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The *BRCA1* syndrome and other inherited breast or breast–ovarian cancers in a Norwegian prospective series

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Abstract

Inherited breast cancer is a heterogenous group of diseases. We examined this heterogeneity in a prospective series of inherited breast and ovarian cancers, previously demonstrated to include 84% of inherited cancers. Ninety-two tumours (65 breast and 27 ovarian) in 82 patients from 70 kindreds were prospectively diagnosed. Fifteen of the breast cancers were *in situ*, 50 were infiltrating. 40 (49%) of the 82 women carried a *BRCA1* mutation, whereas no mutation in *BRCA2* was found. Approximately, two-thirds of the *BRCA1* mutation carriers had one of the four most frequent Norwegian founder mutations. Ninety-five per cent of the epithelial ovarian cancers occurred in *BRCA1* mutation carrying women versus 38% of infiltrating breast cancers and 7% of carcinoma *in situ* of the breast. The *BRCA1* syndrome was phenotypically distinct with invasive, high grade, oestrogen receptor-negative breast cancers and epithelial ovarian cancers. Non-*BRCA1/2* inherited breast cancers included carcinoma *in situ* and lobular carcinoma and were frequently bilateral. Non-*BRCA1/2* inherited breast cancer is not associated with epithelial ovarian cancer and in breast cancers has distinct biological characteristics, indicating that the different subgroups of inherited breast cancer may need different healthcare services.

Keywords: *BRCA1*; *BRCA2*; Inherited; Breast cancer; Ovarian cancer; Oestrogen receptor; Epidemiology

1. Introduction

A number of genes may, when mutated, predispose to inherited breast cancers. All of them predispose to cancers in other organs as well. This is so for *TP53* and *PTEN* underlying the clinically recognised Li-Fraumeni and Cowden's multi-organ cancer syndromes [1,2]. The inherited breast–ovarian cancer syndrome is caused by *BRCA1* and *BRCA2* mutations [3]. Recent data indicate that the *BRCA1* syndrome includes histopathologically distinct inherited breast cancers [4–7]. Most of the knowledge on inherited breast cancers has been derived from retrospective series of highly selected families which may include selection bias for some of the results obtained. Analyses of prospective series may verify previous findings.

We have previously reported how we established criteria to identify women at risk for inherited breast and/or ovarian cancer [8]. Specificity of these criteria are unknown. The women were subjected to close follow-up. Ovarian cancer continued to occur in breast–ovarian cancer kindreds only [9]. Breast cancer continued to occur in the high-risk group, 84% of the prospectively observed cases were in excess of what was expected to occur by chance and were assumed to be genetically caused [10]. We could therefore use the group of prospectively demonstrated cancers for further studies and consider them to be inherited cancers with an 84% specificity. We report here the results of *BRCA1* and *BRCA2* mutation analyses and characteristics of the

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[1] List of group members can be found in the Appendix.

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first prospectively detected 92 tumours from 82 patients belonging to 70 breast cancer kindreds.

2. Patients and methods

Healthy women were selected on a national basis, self referred following attention in media or referred from physicians. They were included and classified according to family history of breast and/or ovarian cancer as previously described and subjected to follow-up aiming at early diagnosis [8,10].

Women included for breast cancer follow-up had no present or previous sign or symptom of breast cancer. Women included for ovarian cancer follow-up had no present or previous sign of ovarian cancer.

Women were included for breast cancer follow-up when having:

- Four affected family members with breast cancer who were first or second degree relatives, or
- Two affected family members with breast cancer who were first degree relatives or second degree relatives related through a male, both $\leqslant 55$ years at diagnosis, or
- One affected family member with bilateral breast cancer $\leqslant 60$ years of age, or
- One affected family member with breast and another cancer $\leqslant 60$ years of age, or
- One first degree relative with breast cancer $\leqslant 50$ years of age.

Women were included for breast and ovarian cancer follow-up when having

- One relative with ovarian cancer and one relative with breast cancer $\leqslant 60$ years of age, both of them being first degree relatives or second degree relatives through a male, or
- One first degree relative or second degree relative through a male with both ovarian and breast cancer, the breast cancer diagnosed $\leqslant 60$ years of age, or
- $\leqslant$Two first degree relatives with ovarian cancer.

Pedigree structure was obtained and all diagnoses were verified in the hospital files or the National cancer register whenever possible. All women were offered genetic counselling.

For breast cancer, the follow-up programme was clinical + mammographic examination annually from 35 to 55 years of age and from 25 years of age in families with early onset of disease. Examination was every second year after the age of 55 years. In 1997, this was changed to annual examination from 30 to 60 years of age, thereafter (screening) mammography every second year. The clinical examinations were to be supplemented with ultrasonography, aspiration cytology or surgical biopsy whenever necessary.

For ovarian cancer, the follow-up programme included transvaginal ultrasonography and determination of CA125 in the serum annually from 25 years of age.

All Norwegian hospitals and outpatient clinics diagnosing breast cancer participated in the follow-up examinations. The programme had been accepted as health service, the results were stored in the medical files and the patients received medical treatment as appropriate. Informed consent was obtained for mutation analyses. The present report includes all prospectively diagnosed cases of breast and ovarian cancers diagnosed on follow-up from December 1991 until December 1999. Patients described in previous reports [10,11] are also included in the present study.

2.1. Tumour classification

As all tumours had been recently diagnosed in the Norwegian healthcare system, breast cancers had been classified as lobular (L) or ductal (D), and as carcinoma *in situ* (CIS) or infiltrating cancers (Ca) with (N+)/ without (N−) nodal spread. Infiltrating cancers were measured for the longest diameter, and scored for the presence/absence of oestrogen (ER) and progesterone (PgR) receptors. DCa were scored for histopathological grade. Ovarian cancers were classified as epithelial International Federation of Gynecology and Obstetrics ((FIGO) stage I–IV), borderline or others. Information was extracted from the medical files. Age at diagnosis was recorded for each tumour.

2.2. Mutational analysis

Initially, affected women were analysed for the two most frequently occurring *BRCA1* mutations, 1675delA and 1135insA. If negative for these mutations, the whole coding region of *BRCA1* was screened using the protein truncation test (PTT) of exon 11 and denaturing high-performance liquid chromatography (DHPLC) of exons 2–10, 12–24, including also the first 300 bp of exon 11, as described in Refs. [12,13]. If negative for *BRCA1*, the whole coding region of *BRCA2* was screened using PTT for exons 10 and 11, and DHPLC for exons 2–9 and 12–27, including also the first 300 bp of exons 10 and 11 [12,13]. Samples with truncated PTT bands or aberrant DHPLC chromatograms were sequenced, using a new polymerase chain reaction (PCR) product as a template [12].

2.3. Statistics

Associations and differences were analysed by the SYSTAT™ 9 PC computer program with Fisher's

Exact P analysis and t-test or Kolmogorov–Smirnov test between groups, as appropriate.

3. Results

40 out of the 82 (49%) women with prospectively detected cancers had *BRCA1* truncating mutations (Table 1). The four most frequent Norwegian founder mutations accounted for 27 (68%) of the 40 mutation-carrying women. No *BRCA2* mutation was found. The 40 mutation carriers developed 42 tumours, compared with 50 tumours in 42 non-carriers ($P=0.08$).

Sixty-five breast tumours were found in 56 women, classified as 15 CIS (23%) and 50 Ca (77%). Twenty-two out of 27 ovarian cancers (81%) were epithelial. Tumour type and mutation status are given in Table 2. All but one (95%) of the epithelial ovarian cancers were found in *BRCA1* mutation carriers, compared with 19/50 (38%) of breast Ca and 1/15 (7%) of CIS ($P<0.01$ between any group).

The distribution of probabilities of detecting a mutation were calculated by the BRCAPRO algorithm [14] as the sum of the probabilities to detect a *BRCA1* or a *BRCA2* mutation. The family history indicated a very high probability for mutations in the patients who later were demonstrated to carry mutations. The mutation negative patients clearly had a bimodal distribution compatible with a mixed population of dominantly inherited cancer with high penetrance and some sporadic cancers without a strong family history. The size of this putative sporadic group was in keeping with our previous finding [10] that 16% of the infiltrative breast cancers were expected sporadic cancers that occur by chance. Considering mutation negative women with CIS separately, 7/14 had a probability for mutation of more than 50%, 7/14 a probability of less than 50%.

Among the breast cancers, 19 DCa were ER-positive and 19 were PgR-positive. Seven tumours were lobular. 9 women contracted bilateral breast cancer during the study. One LCIS and one DCaN− were detected at contralateral prophylactic surgery following prospectively detected DCaN− tumour in the one breast. Three had had ovarian cancer before inclusion.

Presence of ER was strongly associated with presence of PgR ($P=0.000$). Seventeen (89%) out of 19 breast cancers in mutation carriers were ER-negative. Breast cancers in mutation carriers were of high histopathological grade compared with non-carriers. In mutation noncarriers, presence of ER was associated with low/medium grade. Details are given in Table 3. High-grade breast tumours were larger in size ($P=0.02$) than low/medium grade tumours.

The trend that mutation carrying women contracted breast cancer at a lower age than noncarriers ($P=0.09$), disappeared when considering the first breast cancer only. The underlying observation was that 1/19 (5%) mutation carriers contracted bilateral cancers, versus 8/37 (22%) of non-carriers ($P>0.10$).

7 women contracted bilateral ductal breast cancers. Stage and grade for first and second cancers are given in Tables 4 and 5. 2 women had bilateral cancers including at least one lobular cancer. One LCIS was detected at prophylactic contralateral mastectomy in a mutation-

Table 1
BRCA1 mutations detected

Mutation	Number with mutation
1675delA	11
3347delAG	6
1135insA	5
816delGT	5
5194-2a > c	2
913delCT	1
2677ins356	1
2988C > T	1
3203del11	1
3297G > T	1
3450delCAAG	1
3726C > T	1
4148delTCAA	1
5166G > T	1
5382insC	1
5630A > G	1
Total	40

Table 2
Tumour type and mutation status

	CIS BC	CaN− BC	CaN+ BC	Epithelial OC	Borderline OC	Other OC
Mut+	1	14	5	21	1	0
Mut−	14	25	6	1	3	1[a]

BC, breast cancer; OC, ovarian cancer; N−, node-negative; N+, node-positive; CIS, carcinoma *in situ*; Ca, infiltrating cancers; Mut+, presence of mutation; Mut−, absence of mutation.
[a] Granulosacell tumour.

Table 3
Associations between germ-line *BRCA1* mutation, histopathological grade and presence of oestrogen receptor in infiltrating breast cancer tumours

	Mutation−	Mutation+	Oestrogen receptor−	Oestrogen receptor+
Grade 1–2	19	5	4	8
Grade 3	9	13[a]	14	1[b]
Oestrogen receptor−	13	17		
Oestrogen receptor+	17	2[c]		

[a] Mutation± versus Grade, $P=0.008$
[b] Receptor± versus Grade, $P=0.001$
[c] Mutation± versus Receptor±, $P=0.001$.

Table 4
Stage for first and second tumour in the 7 women contracting bilateral ductal breast cancer during the study

	First tumour	
Second tumour	CaN−	CaN+
CIS	1	1
CaN−	4[a]	
CaN+		1

CIS, carcinoma *in situ*; CaN−, infiltrating cancer node-negative; CaN+, infiltrating cancer node-positive.
[a] The one mutation carrier had two CaN− tumours.

Table 5
CIS or Grade for first and second tumour in the 7 women developing bilateral ductal breast cancer during the study

	First tumour	
Second tumour	Ca grade 2	Ca grade 3
CIS	1	
Ca grade 2	2	
Ca grade 3		4[a]

CIS, carcinoma *in situ*; Ca, infiltrating cancer.
[a] The one mutation carrier had two Ca grade 3.

negative woman with a family history including male breast cancer. Her first tumour was a high grade, receptor-negative DCaN−. The other patient was also mutation-negative and had bilateral LCIS diagnosed on follow-up. 5 of the 6 women with lobular breast cancers, were mutation negative ($P > 0.10$).

One woman with a *BRCA1* mutation contracted borderline ovarian cancer after she had been diagnosed with a DCaN− breast cancer in the study. No woman experienced breast cancer after ovarian cancer in the observation period. 10 women who contracted ovarian cancer had had breast cancer before inclusion. Out of five ovarian epithelial ovarian cancers detected at prophylactic surgery, three were FIGO I–II and two were FIGO III–IV.

4. Discussion

Our activity covered the whole nation and included all hospitals diagnosing breast cancers. The distribution of probabilities for dominantly inherited cancer with high penetrance in the families, left little space for low-penetrant mutations to cause inherited breast cancers, while the inclusion criteria used were designed to select such families as well. Under this interpretation, we could proceed to describe the characteristics of both the mutation-carrying groups *and* the inherited breast cancers *not* caused by *BRCA1* or *BRCA2*, and arrived at the following main conclusions.

1. *BRCA1* mutation carriers account for close to all inherited epithelial ovarian cancers, and for approximately one-third of inherited breast cancers. The majority of the *BRCA1* cancers were accounted for by the four Norwegian founder mutations. The *BRCA1* syndrome includes infiltrating, high-grade, receptor-negative, ductal breast cancer and epithelial ovarian cancer. This result is in keeping with previous reports, with the addition that we could exclude CIS which was infrequently seen in the mutation carriers as opposed to the remaining part of the series.
2. *BRCA2* mutations as demonstrable with the employed techniques have no significant occurrence in the population. A few *BRCA2* founder mutations so far not detected may account for some of the inherited breast cancers, but not ovarian cancers because of the lack of demonstrated epithelial ovarian cancers without *BRCA1* mutations. None of the pedigrees indicated Cowden's or Li-Fraumeni syndromes.
3. Non-*BRCA1/2* inherited breast cancers account for over half of the inherited breast cancers, include CIS and lobular cancer, are frequently bilateral, and may include borderline ovarian cancers. Less than half of the infiltrating cancers were high grade and receptor-negative, more than half were low-medium grade and receptor-positive. In addition to sporadic cancers expected to create heterogeneity in the non-carrier group, there was obviously room for more than one non-*BRCA1/2* breast cancer syndrome. Numbers were small and we did not analyse the series further for clusters. A substantial fraction was probably caused by highly penetrant mutations, and this was so not only for women with Ca, but also for women with CIS. The conclusions are in keeping with previous reports [7], with the addition that we could include CIS and the notion of frequent bilateral cancers compared with the *BRCA1* syndrome, and give relative prevalences for each parameter obtained.

Multiple primaries, and especially bilateral tumours in paired organs, are considered clinical signs of inherited cancers — see, for example, the two-hit model for carcinogenesis which was derived from the distribution on unilateral and bilateral retinoblastomas. Our finding of breast–ovarian cancers as a clinical expression of *BRCA1* mutations is in keeping with this concept. The lack of *BRCA1/2* germline mutations in most of the bilateral ductal carcinomas — and in both bilateral breast cancers including lobular carcinomas — strongly supports the hypothesis that a substantial number of the non-mutation carriers in our series indeed had inherited cancers. The phenotypical differences between the

verified *BRCA1* mutation carriers and non-carriers make low sensitivity in our mutation testing unlikely — the lower our testing sensitivity putatively was, the weaker the associations were expected to be. In addition, most non-carriers belonged to large kindreds compatible with autosomally, dominantly-inherited breast cancer with a high penetrance (data not shown).

BRCA1 and *BRCA2* were examined using the same techniques. We have previously published that with these techniques we are capable of demonstrating *BRCA2* mutations [12]. It is not reasonable to believe that we have overlooked a mutational spectrum in *BRCA2* comparable with what we found in *BRCA1*. On the contrary, we find it reasonable to assume that the prevalence of *BRCA1* mutations found in the epithelial ovarian cancers (95%) may indicate the sensitivity of our techniques for mutation detection in *BRCA1* as well as in *BRCA2*. The conclusion is that possibly more than half of the population burden of dominantly-inherited high-penetrant breast cancer is not accounted for by *BRCA1/2*, while close to all epithelial ovarian cancers are accounted for by *BRCA1* alone.

Iceland — a population partly derived from Norway — has a different situation with a dominating *BRCA2* founder mutation [15]. The Swedish population has a distribution of *BRCA1* and *BRCA2* mutations that differs from both Norway and Iceland [12]. . We have previously discussed that one cause of the genetic heterogeneity in the North European populations is the population breakdown during the Bubonic plagues and the rapid expansion thereafter — a typical background for genetic drift. This leads to the conclusions that population prevalences have to be established in all distinct ethnic groups and in all geographical areas to tailor health services to the specific population needs.

Within the group of women at risk for inherited breast cancer, *BRCA1* and non-*BRCA1* carriers have been recognised to need different healthcare with regard to the risk for ovarian cancer [16]. The present report adds to the literature indicating that *BRCA1* breast cancers are biologically different from other breast cancers [4,6,7] and may need special healthcare for the breast cancer risk as well [17]. The challenge is to design studies suitable for uncovering both the genetic heterogeneity and the effect of interventions simultaneously. It is neither justified nor possible to randomise high-risk women to not receive healthcare. We are left with the option of open multicentre trials without randomised control groups. Power analyses indicate that international collaborative studies are necessary to achieve results within a reasonable time frame.

Two receptor-positive, low-grade infiltrating breast cancers without spread were diagnosed in non-mutation carrying women aged 39 and 59 years, both belonging to kindreds with *BRCA1*-associated breast cancer (with 3297G > T and 3347delAG mutations, data not shown). We have previously reported that clusters used to identify *BRCA1* kindreds included breast cancer patients without mutation (phenocopies) [18]. Numbers are insufficient to address these problems statistically, but we find them indicative of non-*BRCA1/2* genetic factors operating in some of our *BRCA1* breast cancer kindreds. These observations may indicate the presence of modifying factors operating in *BRCA1* kindreds — manifesting themselves as capable of producing cancer also in the absence of the major (*BRCA1*) mutation. If so, families with founder mutations may form an excellent model not only for examining the effect of genetic modifiers on *BRCA1* penetrance/expression, but also for identifying low-penetrant genes in the population. The underlying paradigm is no more than the probability of selecting families with more than one predisposing factor, *and* that two segregating genetic factors may increase the number affected in the kindred and/or increase the penetrance of the one factor.

We have undertaken predictive testing in Norwegian breast cancer kindreds with *BRCA1* mutations. The circumstantial evidence for non-*BRCA1* factors operating in the same kindreds may indicate that it is too early to conclude that the non-carrying women in these families have no more than a population risk.

In conclusion, our prospective findings confirmed findings in a retrospective series. We have demonstrated that a substantial fraction of dominantly inherited breast cancers are neither caused by *BRCA1* nor *BRCA2*. We have added information on the distribution of CIS and ovarian cancers which were not selected for in some previous series and we have added information on relative prevalences between the subgroups of inherited breast cancers in the Norwegian population. The combined findings confirm the breast–ovarian cancer syndrome as a clinical entity [19], and describe characteristics of non-*BRCA1/2* inherited breast cancer. Two characteristics of the non-*BRCA1/2* group was the presence of CIS and the absence of epithelial ovarian cancers. We have previously reported [20] that no relapse has so far been seen in high-risk women with CIS, indicating that this group may benefit from the follow-up regimen employed. This leads to the notion that the different subgroups of inherited breast cancers may need different healthcare not only to prevent death from associated cancers; the demonstrated biological differences in the breast cancers may also indicate a need for different strategies to avoid breast cancer deaths.

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Appendix

Additional members of The Norwegian Inherited Breast Cancer Group and The Norwegian Inherited Ovarian Cancer Group, are:

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