PERGAMON

EJC Supplements Vol 1 No. 1 (2003) 13–23

EJC Supplements

www.ejconline.com

Gene screening and prevention of hereditary breast cancer: a clinical view

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Received 15 August 2002; received in revised form 18 February 2003; accepted 18 February 2003

Abstract

Nowadays, the major tasks of the increasing number of family cancer clinics are to provide general information about cancer, to perform risk assessment, to offer (presymptomatic) DNA-testing, to advise on lifestyle, to take steps for early detection and prevention of cancer, for psychological support and to carry out research programmes by a multidisciplinary approach. In approximately 25–30% of the families with a hereditary pattern of breast cancer a germline mutation can be demonstrated, most commonly in the BRCA1 and BRCA2 genes. Mutations in these genes are associated with high life-time risks of breast and ovarian cancer. The introduction of MRI increased the sensitivity for early detection of breast cancer in comparison with mammography. Thusfar, prophylactic bilateral total mastectomy is the most effective and safest way of prevention but prophylactic oophorectomy and chemoprevention are reasonable alternatives. In particular young women with children make use of DNA-testing and surgical prevention. By a shared decision-making process, the patient and her medical doctor have to make the right choice of management policy based on her individual circumstances.
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1. Introduction

In the Western world, the incidence of breast cancer has been doubled since 1940 [1]. There are approximately 1000 new cases per million women each year. World-wide, a yearly incidence of nearly one million new cases has been estimated. Breast cancer concerns 30% of all cancers in women and is the leading cause of death in women between 35 and 55 years of age. In the Western world, the life-time risk is 8–10%. In about half of the women with primary breast cancer, occult metastases (micrometastases) must be present at time of diagnosis in view of the poor disease-free survival after 20 years of follow-up. The chance of metastases and tumour progression is related with tumour stage, tumour biological characteristics and patient age [2]. In the long term, death occurred in 40% of patients with node-negative disease, in 70% in node-positive disease, and in nearly all women with clinically manifest metastatic disease. However, since the improvements in treatment, the large-scale application of adjuvant therapy, the better information and awareness of women, and probably the introduction of population-based breast cancer screening programmes, the breast cancer mortality rate is now decreasing in several countries.

Breast cancer is a multifactorial disease. An accumulation of genetic alterations is responsible for the transformation of normal cells into cancer cells. Several hereditary (germline) and acquired (somatic) genetic alterations are known to induce genomic instability, resulting in a disbalance between cell proliferation and cell death, and ultimately in tumour growth development and progression [2].

15–30% of all women with breast cancer have at least one relative with the disease, but it is currently estimated that only 5–10% of cases are caused by inheritance of germline mutations in highly penetrant susceptibility genes such as BRCA1 and BRCA2 [3].

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doi:10.1016/S1359-6349(03)00005-3

Mutations in the BRCA1 and BRCA2 genes have been found in a quarter of families with familial breast cancer [4]. Apart from germline mutations with a dominant hereditary pattern of disease, an unknown number of undiscovered susceptibility genes and modifying genes conferring a lower risk may play an important role. Possibly, as many as 15–27% of breast cancers may be due to inheritable factors, which is higher than previous estimates based on population studies [5]. Furthermore, apart from hereditary predisposition, body characteristics, endocrine and environmental factors (nutrition, carcinogens, habits, radiation and viruses) are other important causative factors of breast cancer [1]. In addition, there is an interaction between hereditary, reproductive and environmental factors.

In particular, the identification of the breast cancer susceptibility genes BRCA1 and BRCA2 in the mid-1990s [6,7] evoked widespread interest in genetic and oncological counselling and the need for multidisciplinary family cancer clinics. These clinics are served by specialists of different disciplines, which are needed for an adequate support of all these women with different risks, problems and wishes. For instance, in our family cancer clinic, at least 12 disciplines are involved, as indicated in the Acknowledgements.

2. Family cancer clinics

In the early 1990s, a number of these family cancer clinics originated from research laboratories united in the Breast Cancer Linkage Consortium (BCLC) [8–14]. The original main objectives of this consortium were to detect predisposition genes for breast and ovarian cancer and to estimate risks of cancer related with these genes. The localisation and identification of the BRCA1 and BRCA2 genes are a nice example how the results of laboratory research can be translated to the clinic and routine care. In recent years, the number of family cancer clinics is rapidly increasing in line with the ever-swelling numbers of families and individuals with a proven gene mutation. There are also increasing collaborations at the national and international levels. Several collaborative groups and societies developed guidelines and clinical research proposals [15–17].

Nowadays, the major tasks of family cancer clinics are to provide general information about (breast) cancer, to perform risk assessment, to offer (presymptomatic) DNA testing, to advise on lifestyle, to take steps for early detection and prevention of breast cancer, for psychological support and to carry out research programmes (Table 1).

In Rotterdam, shortly after the localisation of BRCA1 in 1990 [18], we established our Rotterdam Family Cancer Clinic, which was in line with our early studies on cell biological prognostic and predictive factors in breast cancers [2]. Since then, more than 1800 families with hereditary cancer have been registered (Fig. 1) and more than 6000 people consulted our clinic. The age at diagnosis of breast cancer in women with a proven BRCA1/2 mutation was young in the majority of the patients (Fig. 2) from the families who consulted our family cancer clinic.

Table 1
The role of family cancer clinics

1.	General information on (breast) cancer	
2.	Risk assessment	
3.	DNA testing	
4.	Advice on	• lifestyle • early detection • prevention
5.	Psychological support	
6.	Multidisciplinary approach	
7.	Research projects	

3. Risk assessment

Risk assessment of breast cancer is originally based on the family history and pedigree, and on other risk factors [1]. Extensive genetic-epidemiological studies in first and second degrees of patients with breast cancer resulted in valuable tables indicating the risk estimates for family members of breast cancer patients [19]. Familial occurrence of breast cancer can increase the life-time risk of breast cancer up to nearly 50%, depending on the number of breast cancer cases, young age of onset, presence of bilateral disease and of other types of cancer such as ovarian cancer. Well known familial breast cancer syndromes are the hereditary breast cancer (HBC) only syndrome, the hereditary breast/ovarian cancer (HBOC) syndrome and Li–Fraumeni syndrome. These syndromes are associated with clearly elevated risks of breast cancer. Other risk factors such as endocrine and dietary factors are associated with much lower relative risks (relative risk <2) [1]. Also, histological characteristics of benign proliferative breast disease are associated with an increased risk (2–4 times) of breast cancer [1,20]. The combination of atypical hyperplasia and familial occurrence of breast cancer showed a strongly enhanced risk (up to over 40% after 20 years of follow-up) [19]. Breast cancer risk assessment can be performed with the use of all these familial and non-familial risk factors [21].

A more refined and accurate assessment can be carried out with the application of a presymptomatic DNA test. Unaffected women with a proven BRCA1 or BRCA2 mutation have a cumulative lifetime risk of invasive breast cancer of approximately 55–85% and of

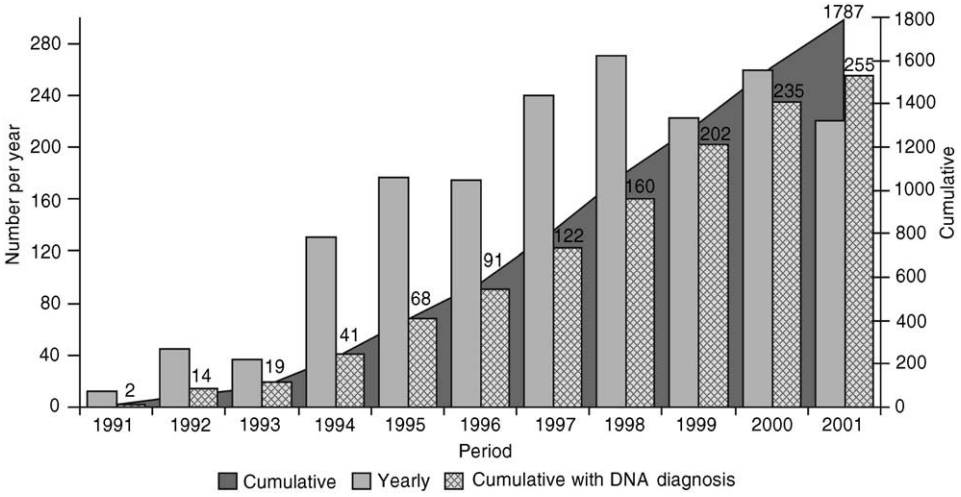

Fig. 1. Accrual Family Cancer Clinic Rotterdam (Dr Daniel den Hoed Kliniek/EMCR): number of families with family cancer syndromes.

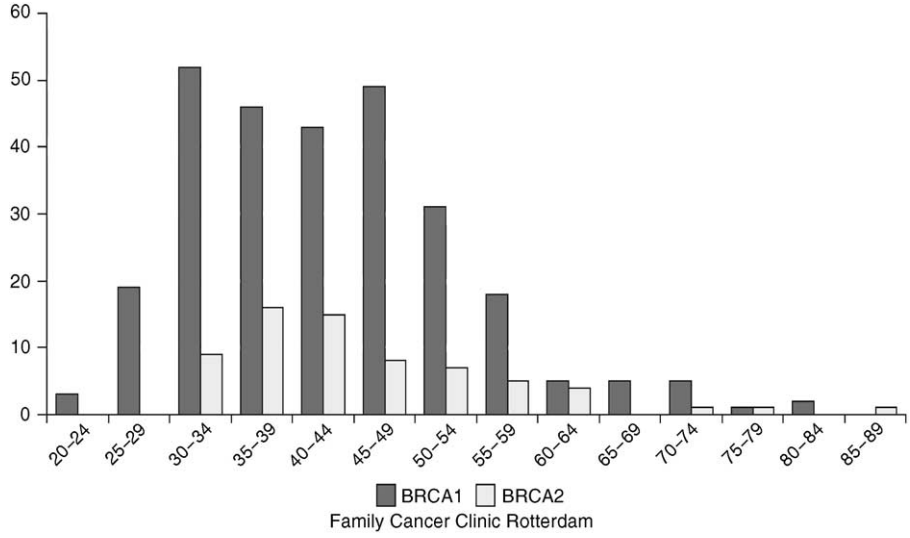

Fig. 2. Age at diagnosis of breast cancer in women with a BRCA1/BRCA2 mutation ($n = 346$).

invasive ovarian cancer of 15–65% [3,8–13,22]. Based on population studies, unaffected BRCA1 or BRCA2 mutation carriers without a clear family history seem to have lower breast cancer risks (36–56%) but, at a family breast cancer clinic, the familial occurrence of breast cancer is mostly the reason for consultation. Compared with BRCA1, the risk of breast cancer in BRCA2 mutation carriers increased at a somewhat later age, thus showing a lower penetrance at young age (less than 50 years) [13].

The BCLC also reported increased risk of other cancers than breast or ovarian cancer in large series of families with BRCA1/2 mutations [8,12,13]. Significantly increased risks were found for prostate cancer, gastrointestinal tumours, pancreatic cancer, gallbladder and bile duct cancer, and malignant melanoma, especially in BRCA2 mutation carriers.

4. Pathobiological characteristics and prognosis

BRCA1- and BRCA2-associated breast cancers show different histological and cell biological characteristics in comparison to sporadic tumours [23–27]. BRCA1-associated tumours show more frequently a high-grade (poorly differentiated), medullary histological type, a high proliferation index, more lymphocytic infiltration, steroid receptor (ER-, PR)-negativity, low pS2 expression, presence of p53 mutations, HER2/neu-negativity, topo-isomerase IIα-positivity, amplication of chromosome 6q 22-24 (the locus of c-myb), and possibly a low expression of cyclin D1. With the exception of low HER2/neu expression, nearly all factors are associated with poor prognosis. Nevertheless, we found that the prognosis of patients with BRCA1-associated tumours

is similar or only somewhat less than those with sporadic tumours matched for patient age and year of diagnosis [28]. A few authors observed a significant poor prognosis for affected BRCA1 mutation carriers [27,29].

With respect to BRCA2-associated tumours, these tumours also show unfavourable tumour characteristics but are less pronounced than for BRCA1-associated tumours. However, there is no significant difference with respect to steroid hormone receptor-positivity in comparison with sporadic tumours. When matched for age and year of diagnosis, for affected BRCA2 mutation carriers also, we found no significantly different (disease-free) survival in comparison with breast cancer patients in the general population [30,31].

In women with a BRCA1 or BRCA2 mutation, the risk of a second primary (contralateral) breast carcinoma is over 50% up to age 70 years. More specifically, we showed that the 5-year rate of metachronous contralateral breast carcinoma in women with a BRCA1 or BRCA2 mutation was 19 and 12%, respectively, while in age-matched controls this rate was 5 and 2%, respectively [28,30,31]. Contralateral breast cancer risk was greater in younger women (<50 years) with a BRCA1-associated primary tumour than in older women without affecting overall survival [32].

5. DNA testing

The identification of the BRCA1 [6] and BRCA2 [7] genes in 1994 and 1995 has had increasing clinical impact. A large variety of mutations in both genes are associated with inherited breast and/or ovarian cancer. So mutation identification is necessary in every family with familial occurrence of breast and/or ovarian cancer. In the context of a known mutation in the family, identification of individuals with or without the mutation is possible by (presymptomatic) DNA-testing [33–36]. Clearly, the absence or presence of a mutation will have considerable medical and psychological significance.

Results of several attitudinal studies have shown that many (81–91%) of healthy first-degree female relatives of patients with breast or ovarian cancer are potentially interested in BRCA1/BRCA2 testing [37,38]. By contrast, actual use of the DNA test was significantly lower in women from families with an identified BRCA1 mutation [33,36]. In our clinical setting, we found in 682 unaffected individuals from 53 consecutive families with an identified BRCA1/2 mutation that only 57% of women and 22% of men with a genetic risk of 50% for a mutation opted for a presymptomatic DNA test [36] (Table 2). Important factors influencing a positive decision for BRCA1/BRCA2 testing were young age, parenthood, young age when for the first time being confronted with a breast cancer case in the family, and the number of family members affected with breast cancer. Also, the wish for surgical prevention by prophylactic mastectomy or oophorectomy was important. BRCA1 and BRCA2 gene mutations are involved in most families with the autosomal dominant inherited breast–ovarian cancer syndrome, and in 60% of families with 4 or more cases of just breast cancer before the age of 60 years [10,13]. However, in the family cancer clinic setting, the chance to find a BRCA1/2 mutation (i.e. detection rate) is much lower because smaller families and families with less than 4 breast cancer cases are more common. Both BRCA1 and BRCA2 genes are large genes and germline mutations in these genes are scattered throughout the coding sequences. Therefore, both for reasons of practicality and cost-effectiveness, the probability that an individual with breast or ovarian cancer may have a mutation in BRCA1/BRCA2 is an important consideration in genetic testing. By using various molecular genetic techniques [39–42] in 517 Dutch families at our Rotterdam family cancer clinic we detected a BRCA1 ($n=98$; 19%) or BRCA2 ($n=21$; 4%) mutation in 119 (23%) families [4]. Predictors for detection of a BRCA1/2 mutation are early-onset breast cancer, one or more cases of ovarian cancer, and bilateral disease. BRCA1/2 mutations were found in 52% of 138 families with HBOC, in 13% of 339 families with HBC, in 36% of 11 families with ovarian cancer only (HOC), and in none of 29 families with only one single young case (<40 years) of breast cancer [4]. Between the different subgroups of families (subdivided by the number of patients, cancer phenotype and age of onset), the proportion of BRCA1/2 mutations detected varies between 6 and 82%. Our results are in accordance with those of others showing detection rates of approximately 20–30% in breast cancer risk evaluation clinics [43–48].

The incidence of specific BRCA1/2 mutations varies between populations. The ethnic background or regional origin can strongly influence the gene-mutation detection rate. Different founder mutations are found in the Ashkenazi Jewish population and in Iceland, Norway, Sweden, Poland, Austria, The Netherlands and other countries [4,40–42,49–53]. In The Netherlands,

Table 2
Predictive factors for utilization of DNA testing in 682 unaffected subjects from 53 consecutive families with a BRCA1/2 mutation in Rotterdam [36]

		Uptake	*P*
1.	Pretest risk for mutation (50 versus 25%)	58 versus 29%	<0.001
2.	Gender (women versus men)	57 versus 22%	<0.001
3.	Age in women (<50 versus ⩾50 years)	66 versus 38%	<0.001
4.	Parenthood (yes versus no) in		
	women	65 versus 46%	<0.004
	men	28 versus 9%	<0.001
N.B. Young women (<50 years) with children		83% (90/108)	
N.B. Women with breast cancer		87% (68/78)	

about 60% of all BRCA1/2 mutations detected concern founder mutations some of them being specific for very small confined regions [4,40–42]. Apart from the migration characteristics of a population, religion and the time period of origin of a specific mutation are important factors with respect to geographical clustering of founder mutations. Therefore, in addition to the familial cancer history (early onset breast cancer, bilateral disease, ovarian cancer, clustering of other cancer types), knowledge about the presence and prevalence of founder mutations in specific populations is of importance for selecting families eligible for BRCA1/BRCA2 analysis and will greatly facilitate the detection of mutations.

6. Risk-reducing strategies

Current risk-reduction strategies aimed at prevention of occurrence and/or death by cancer include changes in lifestyle, early detection of cancer by regular surveillance, prophylactic mastectomy, prophylactic oophorectomy and chemoprevention [3,26,54–56].

6.1. Lifestyle

Women with a genetic predisposition for breast cancer can try to avoid other risk factors as far as possible and to use optimal diets and to avoid alcoholic drinks. These measures may decrease the risk or delay the development of breast cancer, but major effects can probably not be reached. Age of menarche and age at birth of first child are physically and socio-demographically determined and difficult to influence. In this respect, in The Netherlands the average age at birth of first child increased since 1970 from 24 to 30 years presently. Long-term use of contraceptive pills from puberty reduce the risk of ovarian cancer with about 50% [57], but may slightly increase the risk of breast cancer [58], the tumour type which is more common at younger age. Thus, to give advice and to make choices with respect to lifestyle is difficult.

6.2. Early diagnosis by regular surveillance

Although an extensive international debate on the value of population mammographic screening is ongoing since the publication of Olson and Gotschke [59], several randomised trials and population-based screening programmes indicate that mammographic screening in the general population is effective in postmenopausal women and lowers breast cancer mortality by up to over 30% [1,60]. Although results in women between 40 and 50 years are more controversial, it was recently found that screening in this age group can also significantly reduce breast cancer mortality [61]. However, in view of the lower incidence of breast cancer and the larger negative screening effects in young women [62], there is no consensus on the cost-effectiveness and the desirability of introducing population-based screening programmes for women under the age of 50 years. It might be more efficient to limit screening in women under age 50 years to selected groups of high-risk women, such as women with a positive family history of breast cancer. The identification of the BRCA1 and BRCA2 genes and the possibility of gene mutation testing has caused an increasing demand from high-risk women for genetic testing and counselling about strategies to reduce their risk of breast cancer death. One of the options is intensive surveillance. Because, for ethical reasons, no randomised trials in genetically susceptible women are to be expected, the effects of surveillance in these women must be evaluated by means of observational studies. To date, a limited number of studies describing experiences and preliminary results of surveillance in women with a family history of breast cancer have been published [63,64].

Nowadays, a number of countries, including The Netherlands, offer the opportunity of selective breast cancer surveillance to women with a family history of breast cancer. The current policy in 16 European Family Cancer Clinics was recently reviewed by Vasen and colleagues [65]. Current surveillance modalities are breast self-examination, clinical examination and mammography. Magnetic resonance imaging (MRI) is performed mainly in research settings [66–70].

Most clinics recommend mammographic examination every year instead of every 2 years, as the growth rate is higher and the mammographic visibility of breast tumours lower in younger women. There is no consensus on the minimum age at entry: mammography generally is performed for the first time at age 25–35 years or 5–10 years younger than the youngest affected relative in case of young age at onset (<30–35 years).

Recently, we published the results of the first studies in BRCA1/2 gene mutation carriers in comparison with women with high and moderate familial risk of breast cancer [64]. In a study on 1198 women, the ratio of observed number of cases versus breast cancers expected in an average-risk population of comparable age was 23.7 in 128 BRCA1/2 gene mutations carriers, 7.0 in 621 high-risk women (30–50% lifetime risk), and 2.7 in 449 women with a moderate risk (15–30% lifetime risk). Thus, the number of cancers detected was significantly greater than expected and related to the risk category. Overall, the screening results were less favourable in the youngest age group (<40 years) and in BRCA1/2 gene mutation carriers.

In our second study, the yearly detection rate of breast cancer in 139 BRCA1/2 mutation carriers by regular surveillance was 2.5% after a median follow-up of 3 years [68]. Nearly all tumours found were poorly differentiated and ER-negative, and half of them node-positive.

It is uncertain whether mammographic surveillance of premenopausal women with a *BRCA1* or *BRCA2* mutation contributes substantially to early detection of breast cancer [64]. Considering the women's young age in our study cohort and the stage and pathological characteristics of their breast cancers at diagnosis, we estimate that 35–50% of women under surveillance in whom primary breast cancer develops will die of distant metastasis within 10–15 years [28,30]. Assuming that within 10 years, breast cancer will develop in approximately 25% of the women undergoing regular surveillance, we estimate that 10–20% of women who choose surveillance will die of breast cancer within 20 years. During the 3 years of follow-up in our study, there was one death due to breast cancer [68].

Currently, several large, prospective studies are investigating whether MRI screening adds to the efficacy of mammographic screening in women at high risk for breast cancer [66,67]. In our study on prophylactic mastectomy versus surveillance, MRI was performed in six women at the time of diagnosis and detected all six cancers, but mammography was diagnostic in only two of the eight women with breast cancer [68]. In view of the high number of interval cancers (four of eight), the use of high-resolution imaging and more frequent screening might be useful in women with a *BRCA1* or *BRCA2* mutation. Recent MRI studies showed that MRI has a greater sensitivity (80–100%) than mammography (33–45%) in this young age group [66–70], but larger prospective studies with long-term follow-up are needed. In this respect, several national MRI studies are ongoing.

6.3. Prophylactic mastectomy

Early studies on the possible interest in prophylactic mastectomy in untested high-risk women showed a wide range of outcomes [34–38]. At our family cancer clinic, 51% of unaffected women with a proven mutation choose prophylactic mastectomy, and 64% choose prophylactic oophorectomy [36]. Predictive factors for prophylactic mastectomy in unaffected BRCA1/2 mutation carriers are young age and parenthood (Table 3). In particular, young women with children opted for prophylactic mastectomy (70%) [36] as well as young women with a longer awareness of the genetic nature of cancer in the family [71]. No women older than age 55 years opted for prophylactic mastectomy, which is less advisable in view of the significantly declining estimated gains in life expectancy with increasing age by this surgical intervention [72]. In affected mutation carriers with primary breast cancer, 35% of the patients requested prophylactic bilateral/contralateral mastectomy [73].

Table 3
Predictive factors for prophylactic mastectomy in unaffected BRCA1/2 mutation carriers

1	Overall use in eligible women		35/68	(51%)	
2	Age	<40 years	21/38	(55%)	
		40–54 years	13/21	(62%)	
		⩾55 years	1/9	(11%)	$P=0.06$
3	Parenthood	No children	2/14	(14%)	
		With children	33/54	(61%)	$P=0.006$
2+3	Women <50 years with children		28/40	(70%)	

Source: Ref. [36].

In our clinical practice, women increasingly base their decision for prophylactic surgery on proven susceptibility. Overall, since 1998, about 90% of high-risk women based their choice for prophylactic mastectomy on a proven BRCA1/BRCA2 mutation in contrast to less than 20% before 1996 [36].

Until recently, only retrospective studies of the outcome of prophylactic mastectomy (mainly subcutaneous, and thus often incomplete) have been published [26,54–56,74–76]. Hartmann and colleagues [77] reported the results of prophylactic bilateral mastectomy in 639 women with a family history of breast cancer; at least 26 of these women had a *BRCA1* or *BRCA2* mutation [78]. After a median follow-up of 14 years, there was an approximate 90% reduction in the risk of breast cancer; the risk of death was also reduced significantly. All seven breast cancers occurred after subcutaneous bilateral mastectomy; there was none after total mastectomy [77]. Moreover, breast cancer did not develop in any of the women with a confirmed *BRCA1* or *BRCA2* mutation after a median follow-up of 13 years (range 6–28 years) [78], which leads us to anticipate that prophylactic mastectomy will reduce the long-term risk of breast cancer in the women with a *BRCA1* or *BRCA2* mutation whom we studied.

After a number of retrospective studies in high-risk women without a proven BRCA1/2 mutation showing a risk-reduction of approximately 90%, we performed the first (prospective comparative cohort) study in 76 BRCA 1/2 mutation carriers [68]. No cases of breast cancer were observed after prophylactic mastectomy after a mean (±SE) follow-up of 2.9±1.4 years, whereas eight breast cancers developed in women under regular surveillance after a mean follow-up of 3.0±1.5 years ($P=0.003$; hazard ratio, 0; 95% Confidence Interval (CI) 0–0.36). The actuarial mean 5-year incidence of breast cancer among all women in the surveillance group was 17±7%. On the basis of an exponential model, the yearly incidence of breast cancer in this group was 2.5%.

There is little in the literature on the histological findings in specimens obtained at the time of prophylactic mastectomy from women with a *BRCA1* or *BRCA2* mutation. In two studies, in about 35% of unaffected high-risk women, proliferative breast disease (marked or atypical hyperplasia) was found in the

surgical specimens [79,80]. In contrast, this abnormality was found in specimens from only 13% of women with an average risk of breast cancer [80]. In two women with a strong family history of breast cancer, microcalcifications and invasive breast cancer were detected within 1 year after the finding of proliferative disease [80]. In contralateral specimens obtained at the time of prophylactic mastectomy from women with prior breast cancer and either a genetic risk or a family history of breast cancer, a higher prevalence of malignant lesions was observed [54,79]. In our study [68], there was one carcinoma *in situ* and several prophylactic-mastectomy specimens with various degrees of hyperplasia and atypia. However, we cannot exclude the possibility that small invasive tumours were overlooked.

The utilisation of both prophylactic surgery and DNA testing in our centre may differ from those in other countries for several reasons. In The Netherlands, cancer susceptibility is no ground for exclusion by the health insurance system, or in access to employment. Costs for genetic testing, surveillance and prophylactic surgery are covered by both public and private health insurances. Accordingly, families and risk carriers are free from social or financial constraints, something that may be different in other countries. The risk for social and financial discrimination has been noted as an important reason to refrain from BRCA1/2 testing [77,81]. Furthermore, cultural differences in views on health and disease, risks and prevention, paternalism versus autonomy, and femininity may greatly influence interests in presymptomatic DNA testing and prophylactic surgery [54,82].

In a very recent study from Manchester, United Kingdom [83], the utilisation of prophylactic mastectomy appeared to be increased to 61% in BRCA1/2 carriers which results are in agreement with our published data [36,68]. Also in the United States of America there is an increasing demand for prophylactic surgery [75,76]. Unpublished results of a study by Lynch and colleagues [76] showed that 38% of woman considered prophylactic mastectomy before DNA testing: after learning of their BRCA1 or BRCA2 mutation status, 172 (51%) of the 336 mutation-positive women opted for bilateral prophylactic oophorectomy. A follow-up survey found that 27 (19%) of 142 mutation-positive women had actually undergone bilateral prophylactic mastectomy, while 46 (35%) of 131 mutation-positive women had had a bilateral prophylactic oophorectomy.

Prophylactic mastectomy is a highly personal decision. In counselling high-risk women, the protective effect of prophylactic mastectomy must be weighed against possible surgical complications and psychological problems. Up to 30% of the women who undergo the procedure will have surgical complications, depending on the type of surgery and the length of follow-up [74,75,84]. A long-term study of prophylactic mastectomy reported unanticipated repeated operations in 49% of women [85], but these results may not be applicable to prophylactic mastectomies as they are currently performed as also in our experience [86]. Psychological studies of women who had undergone a prophylactic mastectomy did not find that, overall, the procedure had detrimental effects on body image and sexuality [87–90].

In conclusion, our data [68] and those of Hartmann and colleagues [77,78] indicate that prophylactic bilateral total mastectomy substantially reduces the incidence of breast cancer among women with a *BRCA1* or *BRCA2* mutation. Nevertheless, longer follow-up and studies of more patients are required to establish the protective effect and determine the long-term complications of this procedure.

6.4. Endocrine prevention

Endocrine prevention of breast cancer can be performed by ovarian ablation or by treatment with antioestrogens [3,26,54–56,91]. Prophylactic bilateral oophorectomy reduces not only the risk of ovarian cancer with about 95% in BRCA1/2 gene mutation carriers or in women from families with a HBOC syndrome [92], but also reduces the risk of breast cancer by approximately 50%. Rebbeck and colleagues [93] demonstrated in 43 intact BRCA1 mutation carriers a risk reduction of breast cancer by 47% in comparison with 79 controls (Table 4), a reduction which was recently confirmed in a larger series of women [94]. In line with these findings were the results of a study in affected BRCA1/2 mutation carriers with primary

Table 4
Risk reduction of (contralateral[a]) breast cancer by prophylactic oophorectomy or chemoprevention in hereditary breast cancer

Author	Measure	Group	Cases	Controls	HR	(95% CI)
Rebbeck [93]	Oophorectomy	BRCA1+	43	79	0.53	(0.33–0.84)
Narod[a] [95]	Oophorectomy	BRCA1/2+	13	57	0.42	(0.22–0.83)
Powles [98]	Tamoxifen	Familial BC$\geqslant$1	±1230	±1230	No difference	
Fisher [96]	Tamoxifen	Familial BC$\geqslant$1	5036	5004	0.51–0.55	
King [99]	Tamoxifen	BRCA1+	5	3	1.67	(0.32–10.7)
	Tamoxifen	BRCA2+	3	8	0.38	(0.06–1.56)
Narod[a] [95]	Tamoxifen	BRCA1/2+	22	81	0.50	(0.28–0.89)
Narod[a] [95]	Chemotherapy	BRCA1/2+	88	234	0.40	(0.26–0.60)

breast cancer showing that prophylactic oophorectomy reduced the incidence of contralateral breast cancer by 58% [95].

Results of several trials on the efficacy of pharmacological intervention (chemoprevention) with anti-oestrogens such as the selective oestrogen receptor modulators (SERMS) tamoxifen and raloxifen have been published [26,91]. Both the NSABP P-1 trial on 13 388 women (49% reduction with tamoxifen) [96] and the MORE trial on 7705 postmenopausal women with existing osteoporosis (> 70% reduction with raloxifene) [91] showed a significant decrease of the incidence of breast cancer by long-term use of anti-oestrogens. However, two randomised European trials from the UK and Italy showed no significant reduction of the risk of breast cancer by tamoxifen [26,54–56,91]. The results of a fifth chemoprevention study (IBIS 1) testing tamoxifen versus placebo [56] have been presented at the 3rd European Breast Cancer Conference in Barcelona (March 2002) and were recently published [97]. In these studies not all women had an increased risk by a familial history of breast cancer or a proven BRCA1/2 gene mutation. Nevertheless, in the NSABP P1 trial [96] over 10 000 women had a family history of breast cancer and in these large subgroups the risk reduction (45–49%) was similar to that in the total study population. In contrast, in the study of Powles and co-workers [98] on about 2500 women with a family history of breast cancer, no risk reduction by tamoxifen was observed. With respect to proven BRCA1/2 mutation carriers, King found a BRCA1 or BRCA2 mutation in 19 out of 310 participants who developed breast cancer within the P1 chemoprevention trial [99]. From the 11 patients with a BRCA2 mutation 8 were in the placebo group and 3 in the tamoxifen group (risk ratio 0.38; 95% CI 0.06–1.56). In contrast, from the 8 patients with a BRCA1 mutation, only 3 were in the placebo group and 5 in the tamoxifen treatment arm (risk ratio 1.67; 95% CI 0.32–10.7). Such risk ratios might be expected because BRCA2-associated tumours are mostly ER-positive and BRCA1-associated tumours mainly ER-negative [31,99]. However, the numbers are much too small to draw definitive conclusions, as indicated by the wide 95% CIs and consequently the lack of statistical significance. However, in affected BRCA1/2 mutation carriers with a primary tumour, Narod and colleagues showed a 50% reduction of contralateral breast cancer by adjuvant tamoxifen; in addition, adjuvant chemotherapy caused a 60% reduction of contralateral breast cancer [95].

7. In conclusion

Together with the identification of important predisposition genes for breast cancer and better defined associated risks, there is an increasing demand for (presymptomatic) DNA testing. Thus far, prophylactic bilateral total mastectomy is the most effective and safest way of prevention of breast cancer but, for women above the age of 40 years, prophylactic oophorectomy is a reasonable alternative. With respect to chemoprevention, we are in favour of the use of this option mainly within the context of clinical trials. The introduction of MRI will increase the sensitivity for early detection of breast cancer in comparison with mammography, but prevention of death by breast cancer cannot guaranteed. Finally, by a shared decision-making process, the patient and her medical doctor have to make the right choice of management policy based on her individual circumstances.

Acknowledgements

We thank P. Duimelaar and P. Bos for typing the manuscript and our colleagues of the multidisciplinary Rotterdam Family Cancer Clinic (see the Appendix) for their contribution. Our studies were financially supported by the Dutch Cancer Society (grant DDHK 95/953) and the Dutch Government (grant ZON 2100.0013).

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