

**BRCA2 Germ-Line Mutations Are Frequent in Male Breast Cancer Patients without a Family History of the Disease**

Karin Haraldsson, Niklas Loman, Qiu-Xia Zhang, Oskar Johannsson, Håkan Olsson, and Äke Borg

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**Abstract**

Breast cancer is a rare disease in men, affecting less than 0.1% of the male population. Two heritable gene defects have been associated with a predisposition to male breast cancer development, i.e., germ-line mutations in the breast cancer susceptibility gene *BRCA2* and the androgen receptor (*AR*) gene. In this study, the entire coding regions of *BRCA2* and *AR* were screened for mutations in 34 consecutive male breast cancer patients. Five different truncating *BRCA2* mutations were identified in 7 (21%) of the 34 cases, with all mutations being of germ-line origin. Three of the mutated cases carried the same mutation (4186delG), which has been found earlier in two Swedish families with multiple female breast cancer cases. Haplotype analysis supported a common ancestry of 4186delG. One mutation, 6583delTT, was found in a male carrying a previously identified COOH-terminal polymorphic stop codon (Lys3326ter). No differences were seen between mutation carriers and noncarriers with respect to clinical stage and estrogen or progesterone receptor status. Mutation carriers tended to be younger at diagnosis. No germ-line *AR* mutations were found in the present material, but the number of AR polyglutamine repeats tended to be lower among mutation carriers. Most surprisingly, only one of the seven *BRCA2* mutation carriers had a positive family history of breast cancer, suggesting a lower penetrance of some *BRCA2* mutations or an influence of modifying factors for disease development in males and females. The present study implies that approximately one-fifth of all male breast cancer cases in the Swedish population are due to germ-line *BRCA2* mutations.

**Introduction**

It is estimated that approximately 10% of all breast cancer cases in the developed countries are caused by inherited changes in the genome (1, 2). The two major breast cancer susceptibility genes thus far identified, *BRCA1* and *BRCA2*, are considered to account for two-thirds of these inherited cases (3-5), although more recent population-based studies of familial breast cancer suggest a lower rate (6). Mutations in *BRCA1* and *BRCA2* are regarded as highly penetrant in most families, and diagnosis of cancer at an early age is common. Mutations in *BRCA1* and, to a lesser extent, *BRCA2* confer a significant risk also of ovarian cancer. Moreover, the risk of breast cancer is substantially elevated also in male *BRCA2* mutation carriers (1-5).

Breast cancer in males is a hundred times less common than in females and responsible for only 1% of all cancers in men (2, 7-10). Breast cancer in men resembles that seen in women, although age at diagnosis and the proportion of steroid receptor positivity and large-sized tumors tend to be higher in males. Histologically, the diseases are similar, but lobular cancer is rare in men. Suggested risk factors for male breast cancer development include some specific for men such as undescended testes, orchietomy, orchitis, and the Klinefelter syndrome, as well as other factors associated with an elevated estrogen:androgen ratio, including estrogen use, late puberty, obesity, and infertility (7-10). Indeed, breast cancer has been reported in males with germ-line *AR* gene mutations and a partial AIS (11, 12). It has been estimated that up to 30% of all males with breast cancer may have a family history of the disease (13). The frequencies of *BRCA2* mutations thus far reported in male breast cancer vary considerably (4-40%), however, possibly being influenced by the low number of cases investigated or by strong founder effects in certain populations (14-16).

In the present study, we have screened DNA from 34 consecutive male breast tumors for mutations in the *BRCA2* and *AR* gene. We report on the finding of a high frequency (21%) of *BRCA2* germ-line mutations and of a striking absence of a positive family history of breast cancer in mutation carriers.

**Materials and Methods**

**Patient and Tumor Material.** During the years 1971–1989, a mean of 29 new cases of male breast cancer were diagnosed yearly in Sweden, corresponding to an age-standardized incidence rate of 0.7 cases/100,000 inhabitants. The incidence rate for female breast cancer during the same period was 92/100,000 (Atlas of Cancer Incidence in Sweden; Team Offset, Malmö, Sweden, 1995).

In the southern Sweden health care region, a total of 67 new male breast cancers was reported between 1983–1992 [Cancer Incidence in Southern Sweden 1983–1987 (1989) and Cancer Incidence in Southern Sweden 1988–1992 (1994)]. The present study was performed on a series of 34 male breast cancer cases diagnosed in southern Sweden between 1985 and 1996. Provided that the incidence rate is stable, these 34 cases correspond to 42% of the total number of male breast cancer diagnosed during this time period.

The material represented consecutive cases in which frozen tumor specimens were available for DNA extraction. Age at time of diagnosis varied between 45 and 91 years, with a median value of 69 years and a mean value of 67.3 years.

All but one of the males were diagnosed with invasive breast cancer, the remaining male being found to have an *in situ* breast cancer on reexamination of pathological records. One patient was affected by bilateral invasive breast cancer. The family history regarding breast cancer and other malignancies was not known at the time of material collection, except in one case, in which the man in question was the index case of a previously analyzed breast cancer family. Lund 131 (17). Family history of cancer diagnoses was investigated through medical records and, when possible, via the Census Registry and the Swedish Cancer Registry. This evaluation was complete for all but one of the seven *BRCA2* mutation carriers; the seventh patient was a Hungarian immigrant about whom information was available solely from the medical record. Among the 27 cases without detectable *BRCA2* mutation, family history was available from relatives. In some cases, information on second- and third-degree relatives was also obtained. There might be cases of cancer among parents to the index individuals that have escaped our investigations, because information on patients and tumors was obtained through a review of medical records.
BRCA2 GERM-LINE MUTATIONS IN MALE BREAST CANCER

Table 1  Characteristics of male breast cancer patients with a BRCA2 germ-line mutation

<table>
<thead>
<tr>
<th>Sample</th>
<th>Exon</th>
<th>Mutation</th>
<th>Change</th>
<th>Mode of detection</th>
<th>Age</th>
<th>TNM</th>
<th>Stage</th>
<th>ER-PgR</th>
<th>Other malignancies and family history of malignancies (age at diagnosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca 7091</td>
<td>11</td>
<td>G4486T</td>
<td>1320ter</td>
<td>PTT</td>
<td>56</td>
<td>T2N3M0</td>
<td>II</td>
<td>250-140</td>
<td>F: meningioma (70); M: cervix uteri (69); MF: colon (84)</td>
</tr>
<tr>
<td>Ca 7133</td>
<td>4486delE</td>
<td>1447ter</td>
<td>PTT</td>
<td>58</td>
<td>T2N3M0</td>
<td>I</td>
<td>200-260</td>
<td></td>
<td>I: ventricular leiomysoma; S: cervix (44); S: fallopian tube (55); D: cervix in situ (25)</td>
</tr>
<tr>
<td>Ca 11693</td>
<td>4486delE</td>
<td>1147ter</td>
<td>PTT</td>
<td>76</td>
<td>T2N3M0</td>
<td>III</td>
<td>220-250</td>
<td></td>
<td>F: lung (78), prostate (78); B: lung (70); D: malignant melanoma (42)</td>
</tr>
<tr>
<td>BB6795</td>
<td>11</td>
<td>G4486delE</td>
<td>1447ter</td>
<td>PTT</td>
<td>47</td>
<td>T2N3M0</td>
<td>III</td>
<td>170-34</td>
<td>I: chronic lymphatic leukemia (62); F: prostate (?); PA: brain (?); PA: ventricular (?)</td>
</tr>
<tr>
<td>Ca 9167</td>
<td>6503delT</td>
<td>2098ter</td>
<td>PTT</td>
<td>69</td>
<td>T2N3M0</td>
<td>II</td>
<td></td>
<td></td>
<td>B: possibly leukemia (?)</td>
</tr>
<tr>
<td>Ca 11056</td>
<td>23</td>
<td>9326insA</td>
<td>304ter</td>
<td>SSCP</td>
<td>45</td>
<td>T2N3M0</td>
<td>III</td>
<td>2-41</td>
<td>M: breast (47); PA: corpus uteri (54); PU: acute myelocytic leukemia (73)</td>
</tr>
<tr>
<td>Lund 131</td>
<td>25</td>
<td>9653delE</td>
<td>3162ter</td>
<td>SSCP</td>
<td>67</td>
<td>T2N3M1</td>
<td>IV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exon</th>
<th>Variation</th>
<th>Change</th>
<th>Predicted effect</th>
<th>Frequency</th>
<th>Mode of detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>G203A</td>
<td>5'-UTR*</td>
<td>Silent</td>
<td>Frequent</td>
<td>SSCP</td>
</tr>
<tr>
<td>2</td>
<td>T295+362G</td>
<td>Intron</td>
<td>Unknown</td>
<td>1/34</td>
<td>SSCP</td>
</tr>
<tr>
<td>8</td>
<td>T1860-69C</td>
<td>Intron</td>
<td>Unknown</td>
<td>1/34</td>
<td>SSCP</td>
</tr>
<tr>
<td>14</td>
<td>A7470G</td>
<td>Ser2414Ser</td>
<td>Silent</td>
<td>Frequent</td>
<td>SSCP</td>
</tr>
<tr>
<td>18</td>
<td>G8410A</td>
<td>Val2728Ile</td>
<td>Missense</td>
<td>1/34</td>
<td>SSCP</td>
</tr>
<tr>
<td>27</td>
<td>A10204T</td>
<td>Lys3326ter</td>
<td>Protein truncation</td>
<td>1/34</td>
<td>Sequencing</td>
</tr>
</tbody>
</table>

* UTR, untranslated region.

The identified mutations were verified as being of germ-line origin by analysis of blood or normal archival tissue.

**Microsatellite Analysis.** The 5' primer of D13S171 (MapPair; Research Genetics) was labeled in a 10-µl volume containing 1X polynucleotide kinase buffer, 10 units of T4 polynucleotide kinase (Promega), 10 µM 5' primer, and 3 µl of [γ-32P]ATP (10 µCi/µl, 5000 Ci/mmol; Amersham). The reaction was incubated at 37°C for 30 min, and the labeled primer was stored at 4°C. The PCR reactions were carried out in 20-µl volumes containing 1X PCR reaction buffer, 0.2 µM each deoxynucleotide triphosphate, 1.7 mM MgCl2, 0.1 µM labeled 5' primer, 0.1 µM unlabeled 5' primer, 0.75 units AmpliTaq Gold (Perkin-Elmer Corp.), and 100 ng of template DNA. The cycling conditions were: activation of the enzyme at 93°C for 1 min, 50°C for 1 min, and 72°C for 1 min, with a final extension at 72°C for 5 min. Samples were diluted 4:7 with denaturing loading buffer (as above), denatured for 5 min at 95°C, and chilled on ice. Gels containing 6% polyacrylamide/urea (Amresco), 1X Tris-borate EDTA, 8 M urea, 250 µl of 20% ammonium persulfate, and 25 µl of N,N',N''-tetramethylethylenediamine were prerun at 80 W for 30 min before the samples were loaded and then run at 80 W for another 2 h. Gels were transferred to Whatman chromatography paper, covered with plastic wrap, and placed on Cronex-4 X-ray film (DuPont) for 2 h at -70°C.

**AR Gene Analysis.** The eight exons of the AR gene were screened for mutations using SSCP or sequence analysis as described above and 12 primer pairs as described elsewhere. The large AR exon 1 was screened with five overlapping fragments comprising several stretches of repetitive sequences. The long and highly variable polyglutamine (CAG) repeat was investigated in detail using sequence and microsatellite analysis to determine the exact number of repetitive units.

**Results and Discussion.** We analyzed the entire coding region of the BRCA2 and AR genes in breast tumors from 34 male patients. Although no case of AR mutation was observed, five different and presumably disease-causing BRCA2 mutations were identified in 7 (20.6%) of the 34 cases (Table 1). The mutations were detected by either PTT or SSCP and were confirmed by sequencing. These screening techniques have certain limitations that should be pointed out. The mutation detection sensitivity of SSCP has in our hands been estimated to approximately 80% (17). PTT, used to screen exons 10 and 11, is useful for rapid and on cases diagnosed before 1958 is scarce and we rely on medical records and parish registers only.

PTT. PTT was used in screening BRCA2 exons 10 and 11 for nonsense or frameshift mutations, causing truncation of the protein. Exon 10 was amplified in one fragment, and exon 11 was amplified in four partly overlapping fragments, using previously published primers (17). The PCR reactions were carried out in 25-µl volumes, containing 1X PCR reaction buffer [10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM MgCl2, 0.2 mM each deoxynucleotide triphosphate, 0.1 mg/ml BSA, 0.25 µM each primer, 0.75 units of AmpliTaq Gold (Perkin-Elmer Corp.), and 80-100 ng of genomic DNA. The reactions were covered with mineral oil and amplified in an Omnigene Thermal Cycler (Hybaid) as follows: activation of the enzyme at 93°C for 1 min followed by 33 cycles of 93°C for 30 s, 55°C for 30 s, and 72°C for 45 s, with a final extension at 72°C for 5 min. The PCR products were transfected and translated into proteins using the TNT T7 Capped Tuttucyte Lysate System (Promega) and [35S]methionine (Amersham Corp.) according to the manufacturer's protocol. The proteins were size separated on 15-17.5% SDS-PAGE gels and visualized by exposing the dried gels to Biomax X-ray films (Kodak) for 2-48 h.

SSCP. SSCP was used in screening for nonsense, missense, or frameshift mutations in all BRCA2 exons except exons 3, 5, 6, 10, and 11. The larger exons 14, 18, 25, and 27 were divided into two to four SSCP fragments. PCR was carried out as described above, with the exceptions that the reaction volume was 15 µl, and 3.2 µM dCTP and 0.1 µl [α-32P]dCTP (10 µCi/µl, 3000 Ci/ml; Amersham) were used instead of 0.2 µM dCTP. The primer sequences were previously published as us (17). The samples were diluted 1:8 with denaturing loading buffer (95% formamide, 10 mM NaOH, 0.05% bromphenol blue, and 0.05% xylene cyanol), denatured for 5 min at 95°C, and loaded on gels consisting of 5X Hydrolink mutation detection enhancement (AT-Biochem), 0.6X Tris-borate EDTA, 5% glycerol, 240 µl of 20% ammonium persulfate, and 24 µl of N,N',N''-tetramethylethylenediamine. Gels were run at 6 W for 16-18 h at room temperature, except for exon 23, which was run at 35 W at 4°C without glycerol. Gels were transferred to Whatman chromatography paper, covered with plastic wrap, and placed on Cronex-4 X-ray film (DuPont) for 4-48 h at -70°C.

**Sequencing.** In mutation screening, BRCA2 exons 3, 5, and 6 were directly sequenced in all samples. Moreover, positive findings from SSCP and PTT were confirmed by sequencing. PCR was carried out as described above, with the forward primers containing M13 sequences. The primer sequences have previously been published by us (17). Sequencing was performed on an ABI 373 Sequencer with the Dye Primer Cycle Sequencing Ready Reaction 21 M13 kit (Perkin-Elmer) according to the manufacturer's instructions, with 4.75% denaturing acrylamide gels.

4 Q-X. Zhang and Å. Borg, submitted for publication.
sensitive detection of nonsense and frameshift mutations, but it will not detect missense mutations. This may be a considerable limitation considering the presence of functionally important regions, such as the eight evolutionarily conserved BRC motifs in exon 11, shown recently to provide contact with the RAD51 protein (18). Moreover, mutations in regulatory regions, as well as larger deletions or rearrangements within the gene, will be missed by the current screening approach. By analyzing blood or normal tissue, all seven mutations were found to be of germ-line origin. Three of the five mutations were frameshifting deletions of one or two nucleotides, one was a frameshifting insertion of one nucleotide, and one was a nonsense mutation; all were predicted to result in truncated protein products. Three (60%) of the mutations occurred in exon 11, which accounts for 47% of the coding region, whereas the two remaining mutations were located in exons 23 and 25, respectively. Thus, the present study provides no evidence for a variation in the risk of female and male breast cancer with the location of the BRCA2 mutation, in contrast to the suggested association between mutations in a 3.3-kb region of exon 11 and increased risk of ovarian cancer (19).

One mutation, 4486delG, was found in three of the male patients. The same mutation has previously been found in two large Swedish breast cancer families, Lund 10 and 11, unrelated as far back as 1860 (17), but thus far not in other populations. A common ancestry for the five families is supported by their origin in a very small area in the south of Sweden and by the finding of a shared allele for marker D13S171 (data not shown). Thus, 4486delG is probably a unique Swedish founder mutation. On the other hand, two of the five distinct BRCA2 mutations in the present study have been identified previously in other familial breast cancer cohorts. One of these mutations, 9326insA, discovered in tumor Ca 11056 from a Hungarian immigrant, has also been identified in a Hungarian breast cancer family (20). The mutation in tumor Ca 9167, 6503delTTT, has been described earlier in at least five families of western European and North American origin. Interestingly, this mutation was found to coincide with a polymorphic stop codon in exon 27 (Lys3326ter, the result of an A-to-T substitution at nucleotide 10204; Ref. 21). Indeed, the same polymorphism was also found in tumor Ca 9167. It seems most likely that all individuals carrying both the 6503delTTT mutation and the A10204T alteration have a common ancestor. This polymorphic stop codon does not seem to confer an increased risk of breast cancer development; therefore, the last 93 amino acids of BRCA2 (including a putative granin sequence) may be dispensable to the function of the protein (21). In addition to the Lys3326ter polymorphism, several of the other sequence variants identified in the present study were interpreted as polymorphisms (Table 2). The substitution of valine for isoleucine at position 2728 (G8410A in exon 18) has not been reported previously, nor was it present in a control material of >100 chromosomes. However, given that this represents a conservative amino acid shift, both residues having hydrophobic side chains of similar size, its functional effect is probably insignificant.

The reported frequencies of BRCA2 mutations in male breast cancer vary considerably between different investigated populations. Friedman et al. (16) analyzed a population-based series of 54 male breast cancer cases from Southern California and identified only two (4%) BRCA2 mutation carriers. This is strongly contrasted by the observation that 40% (12 of 30 cases) of all male breast cancer diagnosed in Iceland during the past 40 years are carriers of the founder BRCA2 mutation 999del5 (14). An intermediate mutation rate (14%) was reported by Couch et al. (15) in their study of 50 male breast cancer patients unselected for family history. If the potential effect of our own founder mutation (4486delG) is taken into account, the frequency of BRCA2 mutations in male breast cancer cases will be 16% (five distinct mutations in 32 patients).

Interestingly, a positive family history of breast cancer was evident merely in one (Lund 131) of the seven BRCA2 mutation carriers, although other malignancies were frequently present (Table 1). This lack of breast cancer in the families could only to some extent be explained by mutation transmission through unaffected males, by less extensively expanded pedigrees, or by a chance scarcity of female carriers in these particular kindreds. More likely, these observations indicate that some BRCA2 mutations have a lower penetrance and/or that modifying genes and environmental factors may influence the phenotypic expression. A lower penetrance has previously been suggested for the Ashkenazi Jewish 6174delT founder mutation, as compared to previous risk estimates and corresponding BRCA1 founder mutations (22, 23). In the present study, the 4486delG mutation was identified in three males without a family history of the disease. However, the same mutation is obviously highly penetrant in the two extensive breast cancer families, Lund 10 and 11, in which, however, no case of an affected male has been observed. This is in accordance with the study of Icelandic BRCA2 families, in which the 999del5 mutation was reported to have variable penetrance, as well as being associated with various phenotypes, in different families (14). Further studies are required to clarify whether a genetic, hormonal, or exogenous factor may modify the risk and phenotypic expression in BRCA2 mutation carriers. Parity and age at last childbirth have been suggested to influence the risk of breast and ovarian cancer in BRCA1 mutation carriers, as have the number of tandem repeats in the HRAS1 gene (24, 25).

Two germ-line AR mutations have been associated with predisposition to breast cancer. Both of them are located in exon 3, which encodes the second zinc finger, and occurred in males with breast cancer from two unrelated families with partial AIS (11, 12). An Arg607Gln substitution was found in two brothers with breast cancer (ages 55 and 75 years) and the Reifenstein syndrome, and an Arg608Lys substitution was identified in a 38-year-old man with the same partial AIS phenotype. Both Arg residues are highly conserved within the nuclear receptor family and located in the basic region near the tip of the second finger. Whereas other AR mutations affecting the conserved zinc finger residues usually cause a loss of DNA binding and a complete AIS phenotype, these mutants may be deficient in transactivation, not as a result of a DNA binding abnormality, but because of defective interaction with other proteins. Alternatively, although the mutations are not located in the P box (important for hormone-responsive element recognition), the mutant ARs may exhibit an altered sequence-specific DNA binding, possibly having acquired the ability to bind to estrogen-responsive elements and to activate estrogen-regulated genes (11, 12). Thus, an elevated estrogen: androgen activity ratio may promote breast tumor growth in males. However, in the present study, we found no evidence of germ-line or somatic AR mutations.

The highly variable polyglutamine tract (CAG repeat), located in the NH2-terminal transactivation domain of the AR, may also affect receptor activity. The length of this tract varies in different normal individuals from approximately 12–32 residues, mostly commonly being in the range of 20–25 units, and manifests also a population-dependent variation (26). Expansion of the CAG repeat has been associated with reduced AR expression and/or transactivation (27, 28) and results in its extreme measures (>40 repeats) in Kennedy's disease, with symptoms such as partial AIS and muscle atrophy (26). On the other hand, a low number of CAG repeats may result in a transcriptionally more active AR (28) and has been linked to an increased risk of prostate cancer (29). In the present study, there was

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5 This information is available from the Breast Cancer Information Core database at http://www.nchgr.nih.gov/intramural_research/Lab_transfer/Bic.
no significant difference in the number of AR polyglutamine residues in male breast cancer patients as compared to a group of healthy male blood donors, although ≥30 repeats were observed only among the former (Fig. 1). There was, however, among the male breast cancer cases a tendency toward a lower number of repeats in BRCA2 mutation carriers (median, 21 repeats) than in noncarriers (median, 24 repeats). Additional studies, including also female BRCA2 mutation carriers and noncarriers, are needed to evaluate the potential modifying effect of the AR polyglutamine repeat on risk for sporadic and inherited breast cancer development.

The age at disease onset in the BRCA2 mutation carriers (mean age, 62.9 years) was below the average age of that for the men included in this study (mean age for non-BRCA2 cases, 69.5 years), but there was no significant difference with respect to clinical stage at diagnosis (data not shown). It has been reported that about 85 and 75% of male breast tumors are positive for estrogen and progesterone receptors, respectively, a higher frequency than seen in female breast cancers (7-10). This is supported by the results of the present study, also demonstrating that there is no difference in receptor status between patients with BRCA2 mutations as compared to those without (data not shown).

It has been estimated that around 30% of all male breast cancer patients have a family history of breast cancer, with at least one first- or second-degree relative affected by the disease (13, 16). The present study suggests a lower frequency, as only 4 (13%) of 31 investigated cases had a positive family history of breast cancer (Tables 1 and 2). Moreover, this was equally frequent among BRCA2 mutation carriers (1 of 7) as among those without detectable mutation (3 of 24 valid),

Table 3 Characteristics of male breast cancer patients without detectable BRCA2 germ-line mutation

<table>
<thead>
<tr>
<th>Sample</th>
<th>Age</th>
<th>TNM</th>
<th>Stage</th>
<th>ER:PgR*</th>
<th>Other malignancy, and family of malignancies (age at diagnosis)*</th>
<th>Other malignancy, and family of malignancies (age at diagnosis)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca 4187</td>
<td>66</td>
<td>T, N, M</td>
<td>II</td>
<td>250:0</td>
<td>B: Mb Hodgkin (46); F: prostate (87)</td>
<td></td>
</tr>
<tr>
<td>Ca 6178</td>
<td>57</td>
<td>T, N, M</td>
<td>II</td>
<td>300:600</td>
<td>S: breast (52); M: bladder (69); F: osteosarcoma (7)</td>
<td></td>
</tr>
<tr>
<td>Ca 6461</td>
<td>74</td>
<td>T, N, M</td>
<td>II</td>
<td>220:190</td>
<td>S: ovary (63); B: small cell lung cancer (76)</td>
<td></td>
</tr>
<tr>
<td>Ca 6688</td>
<td>80</td>
<td>T, N, M</td>
<td>I</td>
<td>200:140</td>
<td>S: colorectal carcinoma in situ (57); B: prostate (75); B: pancreas (53)</td>
<td></td>
</tr>
<tr>
<td>Ca 6693</td>
<td>91</td>
<td>T, N, M</td>
<td>III</td>
<td>330:5:5</td>
<td>S: malignant melanoma (86); S: acute lymphatic leukemia (68)</td>
<td></td>
</tr>
<tr>
<td>Ca 6752</td>
<td>76</td>
<td>T, N, M</td>
<td>I</td>
<td>240:94</td>
<td>F: skin (73)</td>
<td></td>
</tr>
<tr>
<td>Ca 7046</td>
<td>65</td>
<td>T, N, M</td>
<td>I</td>
<td>260:140</td>
<td>S: colorectal carcinoma in situ (57); B: prostate (75); B: pancreas (53)</td>
<td></td>
</tr>
<tr>
<td>Ca 7160</td>
<td>54</td>
<td>T, N, M</td>
<td>II</td>
<td>100:17</td>
<td>S: malignant melanoma (78); M: unknown cancer, dead at age 81</td>
<td></td>
</tr>
<tr>
<td>Ca 7361</td>
<td>73</td>
<td>T, N, M</td>
<td>I</td>
<td>330:73</td>
<td>D: cervix uteri (46) breast (51); F: prostate (7); S: unknown cancer (7)</td>
<td></td>
</tr>
<tr>
<td>Ca 7737</td>
<td>61</td>
<td>T, N, M</td>
<td>I</td>
<td>440:810</td>
<td>E: NHL (46); S: colorectal carcinoma in situ (72); M: colorectal (72)</td>
<td></td>
</tr>
</tbody>
</table>

* ER, estrogen receptor; PgR, progesterone receptor (values are shown in fmol/mg protein). |
suggesting that family history of breast cancer is an inadequate indicator of disease inheritance in males. Neither was any other malignant tumor type consistently present in relatives of BRCA2 mutation carriers. Among noncarriers, the following other cancer types were present in more than one family: malignant melanoma, prostate cancer, colorectal adenomas/invasive cancer, and nonmelanoma skin cancer (each seen in four families, in all cases including three relatives and the index individual), and cancer corpus uteri and cancer/carcinoma in situ cervix uteri (each seen in two families) (Table 3). Seven (29%) of the 24 non-BRCA2 cases had no family history of cancer. Clear cell carcinoma of the kidney was seen in a man presenting with four primary tumors (also a colorectal cancer and a small bowel carcinoid, in addition to his breast cancer and hypernephroma), as well as in two relatives (father and paternal uncle) within another family. Taken together, these results imply that other hereditary syndromes associated with an increased risk for male breast cancer may exist, malignant melanoma and breast cancer perhaps being the most intriguing combination, as judged from this material.

In conclusion, the results from the present study imply that BRCA2 may account for approximately one-fifth of all male breast cancer cases in Sweden, but also that the recognition of these cases could not be based on family appearance of the disease. From a clinical genetic point of view, all new male breast cancer cases, with or without a family history, should be considered as possible inherited cases.

References

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