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Genetic epidemiology of *BRCA* mutations – family history detects less than 50% of the mutation carriers

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ABSTRACT

Ten *BRCA* mutations were demonstrated to be frequent in the Norwegian population. We present maps verifying the uneven distribution of prevalences according to municipality. We tested incident breast cancer cases treated in Mid-Norway from 1999 onwards for these mutations. Uptake of testing was 97% and 2.5% were demonstrated to be mutation carriers. Ten (77%) were outside families previously known to carry a mutation. Ten (77%) did not meet clinical criteria to be selected for mutation testing.

We tested incident ovarian cancer cases in South-West Norway from 2001 onwards. Uptake of testing was 80% and 23% were mutation carriers. Twenty-one (88%) were outside families previously known. Twelve (67%) did not meet clinical criteria to be selected for testing.

All patients with mutation collaborated actively to give our offer of predictive genetic testing to their relatives. No complaint on the activity was received.

1. Introduction

Carriers of *BRCA* mutations are at high risk for both breast and ovarian cancer.[1] Prophylactic bilateral salphingo-oophorectomy (BSO) after childbearing ages will take away most of the risk for ovarian cancer.[2] BSO will also reduce risk for breast cancer,[3] and use of hormone replacement treatment (HRT) may not oppose this effect.[4] There may be a benefit from early diagnosis and treatment of breast cancer in mutation carriers.[5] Prophylactic mastectomy may take away most risk for breast cancer.[6] To give each mutation carrying woman the opportunity to select such measures, they have to be identified and informed.

Identification of mutation carriers has been achieved through identification of affected families, followed by search for causative mutations within such families, and predictive

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testing within kindred with a demonstrated deleterious mutation.[7] Uptake of predictive mutation testing in such kindred has been demonstrated to be high.[8] More extensive mutation testing has been prohibited by the complexity of the *BRCA* genes and the corresponding costs. However, testing for founder mutations in specific populations has been shown to be successful. Testing of incident breast cancers in young women in Poland for three founder mutations was performed in 18 hospitals from 1996 to 2003.[9] Among 4316 incident cases of early-onset breast cancer, 3472 gave their consent to testing (80.4%). A total of 198 *BRCA1* mutations (5.7%) were identified. Another Polish study explored the consequences of allowing women to be the gatekeepers of their access to testing for genetic susceptibility to hereditary breast cancer by offering genetic testing for three polish *BRCA1*founder mutations through an announcement placed in a popular women's magazine.[10] Women could be included if they were 18 years of age or over, and if they had a first- or second-degree relative with breast cancer before age 50 or ovarian cancer at any age, or if they themselves had had breast and/or ovarian cancer. One hundred and ninety eight out of 5024 tested (3.9%) were demonstrated to be mutation carriers.

Family history, however, fails to identify women without close female relatives who are mutation carriers. In addition, such relatives must have had an early onset of disease for the families to meet the clinical criteria. Most mutation carrying kindred may not have two or more closely related women with early onset disease. Exact calculations on assumed sensitivity of the recommended clinical criteria[7] are difficult, but our estimates were that the majority of families may escape detection.

We have previously reported that, due to the population reduction during the Bubonic plagues in the years 1350–1400, and the genetic isolation our population experienced the following 400 years, most Norwegian mutation carriers are descendants of a limited number of survivors of the plagues.[11] Prevalence of *BRCA1/2* mutation carriers in ovarian cancer patients has been demonstrated to be 6%.[12] Corresponding with penetrance estimates for the mutation carriers[1] and incidence of breast and ovarian cancers in Norway,[13] this should indicate that 2% or more of all breast cancer patients may also be mutation carriers.

Our combined clinical and research activities have included a full *BRCA1* mutation search in about 1000 unrelated individuals and about half that number for *BRCA2*. Predictive testing has been offered to all families with a demonstrated mutation. When finding a new mutation, in addition to the procedures above, potential families in the same region have been tested for that mutation. We have, for many years, tested all families meeting our clinical criteria with a panel of the most frequent mutations. By doing this, we have identified about 1300 carriers of 75 distinct mutations. Close to two thirds carry one of the ten most frequent mutations which are *BRCA1:1675delA, 1135insA, 3347delAG, 816delGT, G3297T, 4864delA, 2470del7, 3203del11,* and*BRCA2: 4075delGT, 3036del*ACAA.

This study reports the uptake and results of genetic testing for locally frequent mutations offered to all breast cancer patients from January 1999 to May 2006 in Mid-Norway (Trøndelag), and ovarian cancer patients in South-West Norway. The results would indicate what fraction of mutation carrying women had been identified prior to the study and thereby provide data to estimate the number of mutation carriers in the population. The present report is an evaluation of health care as recommended by a governmental committee, later supported by the Norwegian Parliament, to test incident cancer this way[14] with the aim of identifying mutation carriers to enable them to select preventive and therapeutic measures against breast and ovarian cancer.

2. Patients and methods

2.1. *Data registries and ethics*

All activity was performed as a health service according to Norwegian legislation. Written informed consent was obtained by the treating physician and stored in the medical files. The results of the genetic testing were kept in the medical files. All identified mutation carriers were referred for genetic counselling, and all families were offered predictive testing as part of our health service, including pre-test genetic counselling and written informed consent. The medical files at Section for Inherited Cancer, RR, are computerised, with data entered through our application constructed by dB+© and stored in our Oracle © database, and for the current report analysed by use of Toad © and ArchView© and by the use of the statistical packages Systat10© and StatExact5©. For this report, no data identifiable to persons were exported from the medical files, and no research registry, including names of the patients, was constructed.

2.2. *The test panel and prevalences of the frequent mutations*

Initially, the test panel included the six most frequent mutations that are present within the Norwegian population. At the time the study was undertaken in 1999, we knew that the *BRCA1 1135insA* mutation was distributed through the eastern part of southern Norway, over the highland to Trondheim and to the coastal area west of Trondheim. We knew that the three other most frequent mutations originated from the South-West area.[15] Within a year three more mutations were added to the test panel. In 2004 we added the last one (*BRCA2 4075delGT*) arriving at a final panel testing for *BRCA11675delA, 1135insA, 3347delAG, 816delGT, G3297T, 4864delA, 2470del7and 3203del11,* and*BRCA2 4075delGT and 3036del*ACAA. The same test panel was used to examine any family seeking advice for familial breast cancer at our institutions during the study period. Table 1 gives the number of genealogically non-related kindred demonstrated to have the mutations included in the panel in our total activity at the end of the study, and the numbers of persons demonstrated to have the mutations.

For the present study, we identified all mutation carriers listed in Table 1 by their postal addresses (zip codes) and related our database to a digital map of Norway including demographic information on population structure. The mutation carriers were displayed as prevalences in all municipalities for each mutation separately, as shown in Fig. 1.

Table 1 – Test panel and families and mutation carriers found in our total activity (see Fig. 1 for geographical distributions of the mutations)

Gene	Mutation	No. Kindred	No. Carriers
BRCA1	*1675delA*	58	244
BRCA1	*1135insA*	51	234
BRCA1	*3347delAG*	24	118
BRCA1	*816delGT*	23	100
BRCA1	*G3297T*	13	46
BRCA1	*4864delA*	6	42
BRCA1	*2470del7*	5	16
BRCA1	*3203del11*	5	14
BRCA2	*4075delGT*	6	37
BRCA2	*3036delACAA*	8	28
SUM		199	879

Compared to our previous reports,[15] it is seen that for the four most frequent mutations, the prevalences are still high where the mutation survived the Bubonic plagues. It is also seen that the less common frequent mutations are even more restricted to local areas. They have not migrated from their genetic isolates to the same extent as the most frequent ones - they have locally high prevalences, but are less frequent in the population as a whole.

Fig. 1 is imperfect, because there may be additional locally frequent mutations we have not identified and not included in the test panel. Fig. 1 is, however, informative because most families having sought our advice for familial breast cancer, since we started the activity in 1989, have by now been examined for most of the mutations shown. We have excluded these mutations from being frequent in the other parts of the population. The results indicate that all parts of the population have separate prevalences of distinct mutations, and that the concept of 'one Norwegian population' may be misleading. The Norwegian population is still genetically heterogeneous following the genetic imbalance (genetic drift) caused by the Bubonic plagues 600 years (25 generations) ago.

3. Results

3.1. *Results of mutation testing of incident breast cancers in Mid-Norway*

Altogether, 1256 patients treated for breast cancer in the area in the period 1999–2006 were tested, which identified 13

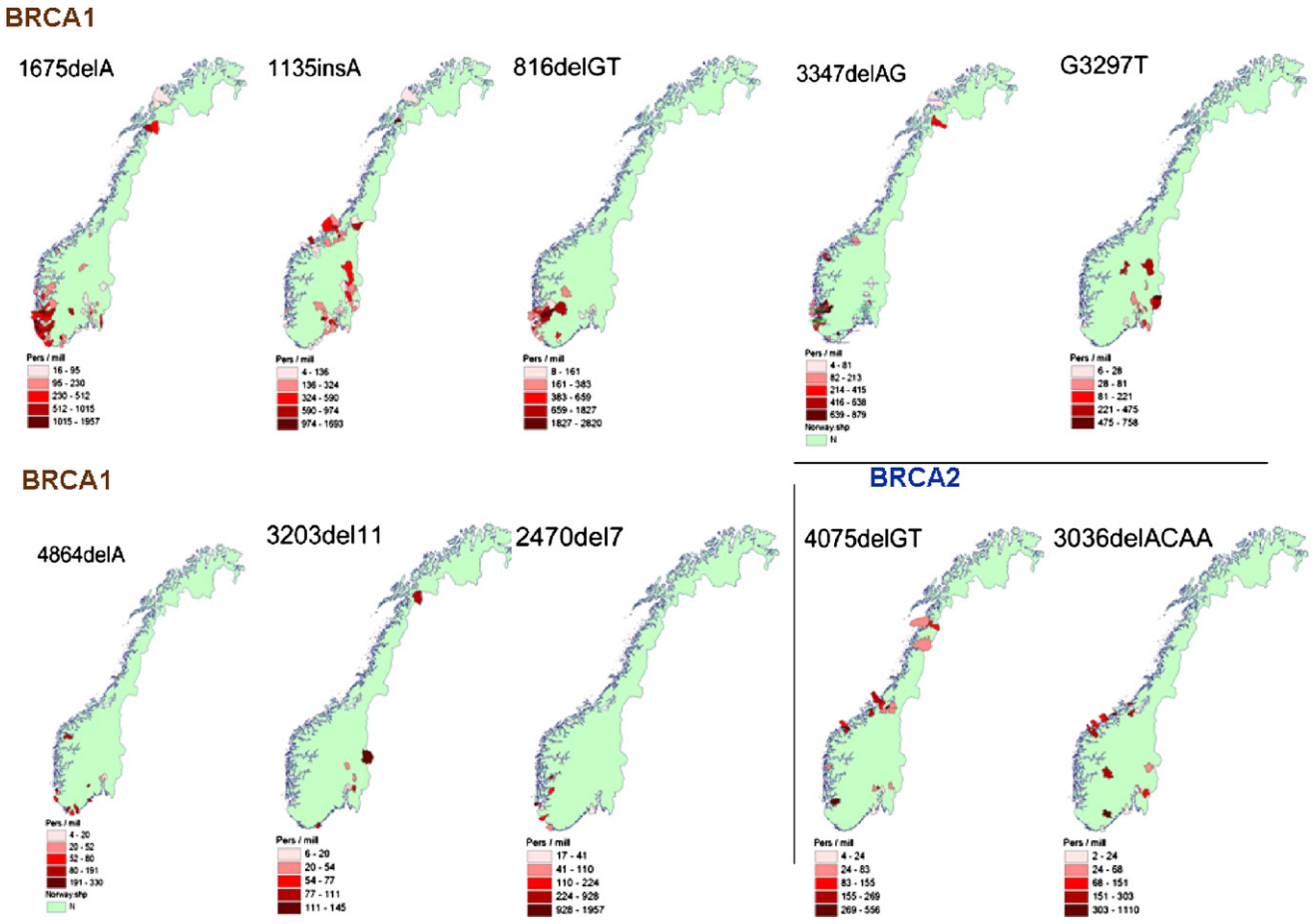

Fig. 1 – Incidence for each mutation tested for, according to municipality, as computed by linking our computerised medical files with the ArchView© digital map of Norway and population structure. Most of the Norwegian population is concentrated in some areas along the coast, and most of the inland; large areas of the coast have only limited numbers of inhabitants, if any. Together, the areas indicated as having high prevalences of one or more mutations indicate the areas where the majority of the population live.

mutation carriers. St.Olav's Hospital, Trondheim University Hospital is treating the large majority of the breast cancer cases in the region. Out of 1246 consecutive patients, 1209 (97%) consented to participate in the study.

BRCA1 1135insA was identified in 9/1256 = 0.7% breast cancer patients. The *BRCA1 1675delA* and *816delGT* mutations were examined for and not found in any of these samples. The most frequent mutation identified in this group of breast cancer patients was *BRCA2 4075delGT*, which was found in 3/199 (1.7%). *BRCA1 3347delAG*was seen in 1/1256 = 0.08%. None of the other mutations demonstrated to be prevalent in other parts of the population were seen. Thus, the observed point estimate for the combined prevalence of the ten mutations tested for was 0.7% + 0.08% + 1.7% = 2.5%. The number of patients tested and number and prevalences of mutation carriers demonstrated according to age is given in Table 2.

Three out of thirteen (23%) mutation carriers were prospectively diagnosed in women previously identified through predictive testing in kindred known to carry this mutation. This indicated that 77% of the mutation carriers in the area were not identified despite our long lasting efforts to identify them through family history and the testing of all identified families with the same test panel. Seven of the ten (70%) new mutation carriers demonstrated were older than 50 years, but two of them were identified when having their second breast cancer and both had experienced their first breast cancer before 50 years of age. All 13 patients demonstrating mutations were genealogically unrelated, implying that we identified ten new mutation carrying kindred through the study. Thus, 2.5% × (10/13) = 1.9% of the tests resulted in a new mutation carrying family identified.

All patients with demonstrated mutations consented to genetic counselling, and all consented to, and actively participated in, informing their families making the information available to relatives as a basis for predictive testing in the kindred as part of our standard health care. Through this process we received extensive information on family structures, and we have verified all relevant diagnoses reported in the families, arriving at detailed description and confirmed diagnoses in the relatives.

Three patients (23%) met clinical criteria to be selected for mutation testing.[7] Probability for having a *BRCA* mutation was calculated by the BRCAPRO software, arriving at the result that three patients (23%) had >10% probability (94.8%, 30.5% and 16.9% respectively), while the remaining ten families (77%) had 0.1–3.5% probability for carrying a *BRCA* mutation as assessed by BRCAPRO. Eight (62%) were older than 50 years, but three of them presented with their second breast cancer and had had their first breast cancer before 50 years of age.

Only one (8%) of the mutation carriers had a mother who had contracted breast cancer before 50 years of age. So far, we have verified that three (23%) of the patients had inherited the mutation from their mothers, two of these mothers had no cancers, one had contracted breast cancer at 54 years of age. Four (31%) of the patients had inherited their mutations from their fathers. So far, it is not determined which of the parent transmitted the mutation in six (46%) of the patients. Only one (8%) had an affected sister, the sister contracted breast cancer at age 48.

No complaint on the genetic testing from any patient tested or their relatives has been filed.

3.2. *Results of mutation testing of ovarian cancer patients in South-West Norway*

Stavanger University Hospital in Rogaland is located in the core area for the three*BRCA1* founder mutations *1675delA, 816delGT and 3347delAG*.[15] During the study period 2001–2006, 131 ovarian cancer patients were treated and 105 (80%) were tested. Some patients were referred to the Norwegian Radium Hospital for treatment, and knowing they would be genetically tested there, they might not have been offered genetic testing locally. Thus, 105/131 (80%) may be an artificially low estimate of compliance.

All patients were tested for all the mutations demonstrated, none were tested for *BRCA2 4075delGT*, and most were tested for all the other mutations mentioned in Table 1. Twenty-four out of 105 (23%) had a deleterious mutation demonstrated. The number of patients tested and number of mutation carriers demonstrated according to age is given in Table 3.

All 24 mutation carriers cooperated in disclosing their family history, and all actively participated in informing their families so that relatives could be offered predictive genetic testing. No complaint from any of the patients examined with respect to being offered genetic testing, or on how the total procedure was carried out, was received.

Out of the 24 mutation carriers, eight (33%) had affected relatives meeting the criteria to be selected for genetic testing based on family history. Nine (35%) had a calculated BRCAPRO probability >= 10% of being a *BRCA1/2* mutation carrier.

Three out of the 24 (13%) mutation carriers were prospectively diagnosed in women previously identified through predictive testing in kindred known to carry this mutation.

Table 2 – Breast cancer patients in mid-Norway (number of patients examined, number of mutation carriers demonstrated, and prevalences of mutation carriers in different groups of ages)

Age group	Patients examined for *BRCA1 1135insA* or *3347delAG*	Carriers of *BRCA1 1135insA* or *3347delAG* (prevalence)	Patients examined for *BRCA2 4075delGT*	Carriers of *BRCA2 4075delGT* (prevalence)
Under 40	316	2 (0.6%)	15	1 (6.7%)
40–49	139	1 (0.7%)	27	1 (3.7%)
50–59	217	3 (1.1%)	53	
60+	530	4 (0.8%)	104	1 (1.0%)
Total	*1256*	*10 (0.8%)*	*199*	*3 (1.7%)*

Table 3 – Ovarian cancer patients in South-West Norway (number of patients tested, number of mutation carriers demonstrated, and prevalences of mutation carriers in age groups)

Age group	Patients examined	Mutation carriers demonstrated
Under 40	3	0 (0%)
40–49	11	5 (46%)
50–59	32	13 (41%)
60+	59	6 (10%)
Total	105	*24 (23%)*[a]

a The mutations were *BRCA1 1675delA* ($n = 11$), *1135insA* ($n = 0$), *3347delAG* ($n = 9$), *816delGT* ($n = 3$), *3297G > T* (E1060X) ($n = 1$).

4. Discussion

As expected, the majority of the mutation carriers identified did not meet our family history based criteria.

The majority of mutation carriers were aged 50 years or more. If the goal is to identify the mutation carriers, mutation testing of incident cancer cases may not be restricted to young patients.

Besides two patients, all mutation carriers possessed the local founder mutations. This high prevalence of local mutations in the series (35/37 = 95%) verifies the impression from Fig. 1 that the population still contains distinct genetic subgroups reflecting genetic drift produced by the Bubonic plagues more than 500 years ago. The Norwegian population is genetically stratified and any infrequent genetic marker may be expected to have an uneven distribution in the population.

Prevalence of mutation carriers in breast cancer patients was as expected. We have previously demonstrated that 6% of Norwegian ovarian cancer patients had a *BRCA1/2* mutation,[12] and expected about half of that prevalence in breast cancer.

The high prevalence of mutation carriers in the ovarian cancer patients was as expected knowing that the hospital was located in the core area of three of the four most frequent founder mutations in Norway.

In conclusion, testing for locally prevalent mutations should be based not only on the mutations prevalent in the whole population, but also on knowledge of locally prevalent mutations where the patients and their forefathers have lived.

Patient compliance to the testing strategy was high, and no complaint was filed. The study number was large enough to conclude that the method is applicable for both groups of patients.

BSO past childbearing ages may reduce penetrances of the *BRCA* genes when mutated, both with respect to ovarian cancer and with respect to breast cancer. In addition, a mutation carrying woman may choose prophylactic mastectomy, thereby eliminating most of the risk for breast cancer, or she may choose programmes for early detection and treatment of breast cancer. To enable mutation carrying women to make these choices, they must be identified and informed. Offering incident cancer cases diagnostic test for locally frequent mutations is within all ethical and legal standards, and may be instrumental to enable women to survive despite having *BRCA* mutations.

Conflict of interest statement

None declared.

REFERENCES

1. Heimdal K, Maehle L, Apold J, Pedersen JC, Moller P. The Norwegian founder mutations in BRCA1: high penetrance confirmed in an incident cancer series and differences observed in the risk of ovarian cancer. *Eur J Cancer* 2003;**39**(15):2205–13.
2. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 orBRCA2 mutations. *N Engl J Med* 2002;**346**(21):1616–22.
3. Eisen A, Lubinski J, Klijn J, et al. Breast cancer risk following bilateral oophorectomy in BRCA1 andBRCA2 mutation carriers: an international case-control study. *J Clin Oncol* 2005;**23**(30):7491–6.
4. Rebbeck TR, Friebel T, Wagner T, et al. Effect of Ssort-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 andBRCA2 mutation carriers: The PROSE study group. *J Clin Oncol* 2005;**23**(31):7804–10.
5. Møller P, Borg Å, Evans DG, et al. Survival in prospectively ascertained familial breast cancer: Analysis of a series stratified by tumour characteristics, BRCA mutations and oophorectomy. *Int J Cancer* 2002;**101**:555–9.
6. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 andBRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol* 2004;**22**(6):1055–62.
7. Moller P, Evans G, Haites N, et al. Guidelines for follow-up of women at high risk for inherited breast cancer: consensus statement from the Biomed 2 Demonstration Programme on Inherited Breast Cancer. *Dis Markers* 1999;**15**(1-3):207–11.
8. Bodd TL, Reichelt J, Heimdal K, Moller P. Uptake of BRCA1 genetic testing in adult sisters and daughters of known mutation carriers in Norway. *J Genet Couns* 2003;**12**(5):405–17.
9. Lubinski J, Górski B, Huzarski T, et al. BRCA1-positive breast cancers in young women from Poland. *Breast Cancer Res Treat* 2006;**99**(1):71–6.
10. Gronwald J, Huzarski T, Byrski T, et al. Direct-to-patient BRCA1 testing: the Twoj Styl experience. *Breast Cancer Res Treat* 2006;**100**(3):239–45.
11. Møller P, Borg A, Heimdal K, et al. TheBRCA1 syndrome and other inherited breast or breast-ovarian cancers in a Norwegian prospective series. *Eur J Cancer* 2001;**37**:1027–32.
12. Kotar K, Brunet JS, Møller P, et al. Ratio of female to male offspring of women tested for BRCA1 andBRCA2 mutations. *J Med Genet* 2004;**41**(8):e103.
13. Cancer Registry of Norway. Breast females. In: *Cancer in Norway. Cancer Registry of Norway.* Oslo: Cancer Registry of Norway; 2004.
14. NOU. *Å vite eller ikke å vite. Gentester ved arvelig kreft. Norwegian Government.* Oslo, Norway: NOU; 1999. p.20.
15. Moller P, Heimdal K, Apold J, et al. Genetic epidemiology of BRCA1 mutations in Norway. *Eur J Cancer* 2001;**37**(18):2428–34.