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Original Paper

Current Policies for Surveillance and Management in Women at Risk of Breast and Ovarian Cancer: a Survey Among 16 European Family Cancer Clinics

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The recent isolation of breast cancer predisposing genes (*BRCA1* and *BRCA2*) allows the identification of carriers within affected families. These carriers have a 50–85% risk of developing breast or ovarian cancer and need careful follow-up. The purpose of this study was to evaluate the management and screening protocols implemented in high risk families at various family cancer clinics in Europe. A questionnaire was mailed to the members of the European Familial Breast Cancer Collaborative Group ($n = 30$) requesting information on the following issues: indication for surveillance of breasts and ovaries, the recommended protocol, coordination of the screening examination, prophylactic surgery, the specific management of breast cancer in a mutation carrier and the use of oestrogen. 16 centres from nine countries responded. Most centres recommend surveillance of the breasts if the lifetime risk exceeds 15–20%. The surveillance protocol that is generally advised comprises monthly self breast examination, examination by a specialist every 6 months and annual mammography, all starting from an age between 25 and 35 years. Surveillance of the ovaries is recommended in *BRCA1* and *BRCA2*-mutation carriers, in members from breast/ovarian cancer families and in some centres in 'breast cancer only' families with an early onset of breast cancer. The recommended protocol includes gynaecological examination, sonography and estimation of CA-125 at yearly intervals starting from the age 30–35 years. Prophylactic mastectomy is considered for proven mutation carriers in some centres. Most centres consider prophylactic oophorectomy in mutation carriers and some centres also consider it for members of breast/ovarian cancer families. This survey provides insight into the guidelines for surveillance and management of familial breast cancer used at various family cancer clinics in Europe; this insight may contribute to the appropriate management of these high risk women. It should be emphasised that most recommendations are based on experts' opinion rather than on any specific studies. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

Approximately 5% of breast cancer is inherited as an autosomal dominant trait [1]. Since the identification of genes (*BRCA1* and *BRCA2*) which predispose to breast or ovarian cancer, more than 200 different mutations have been reported [2–5]. Although reports show wide variation in the risk that carriers of these mutations will develop breast cancer, most studies indicate that the lifetime risk is more than 50% [6–10]. The risk of developing ovarian cancer differs between carriers of a *BRCA1* mutation (risk at age 70 years: 44%) [6] and those carrying a *BRCA2* mutation (risk at age 70 years: 27%) [11]. Studies also indicate that the risk of ovarian cancer is associated with the site of the mutation within the respective genes [12, 13]. Because of these strongly increased risks, women carrying such genes need careful follow up. Unfortunately, the current available techniques of early detection of breast and ovarian cancer are far from ideal. For this reason, such mutilating options as prophylactic mastectomy might be considered in some cases.

The aim of the present study was to evaluate the guidelines followed at all relevant European centres for surveillance and management of high risk women. It is hoped that the results of this assessment will lead to the establishment of preliminary recommendations based on best practice and expert opinion.

MATERIALS AND METHODS

In 1996 a European collaborative group of clinicians specialising in familial breast cancer was established, the European Familial Breast Cancer Collaborative Group. All these specialists were members of the Breast Cancer Linkage Consortium, a collaborative group that played an important role in the identification of the genes involved in familial breast cancer. The members, who are mainly clinical geneticists and oncologists, are directly involved in the care of breast cancer families at family cancer clinics or registries. The present study is part of a project sponsored by the European Community (EC Biomed2: Demonstration Project: Familial Breast Cancer: audit of a new development in medical practice in European centres; coordinator: N. Haites).

In the middle of 1997, a questionnaire was mailed to the members of the collaborative group requesting information on the guidelines for surveillance and management followed in their respective family cancer clinics. The questionnaire was distributed among those members ($n = 30$) of the Breast Cancer Linkage Consortium who were directly involved in the care of breast cancer families.

The questionnaire addressed the following issues:

1. Surveillance of the breasts. Which screening procedures are recommended? Do the recommendations vary between women from different risk categories (see below)? From which age is mammography recommended? Who co-ordinates the screening examinations?
2. Prophylactic mastectomy. Is the option of a prophylactic mastectomy discussed or recommended?
3. Surveillance of the ovaries. Is surveillance of the ovaries discussed or recommended? Which protocol is used?
4. Prophylactic oophorectomy. Is prophylactic oophorectomy discussed or recommended?
5. Management. Which surgical treatment is offered to a patient with breast cancer from a high risk family? Is breast conserving surgery contraindicated? Do you discourage or recommend use of oestrogen (contraceptive or replacement therapy) in high risk families?

We subdivided the women according to the following risk categories: Category A: moderately increased risk (15–25%); Category B: strongly increased risk (25–45%); Category C: mutation carriers (60–85%). Category C (60–85%) represents the estimated risks for *BRCA1* and *BRCA2* mutation carriers and category B (25–45%) the risks for first-degree relatives of affected patients from breast (ovarian) cancer families. The risk of Category A ranges from 15% (i.e. approximately twice the general population risk) to the lower risk limit of category B (25%). Most patients that are in category A are from families with a few cases of breast cancer and their risk is estimated using the widely used tables published by Claus [14].

RESULTS

Completed questionnaires were received from 16 centres in 9 countries (Sweden, Norway, U.K., Italy, Germany, Finland, France, Denmark and The Netherlands). With two exceptions, all centres recommended *surveillance of the breasts* if the lifetime risk of developing breast cancer is more than double the population risk (approximately 15%). The protocol recommended in most centres includes monthly self breast palpation, palpation by a physician every 6 months and annual mammography (Table 1). Sonography was performed only in patients with suspicious breast lesions. In several centres, magnetic research imaging (MRI) was performed within a research setting. The protocol suggested for women from different risk categories did not differ significantly. There was no agreement on the question pertaining to the age at which mammographic examinations should be started: two centres recommended starting from the age of 25 years, two centres advised beginning from the age of 25–30 years, four centres from the age of 30 years, three centres from the age of 35 years and five centres recommended starting mammographies 5 years before the earliest breast cancer diagnosis in the family. At 15 centres, the recommended interval between mammographies was 1 year. Six centres recommended an interval of 2 years for families with a low risk of breast cancer (< 25% risk, category A). In most countries the follow up of the high risk women was coordinated by highly specialised centres (Cancer Family Clinics or University Hospitals) (Table 2).

At most centres ($n = 12$), the option of *prophylactic mastectomy* was discussed only with women with a significantly increased risk of breast cancer (> 25%). Eight centres considered a prophylactic mastectomy in gene carriers.

Table 1. *Which surveillance protocol is recommended?*

	No. of centres
Breast	
Breast self examination	15
Examination by specialist	16
Mammography	16
Ovaries	
Gynaecological examination	15
Transvaginal sonography	16
CA-125	12

Table 2. Who coordinates the screening examinations?

	No. of centres
General practitioner	1
Specialist	
Cancer family clinic	13
University hospital	7
Breast cancer screening unit	5
Cancer institute	3
Local hospital	2

Almost all centres recommended *surveillance of the ovaries* in families with an identified *BRCA1* (15 centres) or *BRCA2* mutation (12 centres) or families with both breast and ovarian cancer cases (16 centres) (Table 3). Five centres also recommended surveillance of the ovaries in families with breast cancer only if this was diagnosed at an unusually young age. The protocol for follow up of the ovaries was similar in most centres, i.e. annual examination by a gynaecologist, transvaginal sonography and estimation of CA 125 (Table 1). The opinion at most centres was that examinations should be initiated at the age of 30–35 years and repeated every year.

At most centres, *prophylactic oophorectomy* was discussed as an option only in families with an identified *BRCA1* (15 centres) or *BRCA2* mutation (13 centres) and families with a combination of breast and ovarian cancer (13 centres). At 13 centres, prophylactic oophorectomy was recommended in families associated with a *BRCA1* mutation; at 10 it was recommended in *BRCA2*-associated families and at 8 centres in breast/ovary families.

Regarding the *surgical treatment* for a breast cancer patient from a predisposed family, twelve centres would perform a total (uni- or bilateral) mastectomy in those cases in which breast conserving surgery would be appropriate if the patient was not a member of a breast cancer family.

The recommendations on the use of oestrogen in high risk families are summarised in Table 4.

DISCUSSION

During the last 5 years, a large number of family cancer clinics have been established all over Europe. These multidisciplinary clinics are specialised in the counselling and genetic testing of those families that are at increased risk of developing cancer. Due both to the relatively high estimated prevalence of *BRCA-1* and *-2* mutations in the general population and also to the ample attention paid by the media to familial breast cancer, most relatives who visit such clinics are from breast cancer families.

Table 3. Surveillance of ovaries recommended?

	No. of centres
BRCA1 mutation carriers	15
BRCA2 mutation carriers	12
Breast/ovarian cancer families*	16
Breast cancer only families*	
With early age at onset (mean age < 55 years)	5
With late age at onset (mean age > 55 years)	1

*Family with at least three affected first-degree relatives.

Table 4. Recommendations for oestrogen use in high risk relatives from breast cancer families

	Number of centres		
	Yes	No	Unsure
Do you discourage use of contraceptives?	5	6	5
Do you discourage postmenopausal hormonal replacement therapy?	9	2	5
Do you recommend hormonal replacement therapy			
After bilateral ovariectomy at the age of 30–40 years?	8	4	4
After bilateral ovariectomy at the age of 30–40 years and bilateral mastectomy?	10	4	2

Surveillance of the breast

The minimal level of risk considered as an indication for surveillance is 15–20%, which is twice the general population risk. Ideally, the decision concerning the risk level at which surveillance is justified should be based on a cost-effectiveness analysis of surveillance of women from different risk categories, but the level of the risk alone might be sufficient to justify surveillance until such studies are available. The recommended surveillance procedures are similar in most centres (Table 1). There was no consensus on the age at which surveillance should be initiated. The risk of developing breast cancer before the age of 30 years reported by Easton is 3.2% [7]. The families included in this study were ascertained using strict criteria; and are hence highly selected. The real risk of developing breast cancer before the age of 30 years might be lower, a suggestion that is supported by the fact that in several ongoing prospective surveillance studies, no breast cancer has been detected below the age of 30 years [15]. On this basis and also in view of the low sensitivity of screening mammography among very young women, one might decide to initiate mammography from the age of 30 years. Another argument that might be used in the decision making is the possibility of induction of breast cancer by radiation if screening is begun at a very young age [16].

Most centres believe that high risk women need to be followed up in highly-specialised centres (i.e. cancer family clinics, University Hospitals). Future studies should reveal whether such centres are indeed able to maintain equally strict quality control procedures as centres with established screening programmes.

Prophylactic mastectomy

Although several reports suggest that surveillance leads to the detection of breast cancer in an earlier stage, they also reveal that the risk of dying of this cancer cannot be eliminated by surveillance [17, 18]. For this reason, at most centres, prophylactic mastectomy is discussed as an option in women with a substantially increased risk (> 25%). At half of the centres, this ultimate option is seriously considered in some mutation carriers. A recent study by Schrag and colleagues supported this option for carriers having a 85% breast cancer risk, as it revealed that the option of prophylactic mastectomy performed between the ages of 30 and 40 years led to a considerable gain of life expectancy (3.7–5.3 years) [19]. Schrag and colleagues assumed that an intensive surveillance programme would lead to a decrease in the

occurrence of lymph node-positive breast cancer from 43% in symptomatic cases, to 20% in screen-detected cases. If instead the results of the most recent study by Møller and associates (proportion of lymph node positive cancer of 13% in screen-detected cases) had been used, the gain in life expectancy due to prophylactic mastectomy would be lower [18]. One concern with regard to prophylactic surgery is that, after this procedure, breast tissue probably remains *in situ* and that there is still a risk of developing breast cancer even after the most 'complete' surgical technique (total mastectomy with the removal of the nipples). A recent study reported at the annual meeting of the American Association for Cancer Research indicated that prophylactic mastectomy in women at higher risk for breast cancer dramatically reduces their risk of developing this disease [20].

Surveillance of ovaries and prophylactic oophorectomy

Most centres recommend surveillance of the ovaries for carriers of *BRCA1* and *BRCA2* mutations and in relatives from breast cancer families that include cases of ovarian cancer. It is controversial whether surveillance of the ovaries should also be recommended for families with breast cancer only. Five out of the 16 centres recommend surveillance in families with an early age of onset. According to the Breast Cancer Linkage Consortium (data not shown), 33% of families with 4–5 cases of breast cancer diagnosed before the age of 60 years must be ascribed to *BRCA1*, and 9% to *BRCA2*. Assuming a 44% maximum risk of ovarian cancer in *BRCA1* [6] and a 27% maximum risk in *BRCA2* [11], the estimated ovarian cancer risk would be 18% (15 + 2.7%) for affected relatives from breast cancer only families and 9% for their relatives. The minimum risk which might justify surveillance of the ovaries is approximately 10–15% (i.e. ten times the general population risk). In conclusion, surveillance of the ovaries might be considered in breast cancer only families with an early age of onset, especially in affected relatives. If genetic testing in a breast cancer only family has not led to the identification of the mutation, the probability that the *BRCA1* or *BRCA2* gene has contributed to the disease is relatively low. In such families, the risk of developing ovarian cancer is much lower and the indication for surveillance is less strong.

The screening protocol appeared to be similar in all centres. Most centres recommend beginning surveillance from the age of around 30 years. It should be emphasised that the effectiveness of ovarian surveillance is completely unknown. Only a few reports suggest that surveillance might lead to the early detection of ovarian cancer [21, 22]. This uncertainty and the typical aggressive nature of ovarian cancer explain why, at most centres, prophylactic oophorectomy is discussed as a reasonable option in high risk women. It also explains why this option is recommended in proven gene carriers after completion of child bearing. A serious drawback of prophylactic oophorectomy is the incidence of peritoneal carcinoma after this procedure; this is reported in 2–11% of the cases [23].

The surgical management of breast cancer

Every single cell in the breast of a *BRCA1* or *BRCA2* carrier harbours the deleterious gene and is theoretically at high risk of becoming cancerous. This is reflected in the high incidence of a second cancer in the contralateral breast after primary breast cancer. This is the rationale for the recommendation that a total mastectomy be performed even in cases in which breast-conserving surgery is an appropriate alternative. Hence, in such cases, unilateral or bilateral mastectomy is recommended at 12 of the 16 centres. However, further studies are needed to establish whether radiotherapy that is usually performed after breast conserving surgery might prevent the development of a second cancer.

Oral contraceptives and hormone replacement therapy

There is general agreement that endogeneous oestrogens play an important role in the aetiology of breast cancer. There is also evidence that administration of oestrogens for therapeutic reasons have an effect on risk. The recently published meta-analysis of oral contraceptive breast cancer studies [24] indicated that of all aspects of oral contraceptive (OC) use, recent OC use is most strongly related to breast cancer risk; after cessation the increase in risk steadily diminishes to become undetectable 10 years after last use. With respect to postmenopausal oestrogen replacement therapy (ERT), it has been shown that long duration (> 5 years) and recent use are associated with an increased risk [25]. However, postmenopausal hormone therapy also has benefits including a decreased risk of osteoporosis and cardiovascular disease. In addition, several studies have consistently indicated that OC is protective against ovarian carcinogenesis.

The effect of oestrogen use on breast cancer risk in individuals with an inherited predisposition to breast cancer is completely unknown. This explains why a substantial number of responders were unsure about what should be recommended. From the centres that responded, a majority discouraged ERT in high risk relatives. In contrast, a majority recommended ERT in young women having surgical menopause with or without bilateral mastectomy. The choice for these women lies between a lower risk of osteoporosis and cardiovascular disease and less postmenopausal symptoms and an increased risk of breast cancer.

CONCLUSIONS

This report presents the results of an evaluation of the protocol used in the various centres for the surveillance and management of breast cancer families. The results reveal agreement on several parts of the protocol, but also conspicuous differences of opinion on other parts. It should be emphasised that most recommendations do not have a strong scientific basis and that future studies are urgently needed. Studies that might preferably be conducted on a European basis are an evaluation of the risk of cancer after prophylactic mastectomy and oophorectomy because such studies require a large number of cases. Also studies on gene-environment interaction in proven gene carriers should preferably be carried out as a Europe-wide effort. Careful education and counselling of patients and their relatives about all details of the disease, including the course of the disease with and without surveillance are, therefore, essential.

1. Newman B, Austin MA, Lee M, King M. Inheritance of human breast cancer: evidence for autosomal dominant transmission in high risk families. *Proc Natl Acad Sci USA* 1988, **8**, 3044–3048.
2. Hall JM, Lee MK, Newmann B, Anderson LA, Huevy B, King MC. Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 1990, **250**, 1684–1689.
3. Miki Y, Swensen J, Shattuck-Eidens D, *et al.* A strong candidate for the 17q-linked breast and ovarian cancer susceptibility gene *BRCA1*. *Science* 1994, **266**, 66–71.

4. Wooster R, Bignell G, Lancaster J, *et al.* Identification of the breast cancer susceptibility gene *BRCA2*. *Nature* 1995, **378**, 789–792.
5. Tavtigian SV, Simard J, Rommens J, *et al.* The complete *BRCA2* gene and mutations in 13q-linked kindreds. *Nat Genet* 1996, **12**, 333–337.
6. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in *BRCA1* mutation carriers. Breast Cancer Linkage Consortium. *Lancet* 1994, **343**, 692–695.
7. Easton DF, Ford D, Bishop DT. Breast Cancer Linkage Consortium. Breast and ovarian cancer incidence in *BRCA1* mutation carriers. *Am J Hum Genet* 1995, **56**, 265–271.
8. 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.
9. Schubert EL, Lee ML, Mefford HC, *et al. BRCA2* in American families with four or more cases of breast or ovarian cancer: recurrent and novel mutations, variable expression, penetrance, and the possibility of families whose cancer is not attributable to *BRCA1* or *BRCA2*. *Am J Hum Genet* 1997, **60**, 1031–1040.
10. Easton DF, Steele L, Fields P, *et al.* Cancer risks in two large breast cancer families linked to *BRCA2* on chromosome 13q12-13. *Am J Hum Gen* 1997, **61**, 120–128.
11. Ford D, Easton D, Stratton M, *et al.* Genetic heterogeneity and penetrance analysis of the *BRCA1* and *BRCA2* genes in breast cancer families. *Am J Hum Genet* 1998, **62**, 676–689.
12. Gayther SA, Warren W, Mazoyer S, *et al.* Germline mutations of the *BRCA1* gene in breast and ovarian cancer families provide evidence for a genotype-phenotype correlation. *Nature Genet* 1995, **11**, 428–433.
13. Gayther SA, Mangion J, Russell P, *et al.* Variation of risks of breast and ovarian cancer associated with different germline mutations of the *BRCA2* gene. *Nature Genetics* 1997, **15**, 103–105.
14. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. *Cancer* 1994, **73**, 643–651.
15. Møller P, Maehle L, Heimdal K, *et al.* Inherited breast carcinoma: prospective findings in 1194 women at risk. *Acta Oncol* 1996, **35**(Suppl. 8), 7–11.
16. 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.
17. Vasen HFA, Beex LVAM, Cleton FJ, *et al.* Clinical heterogeneity of hereditary breast cancer and its impact on screening protocols: the Dutch experience on 24 families under surveillance. *Eur J Cancer* 1993, **29A**, 1111–1114.
18. Møller P, Maehle L, Heimdal K, *et al.* Prospective findings in breast cancer kindreds: annual incidence rates according to age, stage at diagnosis, mean sojourn time, and incidence rates for contralateral cancer. *The Breast* 1998, in press.
19. Schrag D, Kuntz KM, Garbor JE, Weeks JC. 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.
20. Stephonson J. Study shows mastectomy prevents breast cancer in high-risk women. *JAMA* 1997, **277**, 1421–1422.
21. Bourne TH, Campbell S, Reynolds KM, *et al.* Screening for early familial ovarian cancer with transvaginal ultrasonography and colour blood flow imaging. *Br Med J* 1993, **306**, 1025–1029.
22. Dorum A, Kristensen GB, Abeler VM, Trop CG, Møller P. Early detection of familial ovarian cancer. *Eur J Cancer* 1996, **32A**, 1645–1651.
23. Tobacman JK, Tucker MA, Kase R, *et al.* Intraabdominal carcinomatosis after prophylactic oophorectomy in ovarian cancer prone families. *Lancet* 1982, **II**, 795–797.
24. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives; collaborative reanalysis of data on 53297 women with breast cancer and 100239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996, **347**, 1713–1727.
25. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy. *Lancet* 1997, **350**, 1047–1059.

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