. Results from chemopreventive and adjuvant trials suggest that treatment with tamoxifen is associated with an increase in bone-mineral density and a decrease in serum cholesterol levels, especially in postmenopausal women [74,75]. The use of adjuvant tamoxifen following primary surgery for oestrogen-sensitive early breast cancer has been associated with prolonged disease-free survival and a 20–30% reduction in mortality rate [76]. Tamoxifen also produces a significant reduction in the incidence of second primary tumours in the contralateral breast [71–73].

An overview analysis of the major randomised trials of adjuvant tamoxifen among nearly 30 000

women with early breast cancer demonstrated a 47% reduction in the incidence of contralateral breast cancer with 5 years of adjuvant tamoxifen [76]. Tamoxifen treatment appeared to be associated with a significant increase in the incidence of endometrial cancer [76].

Since 1986, four studies explored the hypothesis that long-term tamoxifen treatment reduced the risk of developing breast cancer in women at high risk for this disease [77–82]. In aggregate, these four studies demonstrated that tamoxifen significantly reduced the risk of developing breast cancer. This effect was accompanied by an increase in the incidence of thromboembolic complications and endometrial cancer [77]. These effects were more prominent in women over the age of 50 years, especially those with an intact uterus. No survival benefit has been reported to date from these four trials [80]. The benefit/risk ratio is clearly higher for high-risk women, those who have a greater than 1.7% 5-year probability of developing breast cancer.

In the past decade, reports of significant side-effects associated with the prolonged use of tamoxifen have stimulated research directed toward the development of other selective oestrogen receptor modulators. Among the various products investigated, raloxifene has demonstrated antitumour activity and a favourable toxicity profile [83–85].

Clinical trials are underway to establish the role of *raloxifene* in preventing osteoporosis in postmenopausal women, and preliminary results from randomised clinical trials have recently become available. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial was specifically designed to reduce the risk of fractures in postmenopausal women receiving raloxifene; a markedly reduced risk of newly diagnosed breast cancer was demonstrated with raloxifene compared to placebo (0.21% versus 0.82%) [86,87]. Treatment with raloxifene was associated with a 58% reduction in the risk of developing primary breast cancer [87]. These results have stimulated the design of a second major breast cancer prevention trial, the Study of Tamoxifen And Raloxifene (STAR or P-2), comparing the toxicity, risks and benefits of raloxifene with those of tamoxifen. Women enrolled in the study are to be randomly assigned to receive either 20 mg of tamoxifen or 60 mg of raloxifene for 5 years, with follow-up planned for 2 additional years.

9.2. Retinoids

Retinoids are a family of natural and synthetic compounds structurally related to vitamin A. They modulate biological functions, such as proliferation, differentiation, and the induction of apoptosis [73,88–90]. Retinoids function via two types of nuclear receptors, the retinoid alpha-receptors (RARs) and the retinoid X receptors (RXRs), and their action is modulated by cellular retinol binding proteins (CRBP) [91]. All benign and malignant breast tissues expressed RAR α, β, γ and CRBP-1 mRNAs [92].

Preclinical data have demonstrated that carcinogen-induced mammary carcinomas are sensitive to the antiproliferative effects of retinoids [73,93,94]. Fenretinide, the first retinoid to be tested in clinical trials, is well tolerated at a daily dose of 200 mg with a 3-day monthly drug holiday [95,96].

An Italian prospective randomised trial designed to evaluate the role of fenretinide in reducing the incidence of contralateral breast cancer began in March 1987 and included 2972 women ranging in age from 30 to 70 years, with a history of T1-2, N0 breast cancer [95,96]. Preliminary data suggested that fenretinide reduced the incidence of ovarian carcinomas [96]. Though safer than other retinoids in experimental models, fenretinide produced visual (dark adaptation) and ophthalmological complaints (ocular dryness, lacrimation, conjunctivitis, and photophobia) in 20 and 8%, respectively, of women at 5 years [97].

10. Dietary interventions

Epidemiological studies showing large international differences in the incidence of breast cancer have suggested a relationship between diet and the development of cancer. The age-adjusted incidence of breast cancer varies from 22 per 100 000 individuals in Japan to 68 per 100 000 individuals in The Netherlands [98]. The ratio of breast cancer mortality in the United States to that of Japan is 3:1 for premenopausal women and 8:1 for postmenopausal women [99]. These disparities may be related to differences in dietary fat and calories as well as the higher use of soy products by Asian women [100–102].

The Canadian Diet and Breast Cancer Prevention Study Group conducted a multicentre randomised trial involving women with areas of abnormal breast densities detected on mammography. The study showed a significant reduction in the number of radiographic abnormalities after 2 years of a low fat diet (i.e. less than 15% of calories from fat) [103]. The Women's Intervention Nutrition Study and the Women's Healthy Eating and Living Study are currently evaluating the benefits of limiting fat intake to 15% of calories for women with postmenopausal breast cancer [104]).

Alcohol consumption has also being extensively investigated as a possible risk factor for breast cancer [105]. While most studies have documented that high alcohol intake is associated with a significantly increased incidence of breast cancer, no definitive evidence exists on the favourable effect of reducing alcohol intake.

11. Surgical prophylaxis and modulation of risk

11.1. Prophylactic mastectomy

It seems intuitive that mastectomy would be an effective means of preventing breast cancer. However, data from both laboratory studies and animal models and clinical trials have confirmed that this is not always the case [106–108]. Studies have demonstrated that even total mastectomy (defined as removal of the entire breast, including the nipple–areolar complex, but sparing the axillary contents) is frequently incomplete; microscopic amounts of breast tissue may remain in the skin flaps, attached to the pectoralis fascia, and extending into the axilla [107].

The clinical significance of retained breast tissue in the setting of prophylactic mastectomy for humans is not yet defined. Data on prophylactic bilateral mastectomy in humans are limited. The studies by Pennisi and Capozzi [109] and Woods and Meland [110] each involved at least 1500 women who underwent subcutaneous mastectomies and, in both studies, the post-surgical incidence of breast carcinoma was less than 1% [109,110]. However, both studies have been criticised for their limited applicability to high-risk women, because the women in these series would today be considered to be at only low or intermediate risk for breast cancer. Detailed follow-up information is also lacking in these large series.

It remains to be determined whether a prophylactic total mastectomy is clearly indicated for women with a high-risk for developing breast cancer. Women with *BRCA1* mutations, who may have a cumulative breast cancer risk of 40–85%, would be the obvious candidates [111,112].

Schrag and colleauges [113] developed a statistical model to calculate the benefit of prophylactic mastectomy for individuals with a *BRCA1* or *BRCA2* mutation. Using a risk-reduction estimate of 85% associated with prophylactic mastectomy, this study determined that a 30-year-old *BRCA1* mutation carrier would gain from 2.9 to 5.3 years of life expectancy following preventive surgery. Lynch and colleagues [114] reported on the results of a series of women who had undergone extensive genetic counseling and subsequently tested positive for *BRCA1* gene mutations. Only 35% of these patients said they would consider undergoing prophylactic mastectomy. This finding underscores the complexity of identifying high-risk women who will benefit psychologically as well as clinically from preventive surgery.

Hartmann and colleagues recently reported the results [115] of a retrospective analysis performed on 639 women with moderate or high risk for breast cancer (based on family history) who had undergone bilateral prophylactic subcutaneous mastectomy between 1960 and 1993. The breast-cancer incidence in these women was compared with the number of expected cases based on the Gail model, and to the number of cases that occurred among the patients' female siblings who had not undergone prophylactic surgery; these estimations revealed an approximately 90% reduction in breast cancer risk associated with prophylactic mastectomy.

The Society of Surgical Oncology has delineated categories of patients for whom prophylactic mastectomy may reasonably be considered on the basis of clinical features (and not including genetic testing results) [116]. For women with no history of breast cancer, the indications include atypical hyperplasia; a family history of premenopausal bilateral breast cancer; and dense, nodular breasts associated with atypical hyperplasia. For women with a known unilateral breast cancer, the indications for considering contralateral prophylactic mastectomy include diffuse microcalcifications; lobular carcinoma *in situ*; a large, difficult-to-evaluate breast; a history of lobular carcinoma *in situ*; and a family history of early-onset breast cancer.

11.2. Prophylactic ovarian ablation

Several retrospective, matched control analyses of the effects of ovarian ablation on the incidence of breast cancer in high-risk women have been published over the past few years [117–119]. In general terms, bilateral ovarian ablation reduced the incidence of breast and ovarian cancer in high-risk women, including those with known *BRCA1* or *BRCA2* mutations. Whether chemical ovarian suppression, by using Gonadotropin analogues, would have the same results, remains to be determined.

12. Conclusions

The encouraging results from tamoxifen studies, and the ongoing clinical trials of raloxifene, retinoids, aromatase inhibitors and other approaches suggest that physicians and scientists are increasingly cognizant of chemoprevention and its potentially enormous socioeconomic implications. Breast-cancer chemoprevention is a rapidly evolving field that has the potential to significantly reduce the incidence of breast cancer.

In the past decade, our increasing understanding of the roles that genetic, hormonal, dietary and environmental factors play in the development of breast cancer has greatly improved our ability to determine individual risk of breast cancer and to properly select high-risk groups for interventional studies. Prospective clinical trials of chemoprevention strategies should be limited to high-risk populations identified on the basis of a combination of epidemiological, histopathological and biological data. Ideally, these studies should use surrogate

endpoint biomarkers to evaluate the efficacy of drug interventions. This approach will contribute greatly to reducing the size of patient populations under study, eventually reducing the costs related to these investigations and helping to clarify the biology of each drug's mechanisms of action.

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