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European Journal of Cancer 39 (2003) 2205–2213

European Journal of Cancer

www.ejconline.com

The Norwegian founder mutations in *BRCA1*: high penetrance confirmed in an incident cancer series and differences observed in the risk of ovarian cancer

K. Heimdal[a,*], L. Mæhle[a], J. Apold[b], J.C. Pedersen[c], P. Møller[a]

[a]*Section of genetic counseling, Department of Cancer Genetics, Norwegian Radium Hospital, N-0310 Oslo, Norway*
[b]*Center of Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway*
[c]*Department of Medical Genetics, Ullevål University Hospital, Oslo, Norway*

Received 28 October 2002; received in revised form 24 February 2003; accepted 3 March 2003

Abstract

We aimed to describe the penetrances of the four Norwegian founder mutations in *BRCA1* (816delGT, 1135insA, 1675delA and 3347delAG) with regard to breast and ovarian cancers in families ascertained through cancer family clinics or a consecutive series of women with breast or ovarian cancer. We have extended the families as far as possible and tested all family members that asked for genetic testing. Penetrance is based upon counting the mutation carriers. The series contains sufficient numbers of mutation carriers to minimise variation in the estimates due to a limited sample set. The penetrances for all four mutations were high, both with respect to breast and ovarian cancers. This is in accordance with other reports from cancer family clinics, but contrasts with reports from population-based series of mutation carriers. Risks of first cancer (breast or ovarian), breast cancer, and ovarian cancer at age 50 years were 43, 30 and 17%, respectively. Corresponding risks at age 70 years were 84, 58 and 58%. Risks for breast cancer before age 30 years and for ovarian cancer before 35 years were low. Penetrances with regard to ovarian cancer were different for the four mutations. The risk of ovarian cancer was doubled in carriers of the 1675delA mutation when compared with the 816delGT mutation (24 versus 12% at age 50 years, $P=0.004$). The mutations analysed are high penetrance alleles. No differences in penetrance between the series ascertained through the cancer family clinic or the series of consecutive cancer patients was observed. There are discrepancies between our findings and the low penetrances reported for other mutations in other populations. This may be due to methodological differences, but may reflect differences between mutations and/or modifying factors in different populations.

Keywords: Breast cancer; Ovarian cancer; BRCA1; Risk assessment; Penetrance; Expression; Founder mutation

1. Introduction

The magnitude of cancer risk induced by mutations in the BRCA genes has been the subject of debate. Generally, cancer clinic and research-based series, such as those originally collected for the cloning of the genes, have shown high penetrances [1,2], while population-based series and series ascertained through consecutive cancer cases, especially from the Ashkenazi Jewish population, have reported much lower penetrances [3–6]. These discrepancies may have been due to methodological problems. However, there is evidence that different mutations may have different effects (mutation-position effect and/or mutation-specific effects) [7]. Furthermore, modifying factors may exist [8–10].

Four truncating mutations account for 60–70% of Norwegian *BRCA1* families. As previously discussed, we may consider all carriers of these mutations as belonging to branches of four large ancestral families and use the families to calculate penetrances [11]. The mutations are small deletions (816delGT, 1675delA and 3347delAG) or insertions (1135insA) in exon 11 that are predicted to lead to a premature stop codon and a truncated protein. 1675delA, closely followed by 1135insA, seem to be the most frequently observed.

We have previously reported on the penetrances of 1675delA and 1135insA in the first families identified [12]. We now present the results of similar analyses in an additional set of families for all four founder mutations. In addition, we compare penetrances in families ascertained

* Corresponding author. Tel.: +47-2293-4768; fax: +47-2293-5219.

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doi:10.1016/S0959-8049(03)00548-3

through mutation testing in a consecutive series of cancer cases with families ascertained through cancer family clinics.

2. Patients and methods

2.1. Identification of families

2.1.1. Cancer family-clinic series

Since 1989, the Norwegian cancer genetics clinics have included breast and breast–ovarian cancer families for follow-up based on published criteria [13]. Since 1999, the European Consensus criteria have been used [14]. Branches of families that had been referred to different cancer genetics clinics were collapsed into single pedigrees that were considered as one family. Mutation testing of affected women has been ongoing in these families and we had identified 20 families with 1675delA, 19 families with 1135insA, 15 families with 816delGT and 10 families with 3347delAG.

2.1.2. Consecutive breast and ovarian cancer series

Blood samples have been analysed from 615/727 consecutive ovarian cancer patients from southern Norway diagnosed from May 1993 to January 1996 [15] and from a consecutive series of 116 breast and 60 ovarian cancer cases obtained from mid-Norway (Trøndelag) in 1999 [11]. These series have identified 14 families with 1675delA, 10 families with 1135insA, four families with 816delGT and seven families with 3347delAG.

2.2. Informed consent

All mutation testing was done as part of genetic counselling provided by the health service of Norway. Information, including written informed consent to testing, was included in the medical files according to national legislation. Relevant data from the medical files of the different genetics centres were entered in a research register approved by the Norwegian data inspectorate (Datatilsynet, permit #2988-2, 2001) and in accordance with the written informed consent from each patient.

2.3. Identification of index patients

In the cancer family series, the first affected patient to be diagnosed with the relevant mutation was considered to be the index patient. In the consecutive cancer series, one family had three incident cases included in the series. The first case encountered was designated the index case and the family was counted only once. All analyses have also been done counting this family three times (with 3 different index patients). This did not alter the results (data not shown).

Index cases are identified in the description of the sample sets (Tables 1 and 2), but otherwise excluded from the analyses (Table 3, Figs. 1–4).

2.4. Pedigree extension

The pedigrees were extended in all directions. When two families were demonstrated to have a common ancestor, the families were collapsed into one family and the first demonstrated carrier was considered to be the index patient. Whenever possible, all reported cancers were verified using patient records or the Norwegian Cancer registry. All possible efforts, within the legal and ethical framework of genetic testing, were made to test enough family members to determine the mutation-carrying lineage. Deceased women affected with breast and/or ovarian cancer (in the assumed mutation-carrying lineage) were designated carriers by state. Unaffected women located between demonstrated carriers/carriers by state in the pedigree were considered obligate carriers. All living first-degree relatives (and second-degree relatives through deceased first-degree relatives) were invited to predictive mutation testing. In this way, the pedigrees have been extended continuously and this report includes all sibships that were identified through carriers of one of the four Norwegian founder mutations as of 1 April 2000 (demonstrated and obligate carriers, carriers by state). The analysis is restricted to all female first-degree relatives (sisters and daughters) older than 20 years of mutation carriers as of 1 April 2000. Mothers were excluded if the pedigree analysis (presence of breast and/or ovarian cancer on the father's side) or mutation testing clearly indicated that the father might have been the carrier.

2.5. Statistical analyses

Age-related penetrances were calculated using the Kaplan–Meier method and the Statistical Package for the Social Sciences (SPSS) software version 9.0.1 for Windows (SPSS Inc, Chicago, IL, USA). Women were followed from age 20 years until age of affection, death or 1 April 2000. Reported penetrances were not calculated after 70 years of age. Events were scored in three ways: breast or ovarian cancer (whichever came first, no sensoring at age of prophylactic oophorectomy/mastectomy), breast cancer (censoring women with ovarian cancer or bilateral prophylactic mastectomy at the relevant ages), and ovarian cancer (censoring women with breast cancer or prophylactic oophorectomy at the relevant ages). Among the mutation carriers, two women had had prophylactic mastectomy and 64 women prophylactic oophorectomy (before any first event). Differences between the distributions were considered by log-rank tests.

The series were examined for possible differences in penetrances between the contributing genetic clinics. No

differences were found and the series are therefore considered together.

The material was analysed in three steps: first including only mutation carriers (demonstrated, obligate or carrier by state), second by including all relatives with an unknown mutation status as carriers, and finally by fractioning those not tested as probable mutation carriers according to age (see Results section).

The two consecutive series of cancer patients had been fully analysed for the 1675delA and 1135insA mutations. We compared the penetrance for mutation carriers in families with these two mutations ascertained through the cancer family clinic with the consecutive cancer series. Similar comparisons have not been made for 816delGT and 3347delAG since the analyses for these two mutations are not complete in the consecutive cancer series.

2.6. Molecular analysis

All analyses were done on DNA extracted from peripheral ethylene diamine tetra acetic acid (EDTA)-treated blood samples. Mutations were identified as aberrant bands after electrophoresis of polymerase chain reaction (PCR) products as described in Ref. [11]. In addition, all index cases have been sequenced to verify the identity of the mutations.

All families with the same mutation analysed have previously been shown to have the same mutation-carrying *BRCA1* haplotype, excluding the possibility of closely linked modifiers of penetrances and expressions in the *cis* position [11].

3. Results

Among the 99 index patients, 34 women had breast cancer, 51 had ovarian cancer, and 14 had both breast and ovarian cancers. The median age for breast cancer was 44 years (range 27–68 years) and for ovarian cancer it was 49 years (range 34–81 years).

Tables 1 and 2 show the families in more detail. 328 women were affected, 164 women with breast cancer, 142 women with ovarian cancer, and 22 women with both breast and ovarian cancers. 67 of these women had been demonstrated to carry the family mutation and 250 were carriers by state (Table 2). Almost all of the carriers by state were dead and therefore unavailable for

Table 1
Findings in female first-degree relatives of mutation carriers. Index cases excluded

Age group (years)	Mutation	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70+	Total
Tested mutation-positive	All	18	64	68	42	13	7	212
	816delGT	6	16	17	14	4	1	58
	1135insA	3	14	14	12	5	1	49
	1675delA	7	22	26	10	4	2	71
	3347delAG	2	12	11	6		3	34
Assumed carrier (affected, not tested)	All	5	42	87	72	29	15	250
	816delGT	1	9	15	12	5	2	44
	1135insA	2	4	24	17	7	6	60
	1675delA	1	23	35	23	11	3	96
	3347delAG	1	6	13	20	6	4	50
Obligate carrier (healthy)	All		2	4	5	2	14	27
	816delGT				2		7	9
	1135insA							
	1675delA			3	1	2	3	9
	3347delAG		2	1	2		4	9
Tested mutation-negative	All	12	44	32	38	20	15	161[a]
	816delGT	1	10	12	9	4	3	39
	1135insA	3	9	3	6	8	2	31
	1675delA	7	16	12	14	6	6	61
	3347delAG	1	9	5	9	2	4	30
Healthy relative, unknown carrier status	All	66	78	41	29	26	72	312
	816delGT	12	20	4	7	6	19	68
	1136insA	15	21	15	11	9	21	92
	1675delA	33	21	10	8	7	20	99
	3347delAG	6	16	12	3	4	12	53
Grand total		101	230	232	186	90	123	962

[a] Includes 150 healthy women and 11 phenocopies.

Table 2
Mutation status in different age groups for all female first-degree relatives

Age group (years)	No. of mutations demonstrated/(no. of index cases)/no. in which mutations were absent/no. not tested			Proportion of carriers among tested unaffected	Estimated number of carriers among untested unaffected[a]
	Affected	Unaffected	Total		
20–29	1/(2)/0/5	17/(0)/12/66	18/(2)/12/71	0.59	38.69
30–39	14/(17)/1/42	50/(0)/43/80	64/(17)/44/122	0.54	43.01
40–49	25/(45)/3/87	43/(0)/29/45	68/(45)/32/132	0.60	26.88
50–59	21/(22)/4/72	21/(0)/34/34	42/(22)/38/106	0.38	12.98
60–69	2/(11)/1/29	11/(0)/19/28	13/(11)/20/57	0.37	10.27
70+	4/(2)/2/15	3/(0)/13/86	7/(2)/15/101	0.19	16.13
Overall	67/(99)/11/250	145/(0)/150/339	212/(99)/161/589	0.49	147.96

[a] Number of untested unaffected multiplied by observed proportion of carriers among tested unaffected in the same group.

Table 3
Cumulative age-related penetrances (breast and/or ovarian cancer whichever came first) in mutation carriers and their unaffected first-degree female relatives. Index person in each family excluded

Age group (years)	A: Mutation carriers[a]		B: A + assuming all first-degree relatives not tested were carriers[b]		C: Intermediate between A and B[c]	
	Cumulative proportion affected at end of age period (mean ±SEM)	Annual incidence rate, 10 year period (%)	Cumulative proportion affected at end of age period (mean ±SEM)	Annual incidence rate, 10 year period (%)	Cumulative proportion affected at end of age period (mean)	Annual incidence rate, 10 year period (%)
20–29	0.013 (0.005)		0.008 (0.003)		0.011	
30–39	0.13 (0.02)	1.3	0.09 (0.01)	0.9	0.11	1.0
40–49	0.43 (0.03)	3.0	0.31 (0.02)	2.2	0.38	2.7
50–59	0.72 (0.02)	2.9	0.53 (0.02)	2.2	0.60	2.2
60–69	0.84 (0.02)	1.2	0.62 (0.02)	0.9	0.70	1.0

SEM, standard error of the mean.
[a] From Kaplan–Meier calculations, including tested and obligate mutation carriers and carriers by state.
[b] From Kaplan–Meier calculations, includes tested and obligate carriers and carriers by state. In addition, untested unaffected sisters/daughters were assumed to be carriers.
[c] Based on the probabilities, given in Table 2, that untested unaffected first-degree relatives are carriers (see Ref. [12] for details).

testing. Among the demonstrated mutation carriers, the median age for breast cancer was 47 years (range 28–75 years) and for ovarian cancer was 50 years (range 34–79 years). Nine women with breast cancer and two with ovarian cancer were demonstrated not to carry the family mutation nor any of the other three founder mutations. The age range for these phenocopies is given in Table 2. The ovarian cancer phenocopies occurred at age 37 and 79 years. The phenocopies have been excluded from the Kaplan–Meier analyses.

In addition, there were 634 healthy adult sisters and daughters of mutation carriers. Among these first-degree relatives, 295 had been tested and 145 of these (49.2%) were found to be carriers.

Table 2 details the carrier status according to age and affected status. The table includes all relatives, living or deceased. It can be seen that we have tested only 30% of the unaffected young women (age 20–29 years) and only 16% in the 70+ year age group. Most of the unaffected elderly women had died prior to the time that the mutation was identified in the family. In the age group 30–69 years, 59% of the healthy women were tested. Approximately 50% of those unaffected were carriers. We confirmed our previous findings that, in the younger age groups more than 50% of the healthy first-degree relatives were mutation carriers. The expectation under single selection is 50% and the reasons for this high proportion of mutation carriers among young women are unknown [12]. Due to the fact that increasing proportions of mutation carriers become affected as they age, the proportion of healthy mutation carriers drops significantly in women aged over 50 years. Confidence intervals (CIs) on the estimates of the proportion of carriers in the older age groups are wide since only a few of the relatives were tested. It can be seen that we identified only three healthy mutation carriers in the

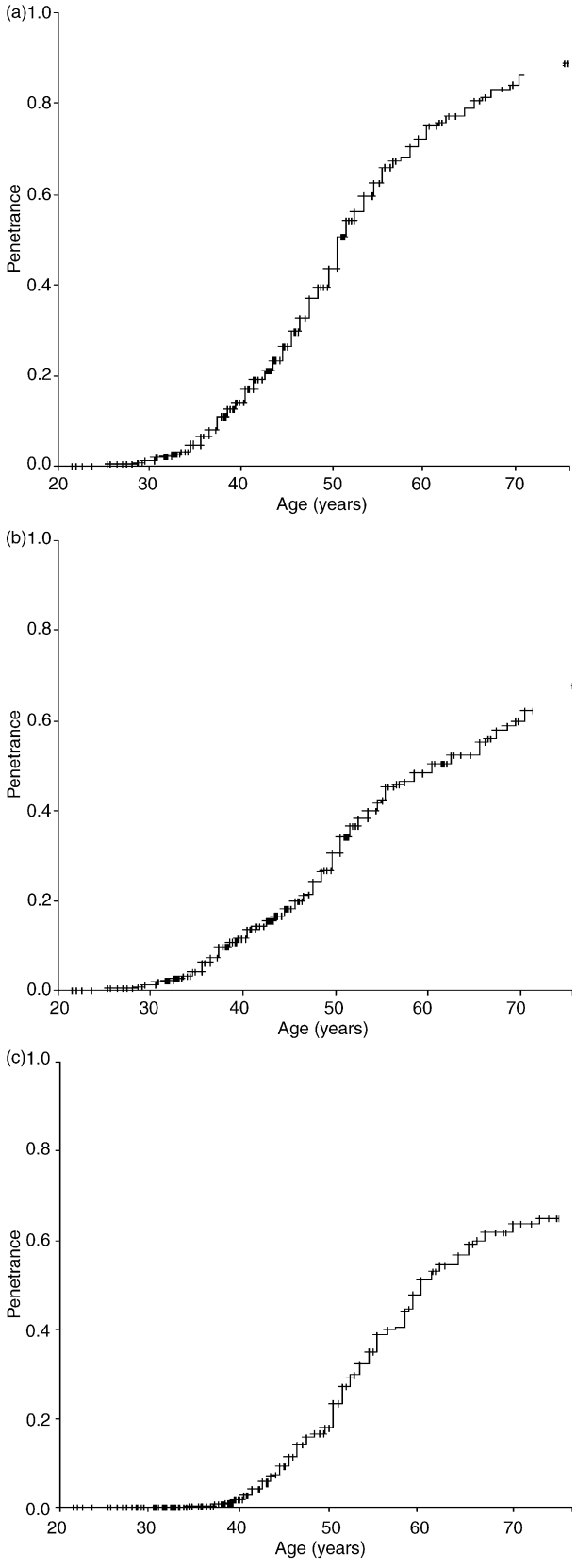

Fig. 1. Time to (a) first cancer, (b) breast cancer and (c) ovarian cancer, all mutations combined.

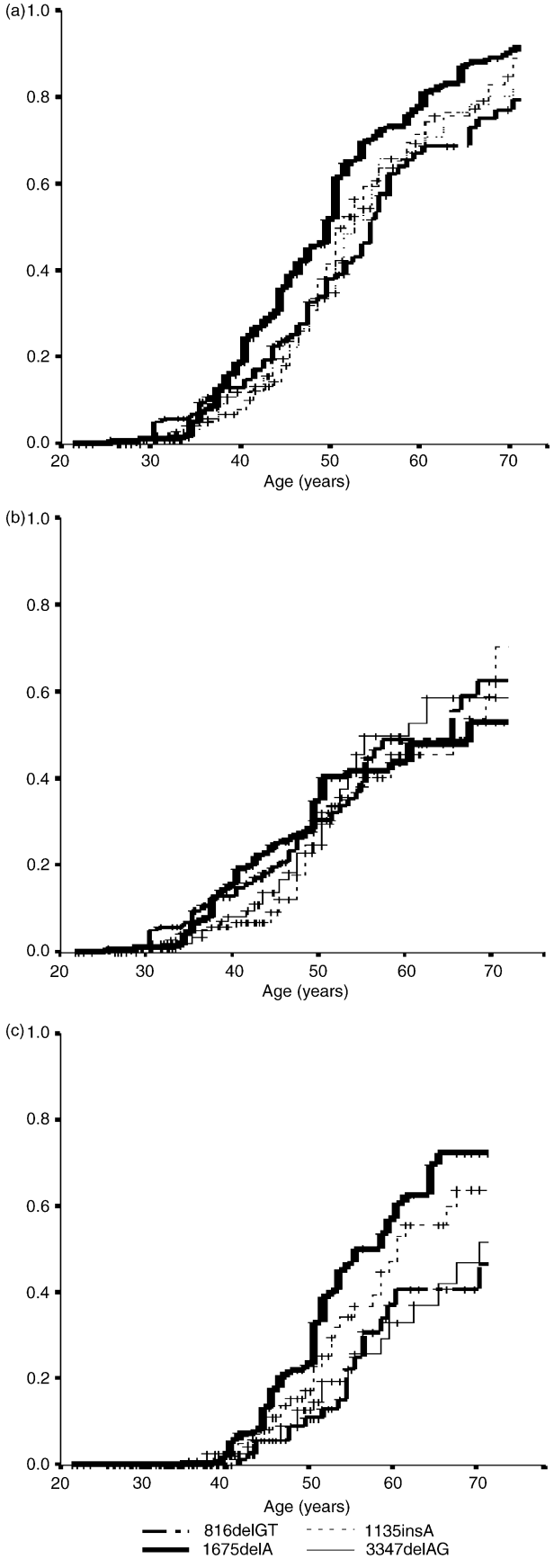

Fig. 2. Time to (a) first cancer, (b) breast cancer and (c) ovarian cancer.

70+ age group and only 11 were identified amongst those aged 60–69 years.

Penetrances, using carriers only and excluding the index subjects, are given in Fig. 1. The estimated penetrance for breast or ovarian cancer, whichever came first, was 84% (95% CI 80–88%) at 70 years. Penetrances for breast cancer and ovarian cancer were the same at 58% (95% CI 51–66%). Six women had breast cancer at age 25 years (2), 28 years (2) and 29 years (2). No women had ovarian cancer before the age of 30 years, and only one woman had ovarian cancer before age 35 years (at age 34 years). At 50 years of age, penetrances were 43% (95% CI 38–48%) for first cancer, 30% (95% CI 26–35%) for breast cancer, and 17% (95% CI 13–21%) for ovarian cancer.

Table 3 gives estimates of the penetrance for all four mutations combined. Column A details penetrances using carriers only. In column B, penetrances were calculated assuming all untested first-degree relatives were mutation carriers (data from Table 2). This may be regarded as a minimum estimate of penetrance, while the estimate using carriers (column A) may be regarded as a maximum estimate. In column C, the final estimate was adjusted by fractionating the proportion of untesteds to be carriers according to the fraction observed in the same age groups (Table 2) to the figures in column B. It can be seen that this reduces penetrances approximately 15%.

There was evidence of heterogeneity in the data-set between the four mutations ($P=0.01$, test pooled over strata, first cancer considered as the event) (Fig. 2). Although all four mutations showed high incidences of both breast and ovarian cancers, 1675delA had higher penetrances especially when compared with 816delGT ($P=0.006$, test pairwise over strata) and 3347delAG ($P=0.02$). The difference seemed to be related to differences in ovarian cancer penetrances ($P=0.02$, test pooled over strata) and not breast cancer ($P=0.77$). In pairwise comparisons, 1675delA showed the highest penetrances for ovarian cancer and these were different from 816delGT ($P=0.004$) and 3347delAG ($P=0.04$).

Families ascertained through the cancer family clinic showed the same penetrances with almost identical curves (Fig. 3) as families ascertained through the consecutive cancer series ($P=0.66$, first cancer considered as the event). No differences were found when calculating the data separately for breast ($P=0.24$) or ovarian cancer ($P=0.89$).

The present series includes women from our previous report in Ref. [12]. The families in the original set had the highest penetrances (93% first cancer at 70 years of age (Fig. 4)) when compared with families that were ascertained later on (80%). This difference is statistically significant ($P=0.003$). The difference was only present in families with 1675delA ($P=0.02$), while there was no differences in the penetrances for families with the 1135insA mutation ($P=0.98$).

4. Discussion

In this cancer family clinic-based material, penetrances were 70% at 70 years of age. The series included sufficient numbers of families and tested women in the families, to conclude that families identified by incident cancer cases have as high penetrances as families identified through the cancer family clinics. This view is supported by the report of Levy-Lahad and colleagues

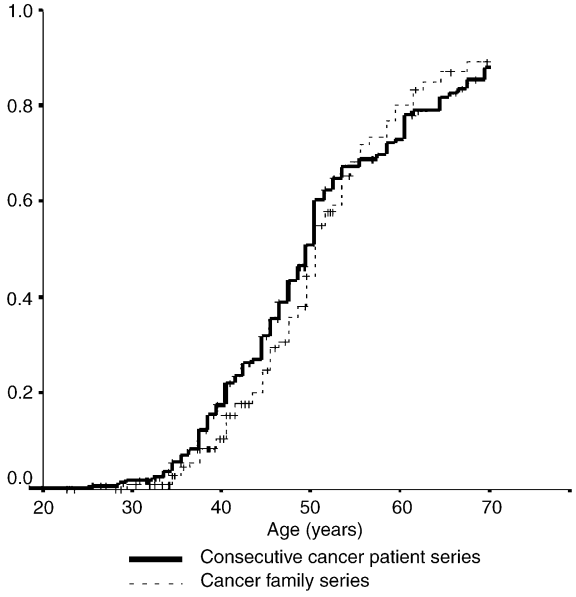

Fig. 3. Comparison of series ascertained through consecutive cancer cases or cancer family clinics.

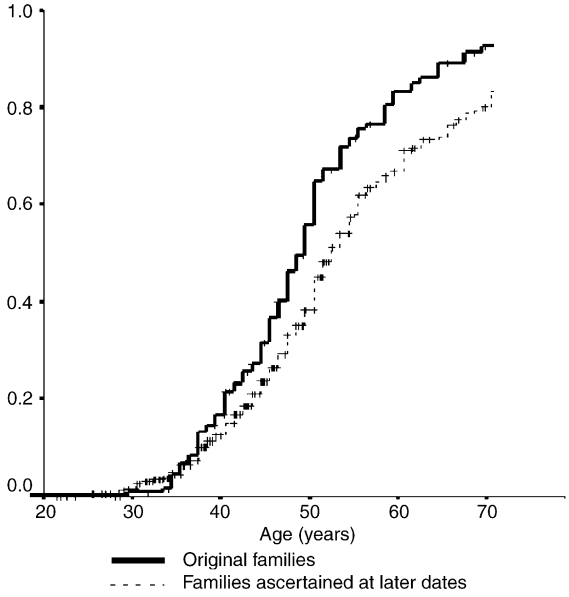

Fig. 4. Comparison of original families and families ascertained at later dates.

[16] who, although they did find higher penetrances in a cancer family clinic series, noted that the differences were small and not statistically significant. There may, of course, be methodological problems in our series. For example, both the low uptake of testing in the elderly women, and ascertainment through high-risk cancer families/cancer cases may lead to inflated penetrance estimates. Similarly, if a significant number of untested old affected women were phenocopies, this would upwardly bias the results. If prophylactic oophorectomy indeed reduces the risk of breast cancer significantly in *BRCA1* mutation carriers, not sensoring women at the time of oophorectomy when calculating the penetrance in the breast cancer analysis may have produced a bias in the opposite direction. The effect of oophorectomy is small in this cohort since the observation time after oophorectomy is generally short. In conclusion, we find it improbable that our estimates are out of order. The clinical impression was that most of the cancer families had an affected, mutation-carrying mother, while some of the seemingly 'sporadic' cases in the consecutive cancer series turned out to have a positive family history on the paternal side.

In our experience, breast cancer appears on average 10 years before ovarian cancer. Breast cancer before 30 years is very rare, while the annual incidence rate in these families is approximately 1.5% thereafter. On average, we find annual incidence rates for breast and/or ovarian cancer of approximately 2% in the age group 30–70 years. Because of the low number of women tested, estimates of penetrance are less reliable in those aged over 60 years, and we stopped our calculations at age 70 years. Furthermore, the numbers of phenocopies would be expected to rise in the older age groups, and problems related to classification may also be substantial. The numbers are also smaller in the younger age groups, but there is a suggestion that the incidence rates are slightly higher in the 40–60 year old age group.

There is some evidence of differences in the penetrance between separate branches of the same *BRCA1-2* families in the literature, but strong and generally accepted effects have not been demonstrated [17,18]. Penetrances were slightly higher in the subjects included in our first report compared with the patients included later. This was expected as the original family branches were ascertained on the basis of multiple cancer cases and adjusting ascertainment by excluding one index person only may be inadequate. However, contrary to our initial expectations, the expansion of the original families did not result in a major reduction in the penetrance estimates and we have so far not identified clusters of female mutation carriers with a low penetrance. The high penetrance estimates, both for breast and ovarian cancers in this series is consistent with other cancer family clinic series and confirms our previous results, but is incompatible with the lowest estimates obtained from population studies. Such variation in risk between studies may be explained by random effects, mutation specific effects, study designs (including methods of ascertainment and analysis), and differences between the populations studied (implying an unequal distribution of specific mutations and/or modifying factors). This has both scientific and practical implications: the Norwegian Government has approved our continued mutation testing in incident cancer cases to identify high-risk families [19]. The present findings verify the penetrances and expressions used to counsel these families in that setting. We caution that the figures may not be relevant to other *BRCA1* mutations or in other settings or populations, since the results are based on Norwegian cancer families with at least one affected member.

The literature on the penetrances and expression of *BRCA1* mutations is extensive, but only a few reports clearly separate the above-mentioned different effects on the phenotype, especially if we accept the existence of mutation-specific effects. A high penetrance in cancer family clinic samples and a low penetrance in population-based series has been consistently found in studies using different methods [16,17,20–23]. It should be noted that these reports include the Jewish founder mutations [16,20,22]. However, even large differences, consistently demonstrated, may be due to random variation and ascertainment bias. All published reports are based on complex models of ascertainment and methods of analysis that rely on assumptions that may not be met [24,25]. In cancer families, the variation in the type (breast or ovarian) and age of onset of cancer (especially breast) seems to be greater within rather than between families [17,26], indicating that much of the variation in phenotype and age of onset may be due to stochastic variation. However, since we were unable to demonstrate major differences related to the ascertainment method, our data indicate that the method of ascertainment may be less important and, hence, the differences between penetrances in the cancer families and population-based series may indicate the presence of modifiers.

Our second main finding is the differences in the risk of ovarian cancer between the different *BRCA1* mutations. Since these differences were demonstrated in sets of families ascertained during the same time interval using the same methods, they are not likely to be due to methodological difficulties. Evidence of differences in the expression of mutations has previously been demonstrated for many genes [27,28] and also seems to be present in the *BRCA1* and *BRCA2* genes [29,30]. It is highly unlikely, from a biological point of view, that there should be one group of DNA changes in the gene, all with identical biological effects (commonly called disease-associated mutations) and that all other variants have no effect (normal variation). Rather, the expectation

would be a spectrum of penetrances and expressions associated with different sequence variants. In the Breast Cancer Linkage Consortium (BCLC) families, there is evidence of a position effect with a higher ovarian cancer risk for mutations in the first two-thirds of the gene and a lower breast cancer risk for mutations in the middle third of the gene [7]. Evidence for allelic heterogeneity has also been found by other authors [16,26,31,32]. The Norwegian founder mutations are similar in nature and reasonably close to one another in the gene sequence. They are all small deletions/insertions in exon 11. 3347delAG is in the middle part of the gene (borders as suggested by the BCLC), the other three are in the last section of the first third of the gene. In contrast to the BCLC, we find the clearest differences with regard to ovarian cancer risk, and not breast cancer risk. Furthermore, the two mutations with the highest penetrances (1675delA/1135insA) are located between the two mutations with the lowest ovarian cancer risk (816delGT/3347delAG). In addition, when looking at the breast cancer risk before 50 years of age, the 1135insA mutation had the lowest rate followed by the 3347delAG mutation. These differences were small and not statistically significant. We find it probable that there may be real differences between the mutations. Whatever the biological explanation, if the differences are real, lumping together all mutations, or all mutations in a particular part of the gene, and calculating averaged penetrances and expressions may be misleading.

Because different populations have different mutations, conflicting results may be misinterpreted as ascertainment biases and/or due to the effects of modifiers. The problem of insufficient numbers cannot be solved by pooling families with private mutations into joint analyses, but data should be subjected to methods of analysis that are designed to resolve the putative differences between mutations, as well as between populations.

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