PERGAMON

European Journal of Cancer 36 (2000) 1143–1148

European Journal of Cancer

www.ejconline.com

Familial breast cancer in southern Finland: how prevalent are breast cancer families and can we trust the family history reported by patients?

H. Eerola [a], C. Blomqvist [a,b], E. Pukkala [c], S. Pyrhönen [d], H. Nevanlinna [e,*]

[a] *Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland*
[b] *Department of Oncology, Uppsala University Hospital, Uppsala, Sweden*
[c] *Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland*
[d] *Department of Oncology and Radiotherapy, Turku University Hospital, Turku, Finland*
[e] *Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Haartmaninkatu 2, PL 140, 00029 HYKS, Finland*

Received 27 September 1999; received in revised form 21 March 2000; accepted 4 April 2000

Abstract

We evaluate the validity of the family history of breast cancer reported by the patient and the number of families and individuals at risk and potentially benefiting from surveillance. Family history of cancer was systematically screened in three different series of breast cancer patients. Breast cancer families were defined by the selection criterion of at least three first- or second-degree relatives with breast or ovarian cancer (including the proband) and their genealogy and cancer diagnoses were confirmed. Family history of breast or ovarian cancer was reported by approximately 30% of the patients and 7–9% were classified as breast cancer families. On average, there were 3.1 healthy female (age: 20–70 years) first degree relatives per family potentially at high risk. Index patients reported 87% of all confirmed diagnoses and the primary site was correct in 93–95% of the reported cases. The incompleteness and errors in accuracy should be considered in epidemiological studies and verification of the diagnoses is important when deciding clinical management.

Keywords: Breast neoplasm; Familial; Genetics

1. Introduction

Breast cancer is the most common malignancy affecting women worldwide, and in Finland, approximately 3200 new breast cancer cases are diagnosed annually among 2.6 million women [1]. One of the strongest risk factors for breast cancer is family history [2,3]. Epidemiological studies have shown increased breast cancer incidence in relatives of breast cancer patients compared with the general population, especially if breast cancer has been diagnosed at a young age [4,5] or if the patient has bilateral disease [5,6]. Genetic models have provided evidence for a rare autosomal dominant gene(s), with susceptibility to breast cancer [7,8]. Elevated risk for ovarian cancer has also been found among relatives of breast cancer patients [9,10] and a breast/ovarian cancer susceptibility gene(s) is (are) estimated to account for 7% of breast cancer cases and 10% of ovarian cancer cases in the general population [11]. Two major dominantly inherited genes predisposing to breast and ovarian cancer have been identified, *BRCA1* and *BRCA2* [12,13] with a high risk of early onset breast cancer and varying risk of ovarian cancer [14]. This has also made predictive diagnostic tests of cancer predisposition possible in some families.

However, selection of families to undergo genetic testing is based on the family history recalled by the patient. Furthermore, in many families no causative gene or mutation can be found and risk assessment is based solely on family history. A few study groups have assessed the accuracy of reported family history of breast cancer. It is considered to be quite precise especially among first degree relatives whilst less accurate

* Corresponding author. Tel.: +358-9-471-72841; fax: +358-9-471-74801.
E-mail address: heli.nevanlinna@hus.fi (H. Nevanlinna).

0959-8049/00/$ - see front matter
PII: S0959-8049(00)00093-9

data are achieved about breast cancer in second degree relatives [15–17] or about some other cancer sites [15–20]. Furthermore, false family histories have been documented with serious implications for risk assessment and clinical management [21]. Altogether, in the clinical family counselling the correct family history is critical in the risk estimation as well as treatment and follow-up decisions.

We report here the results of systematic screening for family history in three different series of breast cancer patients, and systematic confirmation of family history as well as cancer diagnoses within defined breast cancer families. The impact of these on family counselling and the clinical management of the breast cancer families is discussed.

2. Patients and methods

Breast cancer patients from three different series were interviewed for family history. The first two series, young patients (diagnosed before 40 years of age) and patients with bilateral disease, comprised incident cases diagnosed between 1985 and 1993 and referred to the Department of Oncology, Helsinki University Central Hospital (HUCH). Family history questionnaires ($n=348$) were sent and replies were received from 288 patients (83%). Of those, 170 (59%) were diagnosed before the age of 40 years and 118 (41%) with bilateral breast cancer. Patients diagnosed before the age of 40 years with bilateral cancer ($n=5$) were included in the young series of patients. In the third series of unselected patients (in terms of age and laterality) ($n=1282$), family history was systematically asked from all breast cancer patients visiting the Department of Oncology from 10 November 1993 to 10 November 1994, and from all new patients during the following 6 months.

Breast cancer families were identified by one uniform selection criterion: at least three first- or second-degree relatives (including proband) with breast or ovarian cancer in the family, irrespective of age (male relatives were excluded when calculating the degree of relationship for the criterion). The criterion was selected in order to reach all breast cancer cases having a familial background, not just individuals with high risk genes or early onset cases. The criterion was fulfilled by 16 (9%) young cases, 11 (9%) bilateral cases and 92 (7%) unselected cases. These series were partly overlapping as 14 of the young and bilateral patients were visiting our clinic during the collection of unselected patients as well. Five of these cases (4 unselected and 1 bilateral) were excluded as the reported information proved to be already incorrect at the beginning of the study and the families did not fulfil the criterion. Thus altogether 100 families were identified and included in further studies described below.

The genealogy of these 100 families was confirmed through church parish registries and the Population Register Centre. Population registration in church registries in Finland is documented as far back as the 16th century. Families were traced back as far as the first healthy parents of the oldest known breast or ovarian cancer generation and subsequently, information of all the descendants was acquired. Information from church parish registries included offspring, personal identification numbers and dates of death or emigration. Identification numbers have been given to all residents living in Finland since 1967 and when personal identification numbers were obtained, we acquired the dates and causes of death from the Statistics Finland office and Population Register Centre as well.

Cancer diagnoses of the patients and all traced relatives, including those not reported as having cancer ($n=7157$), were confirmed through hospital records of the Department of Oncology, HUCH and through the Finnish Cancer Registry. Cancer registration started in 1953 in Finland and presently, Finnish Cancer Registry contains data on cancer since 1953 with near complete coverage [22]. The data obtained from the registries were compared with data reported by patients in order to assess the validity of the reported cancers.

We determined potential healthy candidates for genetic counselling and presymptomatic screening in 99 families, with verified family and cancer diagnosis data. One family was excluded due to emigration. Potential candidates had to be alive, between 20 and 70 years old and first degree female relatives of breast or ovarian cancer patients. For the analysis, cancer information was updated to June 1997 and the ages of the relatives were calculated for the same year.

This study has been approved by the ethical committees of the Department of Oncology and the Department of Obstetrics and Gynaecology, HUCH and by the Ministry of Social Affairs and Health in Finland.

3. Results

Family history of breast or ovarian cancer was reported by 27–36% of the patients. 9% of the young, 8% of the bilateral and 7% of the unselected patients fulfilled the criterion of at least 3 affected patients with breast or ovarian cancer in the family (Table 1). Ovarian cancer cases were present in 19–23% of the families fulfilling the criterion (Table 2). Among the 88 families of the unselected patients, relatives with bilateral breast cancer cases were found in 23 (26%).

The accuracy of the information reported by the patients was studied in breast cancer families (Table 3). A total of 272 breast and ovarian cancer diagnoses of relatives were obtained in these families; including cases reported by the patients that were not possible to be

Table 1
Family history: number of families (%) in series of young, bilateral and unselected patients*

Series	No. of breast or ovarian cancer cases in families (proband included)						
	Total	⩾5[a]	⩾4[a]	⩾3[a]	2[a]	>1[a]	1[b]
Young (<40 years)	170	5 (3)	10 (6)	16 (9)	30 (18)	46 (27)	124 (73)
<35 years	59	1 (2)	2 (3)	7 (12)	12 (20)	19 (32)	40 (68)
Bilateral	118	2 (2)	5 (4)	10 (8)	32 (27)	42 (36)	76 (64)
Unselected	1282	16 (1)	42 (3)	88 (7)	281 (22)	369 (29)	913 (71)
<35 years	74	2 (3)	4 (5)	9 (12)	13 (18)	22 (30)	52 (70)
<40 years	182	5 (3)	9 (5)	16 (9)	32 (18)	48 (26)	134 (74)
<50 years	564	12 (2)	25 (4)	45 (8)	132 (23)	177 (31)	387 (69)
⩾40 Bilateral	112	3 (3)	4 (4)	9 (8)	33 (29)	42 (38)	70 (63)
⩾40 years/unilateral	988	8 (1)	29 (3)	63 (6)	216 (22)	279 (28)	709 (72)
<40 years/unilateral	169	5 (3)	9 (5)	16 (9)	28 (17)	44 (26)	125 (74)

*Data in families with less than 3 cases is based on patient reports.
[a] First- or second-degree relatives.
[b] No first- or second-degree relatives (series are partly overlapping).

confirmed, but omitting those reported incorrectly (details below). Of the 272 cases, 35 of the diagnoses included were unknown by the proband and were found only from registries. The index patients reported 100% of the first-degree relatives affected with breast or ovarian cancer, 99% of the second-degree relatives, but only 50% of the third- to fifth-degree relatives.

The proband identified correctly 237 (95%) out of 249 reported primary sites (thus, there were 12 (5%) incorrect diagnoses). However, 5 families excluded at the beginning of the study, contained an additional 10 reported affected relatives, and 5 of these were incorrect. Hence the actual percentage of incorrect diagnoses was 7%. Table 4 shows the 24 (10%) unconfirmed diagnoses reported by the patients. 22 (9%) cases were lost to follow-up. 2 (1%) of the reported ovarian cancer cases were actually diagnosed as undefined abdominal cancers.

Potential healthy relatives at risk and thus candidates for genetic counselling and presymptomatic cancer screening were determined in 99 families (Table 5). There were 110 healthy first-degree female relatives of breast or ovarian cancer patients (age: 35–50 years) in the families, 1.1 individuals per family. In the age group 20–70 years, there were 307 healthy first-degree relatives i.e. 3.1 individuals per family.

Table 2
Family history of ovarian cancer (ovca) among breast cancer families

Series	Number of families[a]			
	Total	With ovca (%)	One ovca	Two ovca
Young	16	3 (19)	2	1
Bilateral	10	2 (20)	2	0
Unselected	88	20 (23)	16	4

[a] ⩾3 breast or ovarian cancer patients within a family.

4. Discussion

The Finnish population registration and cancer registration offered us the possibility to construct full pedigrees with very reliable cancer data. We did not have to rely on information reported by the patients, and precise information about diagnoses and ages of onset could be obtained. Also distant relatives not sharing so much common genetic information but having less confounding environmental risk factors, could be traced

Table 3
Number of relatives with breast or ovarian cancer reported by patients: accuracy of patient reports

Relationship of cases to patient	Total no. of cases in families[a]	No. of cases reported by patients	Cases reported correctly	% of cases reported (sensitivity)	% of cases reported correctly
First-degree	94	99	94	100	95
Second-degree	110	114	109	99	96
Third-degree	49	32	30	61	94
Fourth-degree	13	3	3	23	100
Fifth-degree	6	1	1	17	100
Total	272	249	237	87	95

[a] Unconfirmed cases included.

Table 4
Incorrectly reported or unconfirmed cases

	n (%)
Total no. of reported diagnoses	249 (100)
Incorrect or unconfirmed diagnoses	36 (14)
Incorrect diagnoses	12 (5)
Non-existent malignancy quoted	4 (2)
Mistaken site of malignancy	8 (3)
Unconfirmed diagnoses	24 (10)
Pathology report unclear	2 (1)
Lost to follow-up	22 (9)
Abroad	12 (5)
Died before 1953[a]	4 (2)
Information lost or inaccurate	6 (2)

[a] Before founding of Finnish Cancer Registry.

Table 5
Potential female candidates for genetic counselling, diagnostic testing or presymptomatic screening

Cases and relatives in 99 families	Individuals	Individuals/ family
Breast or ovarian cancer cases	369	3.7
First-degree female relatives (healthy)	404	4.1
Age 20–70 years	307	3.1
Age 35–70 years	233	2.4
Age 35–50 years	110	1.1

in contrast to most of the previous family history studies which are usually based on first degree relatives. Thus, we could obtain reliable data of the number of families, individuals at risk and the accuracy of the information reported by the patients.

In the present study, family background of breast cancer appeared relatively common as approximately 30% of patients reported at least one first- or second-degree relative with breast or ovarian cancer in all series of patients. This is in agreement with other studies where 30–35% of patients have reported family history of breast cancer among first- or second-degree relatives [23,24].

Breast cancer families were defined by the criterion of at least 3 or more first- or second-degree relatives affected with breast or ovarian cancer in the family. The criterion identified 7–9% of the cases in the different series of patients which is exactly in accordance with the estimation of 7–9% of all breast cancer being caused by hereditary predisposition [2,11]. If we define families with a more strict criterion of 4 or more cases, the proportions would be 3–6% depending on the series of patients. The proportion was highest if the probands age of onset was under 40 years of age or if the breast cancer was bilateral, in accordance with earlier epidemiological studies [4–6]. It may be that cases not participating in this study and answering the questionnaires about family history have not family background of the disease. If that is the case the proportion of breast cancer families identified here would be approximately one percentage unit lower.

As breast cancer is a common disease, many cases may be clustered in the families by chance, not forgetting the influence of shared environmental risk factors. However, even the families with less affected cases but fulfilling this criterion are worried and will probably be the major fraction of families needing genetic counselling. Criteria for referral to genetic counselling and diagnostic testing as well as presymptomatic screening or clinical trials is a complex question and needs to be carefully considered. Mutations in the known susceptibility genes *BRCA1* and *BRCA2* account for the majority of the early onset families with several breast cancer patients and ovarian or male breast cancer cases [14], providing means to identify high risk individuals in such families. However, the situation is complicated by the identification of *BRCA1* and *BRCA2* mutations in patients with few affected relatives or without any family history [25,26]. Furthermore, while such mutations may be highly prevalent in founder populations like in Iceland and among the Ashkenazi Jews, accounting for a large fraction of all breast cancer (10–12%) [27,28], in other, outbred populations these mutations may account for less than 3% [25]. Several studies have also suggested that a majority of families with 5 or fewer cases of female breast cancer only is not due to either *BRCA1* or *BRCA2* [14,33]. Susceptibility alleles in other yet unknown breast cancer genes may confer risks lower than those conferred by these two genes but may be more common in the populations [14,25]. Overall, estimating the genetic susceptibility in the family as well as the need and possibility of genetic testing or presymptomatic screening is based on the family history of the disease.

In this study, the information reported by the patients proved to be quite accurate. Only approximately 5–7% of all reported diagnoses among breast cancer families were found to be incorrect. Reported diagnoses were considered incorrect if an individual had an identification number but could not be found in the cancer registry data or had some other cancer diagnosis. These relatives may have had breast or ovarian cancer before the cancer registry was founded and the percentage of incorrect diagnoses may thus be even smaller. However, 5 families (5%) were originally excluded due to incorrect reports of diagnoses. Thus, we consider verification of the cancers important when making decisions about patient management based on family history. Diagnostic testing, intensive surveillance, chemoprevention or even prophylactic operations may extensively affect the quality of life of these women and should be based on the most reliable information available.

Accuracy of the information reported by the patient has previously been studied by a few study groups [15–21].

In the studies by Love and colleagues [15] (USA) and Theis and associates (Canada) [16], the information about breast cancer in first-degree relatives was found to be 94–99% accurate which is similar to our finding where reported information was 95% accurate. In our study, the percentage was similar in all degrees of relationship. If the proband reported an affected family member, near or distant relations, it was generally true. In the study by Love and coworkers, this percentage decreased with increasing remoteness of the relative. Love and coworkers and Theis and associates found that reported breast cancers among second- or third-degree relatives were only approximately 85–88% accurate while no information on more distant relatives was available. In some studies, ovarian cancers are reported less accurately and mixed with some other cancers in the pelvic area [16,18,20]. In our study, 2 of the 29 reported ovarian cancers, that we were able to confirm, were actually uterine cancers, others were identified correctly.

Sensitivity of reporting cancer cases has rarely been studied elsewhere [19,20]. Kerber and Slattery [20] compared the information from interviews of 125 colon cancer cases and 206 controls with data from the Utah Cancer Registry. They found 83% sensitivity in reporting breast cancer and 60% sensitivity in reporting ovarian cancer among first-degree relatives. However, the study was carried out with unselected patients compared with our study of defined breast cancer families. It is possible that individuals in high risk cancer families are more open about cancer in the family, or there may be cultural differences in the tendency to hide a malignant diagnosis from other family members. In a Canadian study [19], 197 ovarian cancer cases and 210 controls missed altogether 0.8% malignancies of first-degree relatives and 3.8% malignancies of second-degree relatives.

Sensitivity of reported cancer data on more distant relatives has not been studied previously. In the present study, the cancer cases among distant relatives; third- (e.g. cousins) and fourth-degree relatives were not well known by the proband, in contrast to first-degree relatives. The probands knew only 61% of cancer cases among third-degree relatives and 23% among fourth-degree relatives. However, this information on cancers of third-, fourth- and fifth-degree relatives, may also be important for risk estimation in the family and when considering diagnostic testing and cancer surveillance. Some families may be excluded from testing or screening procedures because of an unawareness of the diseases in the families. Patients with suspicious family background could be encouraged to discuss cancer in the family.

The number of women identified here in the breast cancer families as being potentially at high risk (3.1 individuals aged 20–70 years per family) is similar to that found in a study by Narod and colleagues [9]. Although breast cancer is quite common, the hereditary breast cancer cases account for only a minor fraction of all cases. The number of healthy relatives at highest risk who could especially benefit from the recommended presymptomatic screening or preventive measures [29] is not high compared with the population screening programmes of specific age groups already carried out in many countries with public healthcare systems. For example in Helsinki with a population of 0.5 million, approximately 380 new breast cancer cases are seen each year [1]. Based on this study, 26 of these would be familial and in their families there would be 28 potential new screening candidates per year. This number would be cumulative in the first years but slowly, when most of the families are found, the individuals would belong to the same families. Altogether it is a small number compared for example with the 19 800 women aged 50–58 years who were invited to mammographic screening in 1997.

In summary, family history of breast and ovarian cancer is used to estimate the probability of a family harbouring a cancer predisposing mutation [30]. The availability of diagnostic testing for *BRCA1* and *BRCA2* cancer predispositions has made it possible to identify carrier families and in those, individuals at highest risk. However, a large proportion of breast cancer families is not explained by these two genes, or mutations can not be found [14,31–33]. In those cases, risk estimation remains based on family data alone. Correct identification of families and relatives at high risk is an important basis for the counselling, diagnostic testing and the clinical management of the families.

Acknowledgements

The authors wish to thank the Finnish Cancer Registry for the cancer data and Dr Risto Sankila, Dr Timo Muhonen, Dr Katja Aktan-Collan and Nurse Minna Merikivi for their kind help. The patients' participation in the study is gratefully acknowledged. Grants: The Cancer Society of Finland, Clinical Research Fund of Helsinki University Central Hospital, The Ida Montin Fund.

References

1. Finnish Cancer Registry. Cancer Incidence in Finland 1995. *Cancer Statistics of the National Research and Development Centre for Welfare and Health*. Helsinki, Cancer Society of Finland, 1997, Publication No. 58.
2. Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN. Proportion of breast cancer cases in the United States explained by well-established risk factors. *J Natl Cancer Inst* 1995, **87**, 1681–1685.
3. Dupont WD, Page DL. Breast cancer risk associated with proliferative disease, age at first birth, and a family history of breast cancer. *Am J Epidemiol* 1987, **125**, 769–779.

4. Claus EB, Risch NJ, Thompson WD. Age at onset as an indicator of familial risk of breast cancer. *Am J Epidemiol* 1990, **131**, 961–972.
5. Tulinius H, Sigvaldason H, Olafsdottir GH, Tryggvadottir L. Epidemiology of breast cancer in families in Iceland. *J Med Genet* 1992, **29**, 158–164.
6. Houlston RS, McCarter E, Parbhoo S, Scurr JH, Slack J. Family history and risk of breast cancer. *J Med Genet* 1992, **29**, 154–157.
7. Claus EB, Risch N, Thompson D. Genetic analysis of breast cancer in the cancer and steroid hormone study. *Am J Hum Genet* 1991, **48**, 232–242.
8. 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* 1988, **85**, 3044–3048.
9. Schildkraut J, Risch N, Thompson W. Evaluating genetic association among ovarian, breast and endometrial cancer, evidence for a breast/ovarian cancer relationship. *Am J Hum Genet* 1989, **45**, 521–529.
10. Narod SA, Madlensky L, Bradley L, *et al*. Hereditary and familial ovarian cancer in Southern Ontario. *Cancer* 1994, **74**, 2341–2346.
11. Claus EB, Schildkraut JM, Thompson WD, Risch NJ. The genetic attributable risk of breast and ovarian cancer. *Cancer* 1996, **77**, 2318–2324.
12. Miki Y, Swensen J, Shattuck-Eidens D, *et al*. A strong candidate for the breast and ovarian cancer susceptibility gene *BRCA1*. *Science* 1994, **266**, 66–71.
13. Wooster R, Bignell G, Lancaster J, *et al*. Identification of the breast cancer susceptibility gene *BRCA2*. *Nature* 1995, **378**, 789–792.
14. Ford D, Easton DF, 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.
15. Love RR, Evans AM, Josten DM. The accuracy of patients reports of a family history of cancer. *J Chron Dis* 1985, **38**, 289–293.
16. Theis B, Boyd N, Lockwood G, Tritchler D. Accuracy of family cancer history in breast cancer patients. *Eur J Cancer Prev* 1994, **3**, 321–327.
17. Douglas FS, O'Dair LC, Robinsson M, Evans DGR, Lynch SA. The accuracy of diagnoses as reported in families with cancer, a retrospective study. *J Med Genet* 1999, **36**, 309–312.
18. Gladstone A, Adatto P, Cunningham J, *et al*. Family history of cancer in patients with glioma, a validation study of accuracy. *J Natl Cancer Inst* 1998, **90**, 543–544.
19. Koch M, Gaedke H, Jenkins H. Family history of ovarian cancer patients, a case–control study. *Int J Epidemiol* 1989, **18**, 782–785.
20. Kerber RA, Slattery ML. Comparison of self-reported and database-linked family history of cancer data in a case–control study. *Am J Epidemiol* 1997, **146**, 244–248.
21. Kerr B, Foulkes WD, Cade D, *et al*. False family history of breast cancer in the family cancer clinic. *Eur J Surg Oncol* 1998, **24**, 275–279.
22. Teppo L, Pukkala E, Lehtonen M. Data quality and quality control of a population-based cancer registry. *Acta Oncol* 1994, **33**, 365–369.
23. Lynch HT, Watson P, Conway T, Fitzsimmons ML, Lynch J. Breast cancer family history as a risk factor for early onset breast cancer. *Breast Cancer Res and Treat* 1988, **11**, 263–267.
24. Thompson WD. Genetic epidemiology of breast cancer. *Cancer* 1994, **74**, 279–287.
25. Peto J, Collins N, Barfoot R, Seal S, *et al*. Prevalence of *BRCA1* and *BRCA2* gene mutations in patients with early-onset breast cancer. *J Natl Cancer Inst* 1999, **91**, 943–949.
26. Hopper J, Southney M, Dite G, *et al*. Population-based estimate of the average age-specific cumulative risk of breast cancer for a defined set of protein-truncating mutations in *BRCA1* and *BRCA2*. *Cancer Epidemiol, Biomarkers and Prev* 1999, **8**, 741–747.
27. Thorlacius S, Struewing J, Hartge P, *et al*. Population-based study of risk of breast cancer in carriers of *BRCA2* mutations. *Lancet* 1998, **352**, 1337–1339.
28. Warner E, Foulkes W, Goodwin P. Prevalence and penetrance of *BRCA1* and *BRCA2* gene mutations in unselected Ashkenazi Jewish women with breast cancer. *J Natl Cancer Inst* 1999, **91**, 1241–1247.
29. Vasen HFA, Haites NE, Evans DGR, *et al*. Current policies for surveillance and management in women at risk of breast and ovarian cancer, a survey among 16 European family cancer clinics. *Eur J Cancer* 1998, **34**, 1922–1926.
30. Parmigiani G, Berry DA, Aguilar O. Determining carrier probabilities for breast cancer-susceptibility genes *BRCA1* and *BRCA2*. *Am J Hum Genet* 1998, **62**, 145–158.
31. Serova OM, Mazoyer S, Puget N, *et al*. Mutations in *BRCA1* and *BRCA2* in breast cancer families, are there more breast cancer-susceptibility genes? *Am J Hum Genet* 1997, **60**, 486–495.
32. Vehmanen P, Friedman LS, Eerola H, *et al*. Low proportion of *BRCA1* and *BRCA2* mutations in Finnish breast cancer families, evidence for additional susceptibility genes. *Hum Mol Genet* 1997, **6**, 2309.
33. Schubert EL, Lee MK, 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 possibility of families whose cancer is not attributable to *BRCA1* or *BRCA2*. *Am J Hum Genet* 1997, **60**, 1031–1040.