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Current Controversies in Cancer

Should Prophylactic Surgery Be Used in Women with a High Risk of Breast Cancer?

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INTRODUCTION

DUE TO recent breakthroughs, the results of molecular genetic studies are now in the transitional phase from the laboratory to the clinic. In particular, the identification of the breast cancer genes 1 and 2 (*BRCA1* and *BRCA2*) has had a rapid clinical impact, which has resulted in uncertainty and ethical discussions [1]. In this paper, we discuss the oncological implications especially with respect to preventive surgery.

PATHOLOGY OF FAMILIAL BREAST CANCERS AND PROPHYLACTICALLY REMOVED BREASTS AND OVARIES

In our experience, benign breast disease not uncommonly precedes the development of breast cancer in families with hereditary site specific breast cancer (HBC) or hereditary breast/ovarian cancer syndrome (HBOC), causing serious distress in these women at high risk of breast cancer. Early studies by Dupont and Page [2] have already shown that women with atypical hyperplasia and a family history of breast cancer have an 11-fold relative risk of breast cancer. Skolnick and associates [3] found, using four-quadrant fine-needle breast aspirates, proliferative breast disease (marked or atypical hyperplasia) in 35% (27/77) of first-degree relatives of familial breast cancer cases in contrast to only 13% (4/30) in control women ($P = 0.02$). In 2 cases proliferative breast disease preceded detection of microcalcifications and breast cancer within one year. These authors concluded that genetic susceptibility causes both proliferative breast disease and breast cancer in these kindreds. In prophylactally removed breasts of women at high risk of breast cancer, we also found a high incidence of benign breast lesions [4, 5], even small invasive or *in situ* carcinomas in 3 (6%) out of 50 specimens. Also in prophylactically extirpated ovaries from women at risk in HBOC families, especially when a *BRCA* mutation was proven, we quite frequently found benign and even malignant lesions, while histological premalignant epithelial lesions were not uncommon [4, 6]. Similar findings were recently reported by Salazar and associates [7].

Primary hereditary breast cancers show frequently unfavourable characteristics such as poor differentiation (grade 3), high proliferation indices, aneuploidy, oestrogen receptor (ER) negativity and medullary histological type [8–11]. However, in spite of these unfavourable ominous histological characteristics, there is no consensus over whether *BRCA1* mutation carriers have a better or worse clinical outcome after diagnosis of primary disease in comparison with patients with somatic tumours.

SURVEILLANCE OF WOMEN AT RISK

Overall, population screening reduces mortality from breast cancer by approximately 25–40% in women between the ages of 50–70 years [12], but there is considerable debate over the value of screening in premenopausal women in view of the lower incidence in this age group, lower sensitivity of mammography and a higher proliferation rate in young patients [13–15]. Nevertheless, a recent meta-analysis showed a mortality reduction of 24% in women between 40 and 50 years of age [15]. One of the greatest potential benefits of genetic screening for breast cancer susceptibility might be the identification of younger women who may benefit from intensive surveillance by half-yearly physical examination and yearly mammography. However, the effectiveness of screening in this particular population is not yet known and associated with psychological distress [16, 17] in some women while others are reassured. The sensitivity of mammography appears to be lower among women with a family history of breast cancer [13], maybe as a consequence of a higher

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incidence of mastopathic changes in these women and/or rapid growth rates of interval cancers. Furthermore, there is probably an increasing radiation risk when screening starts at a younger age [18–20]. Magnetic resonance imaging might overcome this problem in the future [21], but this imaging technique is not (yet) accepted as a screening method. The results of a few small retrospective [22–24] and recently reported prospective studies [25–27] suggest that screening may lead to the detection of a greater proportion of smaller tumours and node-negative breast cancer. The percentage of node positivity varies between 8 and 28%. Therefore, based on the reported stage distribution, at least a quarter of these patients will ultimately die in spite of a relatively early diagnosis.

PREVENTION OF BREAST CANCER

In principle, preventive measures can consist of changes in lifestyle, diet, use of antihormonal agents and prophylactic surgery [1, 28, 29]. Women with a genetic predisposition for breast cancer can try to avoid other risk factors as far as possible and to use optimal diets. These measures may decrease the risk or delay the development of breast cancer, but major effects can probably not be expected. The anti-oestrogen, tamoxifen, can decrease the occurrence of contralateral breast cancer in patients with primary disease and can improve (disease-free) survival in the adjuvant setting [30]. At present, this drug is being tested in three large randomised prevention trials in women at risk of breast cancer, but it will take at least 10 years before any definitive conclusions can be drawn. In any case, prevention can certainly not be guaranteed and the side-effects of long-term treatment with tamoxifen are still a matter of debate [31, 32]. In addition, in young premenopausal women this drug induces chronic hyperstimulation of the pituitary–ovarian axis with ovarian cyst formation and cannot be given to women of childbearing age. Other endocrine agents (such as LHRH analogues, antiprogestins, retinoids) potentially can be used in future prevention studies, but need decades for adequate development in this respect.

The literature contains several reports of breast cancer occurring in women following subcutaneous (thus incomplete) mastectomy [33, 34]. An overview of studies concerning the risk of breast cancer after subcutaneous mastectomy in 1500 women, of whom 510 had a family history of breast cancer, indicates a breast cancer incidence of approximately 1% after a median follow-up of 9 years [34]. Of much greater importance are the results of a large study at the Mayo Clinics, Minnesota, U.S.A., recently presented by Hartmann and associates at the annual meeting of the American Association for Cancer Research [35], showing strong evidence that prophylactic mastectomy in women at high risk of breast cancer dramatically (> 90%) reduces their chances of developing the disease [35, 36]. In a group of 950 women with bilateral prophylactic mastectomy (in more than 600 because of a positive family history) performed between 1960 and 1993 with a mean follow-up of 17 years and a mean age of 43 years at time of surgery, only 7 breast cancers were observed against 76 expected. This great reduction of risk was reached in spite of the fact that approximately 90% of the women underwent only subcutaneous mastectomy. None of the 100 or so women who had total mastectomy later developed breast cancer. Furthermore, another recent study indicates that prophylactic mastectomy and prophylactic oophorectomy provides substantial gains in life expectancy, even though intensive surveillance results in early detection of cancers with a favourable stage at diagnosis [37].

THE ROTTERDAM EXPERIENCE

In order to comply adequately with the increasing requests for professional advice, in 1990 we established, in collaboration with some colleagues from Leiden, a Committee for Genetic and Medical Counselling on Hereditary Tumours and a family cancer clinic in Rotterdam, reflecting the need of a multidisciplinary approach. Between 1991 and 1997, over 300 families with familial breast and/or ovarian cancer (HBC or HBOC) consulted our family cancer clinic [4]. Recently, we evaluated the effects of the progress in molecular genetic technology and the increased awareness of patients at high risk of cancer on medical conduct, clinical genetic [38–41] and oncological findings [4, 42]. Especially at the time of the identification of *BRCA-1* and mapping of *BRCA-2* (1994), there was a peak accrual of families requesting genetic and medical counselling (up to 20 families per month). Presently, approximately 150 families have been tested by at least one technique (protein truncation test, DNA sequencing or linkage analysis) for *BRCA* gene mutations. Thus far, mutations in *BRCA1* and *BRCA2* have been found in 23 and 2 families, respectively, i.e. a success rate of ± 15–20% which is in accordance with that of a national Dutch collaborative study in 517 families [40]. Young age at diagnosis is an important indicator [41]. The utilisation of genetic testing in 20 investigated families with proven gene mutation was 64% in women (121/190) and 24% in men (29/122), who were informed by the index person(s); these percentages may increase in time [42], certainly when death anxiety increases due to (recurrence of) cancer in a relative [43–45]. As a consequence of both the growing awareness of the risk of familial breast cancer (as based on the pedigree) and the rapidly increasing number of proven gene mutation carriers, the number of prophylactic mastectomies and/or oophorectomies strikingly increased from approximately 4 per year before 1994 to more than 20 in 1996 (Figure 1). In total, prophylactic bilateral or contralateral mastectomy was carried out in 22 unaffected women at risk and in 28 affected patients. Cancers were found in 3 (6%) prophylactically removed breasts (not detected before surgery), while florid and/or

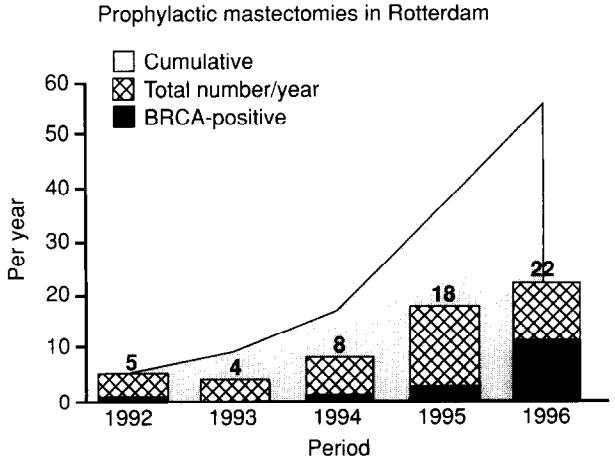

Figure 1. Increasing numbers receiving prophylactic mastectomy in Rotterdam, especially in proven gene mutation carriers.

atypical hyperplasia, microcalcifications, sclerosing adenosis and/or fibrocystic lesions were found in a high percentage (25–80%) of these 'normal' breasts [4, 5]. 46 women (mean age 48 years, range 33–60 years) opted for prophylactic oophorectomy, in 18 cases based on a proven gene mutation (group A) and in 28 cases based on the pedigree (group B). In group A, 5 (28%) showed small malignant ($n = 2$) or benign tumours ($n = 3$) in contrast to 2 with benign tumours (7%) in group B. Most strikingly, in comparison with 13 controls, epithelial abnormalities (> 90%), complex inclusion cysts (30%) and embryonal remnants (70%) were frequently found, especially in *BRCA1* mutation carriers, indicating the presence of premalignant lesions [4, 6]. One patient developed a peritoneal carcinoma 16 months after prophylactic oophorectomy. No primary breast cancers were observed after prophylactic total bilateral mastectomy, but the follow-up is still short.

DISCUSSION

In the past and sometimes still present, women from families with familial breast cancer were/are more aware of their potential risks than medical doctors in general and they received no or only minimal attention. Women from these families often have a fear of cancer for many years. Due to recent discoveries in molecular-genetic research, such as the identification of the *BRCA* genes and the publicity about these findings, a rapidly increasing number of these affected women or relatives at risk now request genetic and medical counselling [1, 28, 29]. In this respect, the American (ASCO) and European (ESMO) Societies of Clinical Oncology are rightly paying increasing attention to these problems at their annual meetings, and ASCO with an official statement has endorsed the responsibilities of clinical oncologists [46].

Predictive testing for breast cancer and other cancers will soon become standard medical practice. It is this author's opinion that women (and also men) have the right to be informed of the possibilities concerning presymptomatic testing, risk assessment, surveillance, prevention and psychological support both with respect to the potential benefits and limitations. The majority of relatives of women with breast and ovarian cancer are in favour of such an approach [47–49]. However, we have to respect the right 'not to know' or not to choose for any consequence as expressed by a minority.

The identification of genes that predispose to cancer and are associated with high risks raises a number of dilemmas for the gene mutation carriers and the clinical oncologists. This also concerns women with a high risk of cancer based on the family pedigree when genetic alteration cannot be detected with current techniques. Some women wait for years for the test results and in the meantime are very worried about their cancer risk, especially when mastopathic or premalignant changes have already been shown in breast biopsies. Decisions have to be made about lifestyle, surveillance, possible prevention and timing. When we inform the women at risk about the (potential) advantages of surveillance, at the same time we have to inform them that even early detection of a breast cancer cannot guarantee that tumour cells have not already spread into the body. In our experience (even inoperable) breast cancers can occur between two mammographic screenings, can sometimes be undetectable, or at the time of detection have already microscopically disseminated to other organs even in the case of very small tumours. Based on literature data (see above), at least 25% of women will ultimately die in spite of relatively early diagnosis. With respect to ovarian cancer, the value of regular screening is even more doubtful and probably very low or nil [1, 28, 29, 37]. Therefore, prophylactic surgery has to be seriously considered and discussed with these women at high risk of cancer [1, 12, 28, 29, 50–53].

In this respect, we use a modification of a decision tree, as advised by the American Society of Surgical Oncology [50], including aspects such as family history, reproductive history, other risks, presence of benign breast pathology, prior breast cancer, age, competing causes of mortality, breast examination, evaluability of mammogram and psychological situation. Finally, after extensive counselling it is the patient who makes the choice between no surveillance, regular surveillance or prophylactic surgery with or without breast reconstruction. In our experience, an increasing number ($\geq 50\%$) of (especially young) gene mutation carriers opt for prophylactic bilateral mastectomy, mostly in combination with breast reconstruction and sometimes together with prophylactic oophorectomy during the same operation. In case of prophylactic oophorectomy, hormonal replacement therapy will be instituted when the breasts are removed. In our and other's [53] experience, women having followed this course after adequate counselling do not regret their decision but are relieved of the fear of cancer.

Table 1. *Considerations in favour of prophylactic surgery*

Carriers of *BRCA1* and *BRCA2* gene mutations have a very high life-time risk of breast (85%) and ovarian (20–64%) cancer
Bilateral breast cancer frequently occurs with a life-time risk of contralateral breast cancer of 64%
Early age of onset of both ovarian and especially breast cancer
In general, the age of onset of cancer occurs at a younger age in each succeeding generation: in the majority of the cases, daughters develop their breast cancers at an age of 1–40 years younger than in their mothers or aunts
During this century the standardised mortality ratio in HB(O)C families showed a step-wise increase from 2.4 to 8, especially over the last 3–4 decades
In HB(O)C families, proliferative benign breast disease is frequently present and also associated with very high relative risk of breast cancer
Women with benign breast disease and a family history of breast cancer are very worried about getting breast cancer, certainly when a gene mutation is proven
Prophylactically removed breasts and ovaries frequently show premalignant lesions and even sometimes invasive or *in situ* carcinomas.
Primary hereditary breast cancers frequently show unfavourable tumour characteristics
The sensitivity of mammographic screening decreases at a younger age, especially in women with a family history of breast cancer
Intensive surveillance and early detection of breast cancer does not guarantee prevention of death by breast cancer; in spite of 'early' detection at least 25% of the cases will ultimately die of breast cancer
At present, prophylactic total mastectomy is by far the most safe measure in the prevention of hereditary breast cancer and results in gains of survival

The timing of preventive surgery needs special attention. In this respect, a key issue in decision-making is the early age of onset of familial breast cancer in general and especially the observed occurrence of the onset of cancer at a younger age in each succeeding generation. In a family—as presented by Dr Cortès-Funes, chairman of a special controversy session at the 21st Congress of the ESMO (Vienna, November 1–5, 1996)—in which the grandmother died at the age of 68 years, the mother at the age of 36 years and a sister at the age of 30 years all by breast cancer, it is not logical to expect that a 22 year-old *BRCA1* gene mutation carrier will get breast cancer at an age of 80 years, but probably also at very young age. Therefore, in such cases it is advisable to perform prophylactic mastectomy before the age of 25–30 years, especially because the gains in life expectancy decline with age at the time of prophylactic surgery [37]. Because ovarian cancer rarely develops before the age of 35 years, prophylactic oophorectomy can be performed later when the family is complete. However, the women have to be informed that there is still the risk of peritoneal carcinoma, which has been reported to occur in 6 (1.9%) of a series of 324 women at risk with an interval of 1–27 years after prophylactic oophorectomy [54]. This percentage might increase to 4–8% after longer follow-up and when women at risk are selected only on the basis of a DNA test. Nevertheless, this means a considerable reduction of the risk of ovarian/peritoneal cancer.

Finally, it is currently difficult to predict whether a gene mutation carrier, who avoids death due to breast or ovarian cancer by prophylactic surgery, will die by another cancer type and if so at which age. However, it is clear that preventive surgery will at least significantly prolong survival [37]. Especially in view of the reported increased incidence of breast cancer at younger ages [55], genetic testing may result in a decline in age-adjusted mortality from breast cancer especially among younger people. In this respect and in view of different reasons as summarised in Table 1, we are in favour of prophylactic surgery, certainly in young women at very high risk of cancer.

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INTRODUCTION

MOST CLINICIANS involved in genetic counselling adopt a non-directive approach. The role of a genetic counsellor is to ensure that correct diagnosis and risk estimate have been made and that those being counselled have correctly understood the situation [1]. It is not the duty of a genetic counsellor to recommend a particular line of action if a genetic risk has been identified. Dr Klijn and I were asked to take positions as if we were acting paternalistically when counselling and we accepted playing the role of a ridiculous counsellor who possesses the infallible scientific truth and who always gives the same authoritative solution to a very complex human problem. The aim of this unrealistic role game is, of course, not to persuade the audience that one of us is right

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