Review

Counseling for male BRCA mutation carriers — a review

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Abstract

BRCA mutations in women confer a high risk for breast and ovarian cancers. The risks to male carriers are poorly understood and risk management strategies undescribed. This review summarizes current evidence and gives recommendations for counseling male BRCA mutation carriers.

Reported risks for breast, prostate, pancreatic, gastric and hematologic cancers are higher in male BRCA mutation carriers vs non-carriers. Especially in male BRCA2 mutation carriers under age 65 prostate and pancreatic cancer risks are increased. The risk increase for primary cancers of organs like the liver, bone and brain is difficult to assess as these organs are common sites for metastases. Reports on colorectal cancer and melanoma risks are inconclusive. On the current limited evidence available, male BRCA mutation carriers should be regarded as at high risk for breast, prostate, gastric, pancreatic and colorectal cancers; surveillance by appropriate investigations should start at age 40 years.

Keywords: BRCA; Male; Prostate; Pancreas; Colon; Gastric cancer

Introduction

Mutations in BRCA1 and BRCA2 are responsible for the largest number of inherited breast cancers and a large proportion of ovarian cancers.1 Both BRCA1 and BRCA2 are involved in pathways important for DNA damage recognition, double-strand break repair, checkpoint control, transcription regulation, and chromatin remodeling. These functions are essential and important for all cell types. Mutation of these genes will lead to initiation and proliferation of cancer cells.2

BRCA gene mutations are inherited as autosomal dominant. There are equal chances of both male and female offspring to inherit the mutated genes from their parents. Despite the general nature of BRCA functions, tumors in female mutation carriers predominantly occur in breast and ovary. The risk for cancers other than breast or ovarian in female BRCA1 or BRCA2 mutation carriers has been examined with conflicting results (Table 1). As men may also be carriers of the mutations, it is important to estimate, whether there is also an increased risk of malignancy in male mutation carriers and consequently, how male carriers should be counseled. This paper examines the available evidence and gives recommendations for counseling in male BRCA mutation carriers.

Mechanism of actions of the BRCA genes

Biochemical, genetic and cytological studies have revealed multiple functions for BRCA1 and BRCA2.3–6 However, their primary roles as a tumor suppressor gene are to maintain genomic stability through DNA repair system and involved in transcriptional regulation process. Within minutes of DNA damage, the BRCA1 gene product is recruited to sites of double-strand DNA breaks7 and initiates repair by modifying the local chromatin structure, thereby allowing other DNA repair proteins access to the damaged site. It interacts directly and indirectly with many other proteins, including a large number of cell cycle and checkpoint control proteins.8
Table 1
Epidemiologic studies on BRCA gene mutation with data on the risk of prostate and other cancers

<table>
<thead>
<tr>
<th>Authors</th>
<th>Base of study</th>
<th>Number of individuals studied</th>
<th>Risk of prostate cancer</th>
<th>Risk of other cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ford et al., 1994&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Studied 33 families collected by research groups in North America and Western Europe, comprising the Breast Cancer Linkage Consortium</td>
<td>464 BRCA1 mutation carriers</td>
<td>Significant increase in prostate cancer (RR = 5.12)</td>
<td>Significantly increased risk in colon cancer (RR = 4.11), liver (RR = 3.51), stomach (RR = 3.25), bone (RR = 2.02), and brain (RR = 2.08)</td>
</tr>
<tr>
<td>Easton et al., 1997&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Cancer risks in two large breast cancer families linked to BRCA2 on chromosome 13</td>
<td>Extended families including nearly 500 individuals</td>
<td>By the age of 70 years, estimated risk 16% vs 1%: by age 80 years, estimated risk 39% vs 10% for BRCA1/BRCA2 mutation</td>
<td>The cumulative risk of breast cancer in male carriers was estimated to be 6.3% by age 70 years. RR for laryngeal cancer 7.67</td>
</tr>
<tr>
<td>Struweing et al., 1997&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Ashkenazi Jew population in Washington DC who filled up the epidemiologic questionnaires were analysed for BRCA mutation status</td>
<td>5318 subjects. (Risk of cancers were estimated by comparing the cancer histories of relatives of carriers of the mutations and non-carriers) 120 carriers of BRCA1/BRCA2 mutation</td>
<td>By the age of 70 years, estimated risk 16% vs 1%: by age 80 years, estimated risk 39% vs 10% for BRCA1/BRCA2 mutation</td>
<td>Incidence of colon cancer not elevated. Observed elevation in pancreatic cancer and lymphoma but not statistically significant.</td>
</tr>
<tr>
<td>BCLC, 1999&lt;sup&gt;19&lt;/sup&gt;</td>
<td>173 breast-ovarian cancer families with BRCA2 mutations identified at 20 centers in Europe and North America</td>
<td>3728 individuals, of whom 50 were men with breast cancer and 631 were women with breast cancer below the age of 60 years or with ovarian cancer at any age. Incidence rates were compared with population numbers were small</td>
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<tr>
<td>Risch, 2001&lt;sup&gt;38&lt;/sup&gt;</td>
<td>A population-based series of 649 unselected incident cases of ovarian cancer diagnosed in Ontario, Canada, during 1995–1996 was screened for germinal mutations in BRCA1 and BRCA2</td>
<td>Among the 515 women with invasive cancers, 60 mutations were identified, 39 in BRCA1 and 21 in BRCA2. No mutations were seen in the 134 women with borderline tumors</td>
<td>By the age of 70 years, estimated risk 16% vs 1%: by age 80 years, estimated risk 39% vs 10% for BRCA1/BRCA2 mutation</td>
<td>Multiple myeloma, Hodgkin’s disease and lung cancer were more common among mutation carriers but numbers were small</td>
</tr>
<tr>
<td>Thompson and Easton BCLC 2002&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Family of BRCA1 mutation carriers. (The observed cancer incidence was compared with the expected cancer incidence-based on population cancer rates)</td>
<td>11,847 individuals from 699 families segregating a BRCA1 mutation that were ascertained in 30 centers across Europe and North America</td>
<td>Elevated risk of prostate cancer for BRCA mutation carrier younger than 65 years (RR = 1.82), but not for those 65 years old or older, RR = 0.84</td>
<td>Risks of stomach cancers and leukemias/lymphomas were increased, six-(RR = 6.2) and three-fold (RR = 2.6), respectively, among first-degree relatives of cases carrying BRCA1 mutations, compared with relatives of non-carriers; risk of colorectal cancer was increased three-fold for relatives of cases carrying BRCA2 mutations (RR = 2.5)</td>
</tr>
<tr>
<td>Foulkes et al., 1999&lt;sup&gt;21&lt;/sup&gt;</td>
<td>N. American AJ women with breast cancer</td>
<td>412</td>
<td>Risk of prostate cancer by the age of 85 years among first degree relatives of Jewish breast cancer cases: with mutations in BRCA2 mutation carriers 34%, without mutations 13%</td>
<td>Significantly increased risk of pancreatic cancer (RR = 2.26). This RR was similar in men and women but declined with age. Cancers of the colon (RR = 2.03) no excess risk of colorectal cancer was observed in men (RR = 0.93), liver (RR = 4.06), other cancers (RR = 7.40), and cancers of unknown site (RR = 3.45), there was no evidence of an increased risk of other cancers in men (carrier RR = 2.10; non-carrier RR = 3.36). The cancer risks in men younger than 65 years old were also very similar to those expected (RR = 1.05)</td>
</tr>
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</table>
The BRCA2 protein is part of the homologous recombination DNA repair complex. The complex repairs double-strand breaks by homologous recombination through interaction with RAD51, a key component of the double-strand break repair pathway. In the absence of BRCA2, critical events in the initiation of homologous recombination are impaired; repair and replication errors accrue with each cell cycle. Cells lacking BRCA2 are highly sensitive to DNA damage and display marked genetic instability.

Cells that have inactivating mutations of BRCA1 or BRCA2 are unable to repair DNA damage sustained in the successive cell cycles and eventually die. Few surviving cells accumulate chromosomal abnormalities such as chromosomal breaks, severe aneuploidy and centrosome amplification. These accumulated genetic instabilities enable additional mutations and often occur in genes essential to cell cycle checkpoint activation. Mutation of a checkpoint genes enables a BRCA mutation carrying cells to escape death permanently and to proliferate, resulting in tumor formation.

### BRCA gene mutation with risk of cancer in men

#### Male breast cancer

Male breast cancer (MBC) is a rare disease. Its incidence varies by race and geographical location, suggesting that ethnic and local environmental factors may modify the disease risk at population level. BRCA2 gene mutations have been shown to confer a significantly higher risk of breast cancer in men than BRCA1 mutations (Table 2). In high risk breast/ovarian cancer families, BRCA1 and BRCA2 gene mutations are estimated to be associated with 16 and 76%, respectively of the MBCs. In MBCs unselected for family history, the prevalence of BRCA1/BRCA2 mutations has been investigated in populations, such as the United Kingdom, Iceland, continental Europe, the United States and Israel. The frequency of BRCA2 mutations varied considerably. Friedman et al. identified only two germ-line BRCA2 mutations in 54 (4%) male breast cancer cases from Southern California.

### Table 1 (continued)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Base of study</th>
<th>Number of individuals studied</th>
<th>Risk of prostate cancer</th>
<th>Risk of other cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brose et al., 2002</td>
<td>Clinic-based study. 483 patients (381 female, 102 male) from 147 families with documented BRCA1 mutations</td>
<td>316 (260 female: 56 male) tested positive for BRCA1 mutation: 167 presumed carrier</td>
<td>Cumulative age-adjusted risk 6.2% vs 15.9% of population risk (SEER 2000 data) (significantly lower — possible underestimate due to small number of older men in the study)</td>
<td>RR vs SEER 2000 data of colon cancer 2.0, RR of gastric cancer 6.9, RR of pancreatic cancer 2.8 RR of male breast cancer 58.2 (cumulative age-adjusted risk 5.8% vs 0.1% of population risk)</td>
</tr>
<tr>
<td>Bermejo and Hemminki, 2003</td>
<td>The families of the Swedish Family-Cancer Database with at least three generations</td>
<td>944,723 who eligible for BRCA1/BRCA2 test. Subgroup 2 bcs &lt;50 years, 2 bcs one &lt;50, bilateral bc &lt;50, 1 bc &lt;35, bc and oc. *Compared to incidences in general population. SIR = standardized incidence ratio</td>
<td>Increased early onset of prostate cancer SIR families with 2 bcs one &lt;50 (1.18), 2 bcs &lt;50 (1.31), bilateral bc &lt;50 (1.45)</td>
<td>Increased risk of breast, stomach and primary liver cancer. Families with 2bcs &lt;50 years showed increased risk of cancer pancreas before 50 SIR 5.5; families with bc and oc presented increased incidences for ocular cancers SIR 3.84 and stomach cancer before age of 70 years SIR 2.04; families with 2 bcs; one &lt;50 years, showed increased risks of primary liver cancers SIR 1.77 Pancreas (RR = 5.9), bone (RR = 14.4) and pharynx (RR = 7.3). The risks for carriers younger than 65 years were higher for cancer of the pancreas (RR = 37.1) and pharynx (RR = 15.7). Furthermore, a significantly increased RR was observed for colon cancer before the age of 65 years (8.0). For those aged 65 years and older, a significant increase was only observed for pancreatic cancer (2.5). A small increase was observed for cancer of the digestive tract (RR = 1.5), brain (RR = 3.9)</td>
</tr>
<tr>
<td>van Asperen et al., 2005</td>
<td>1811 individuals from 139 BRCA2 families in The Netherlands. The RR for each cancer site was determined by comparing observed numbers with those expected, based on Dutch cancer incidence rates</td>
<td>441 tested for BRCA2 mutation (303 identified as carrier)</td>
<td>RR for prostate cancer 2.5, the risks even higher for younger carriers (&lt;73 years old) (RR = 8.0)</td>
<td></td>
</tr>
</tbody>
</table>

*bc, breast cancer; bcs, breast cancers; oc, ovarian cancer.
contrast, Thorlacius et al.\textsuperscript{15} found 40\% of all male breast cancer cases diagnosed in Iceland during the past 40 years carried a founder mutation in the BRCA2 gene. In other studies of unselected MBC patients, the incidence of gene mutations was between those extremes (Table 2). The incidence BRCA1 mutations was up to 11\%.\textsuperscript{16} In populations with known founder mutations, the incidence of BRCA mutations is usually higher.\textsuperscript{15,17} It stands to reason, however, that the frequency of BRCA mutations is probably underestimated in MBCs from populations without known founder mutations. In fact, the sensitivity of the most commonly used mutation screening techniques is regarded to be only about 70–80\%.\textsuperscript{13}

In addition, Brose et al.\textsuperscript{18} noted that male BRCA mutation carriers have a cumulative age-adjusted risk of 5.8\% to develop breast cancer vs 0.1\% for the normal population.

### Prostate Cancer

Early reports from the Breast Cancer Linkage Consortium and other family-based series suggested that families with deleterious mutations in BRCA1 and BRCA2 genes had an increase in risk of prostate cancer between three-fold to five-fold compared to families without known inherited predisposition (Table 1).\textsuperscript{1,19–24}

Several other groups have examined the incidence of deleterious BRCA1 and BRCA2 mutations in unselected series of patients with prostate cancer (Table 3)\textsuperscript{25–27} in Ashkenazi populations; deleterious BRCA mutations were not found to significantly increase prostate cancer risk in this population. This finding was also supported by two recent family-based series by Brose et al.\textsuperscript{18} and Thompson et al.,\textsuperscript{28} even though in Thompson series, an increased risk was observed in mutation carriers younger than 65 years old.

Kirchhoff et al., in a case control study of 251 cases of prostate cancer vs 1472 control cases screened for BRCA gene mutations, showed that, after the results were adjusted for age, the presence of an Ashkenazi Jew founder mutation in BRCA1 or BRCA2 had a significant association with prostate cancer risk. However, only BRCA2 mutations were associated with a significantly increased risk of prostate cancer while in BRCA1 mutation carriers the risk increase did not reach significance.\textsuperscript{29}

The association of BRCA2 mutation and increased risk of prostate cancer is also supported by family-based series in populations other than Ashkenazi Jews such as in The Netherlands\textsuperscript{30} and Sweden.\textsuperscript{31}

### Table 2

<table>
<thead>
<tr>
<th>Authors</th>
<th>Base of study/characteristic</th>
<th>Number of individuals studied</th>
<th>Incidence of carrier in cancer patients</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Couch et al., 1996\textsuperscript{64}</td>
<td>Analyzed 50 male breast cancer patients (unselected family history) for BRCA mutation</td>
<td>50</td>
<td>7/50 (14%) BRCA2 mutation</td>
<td></td>
</tr>
<tr>
<td>Friedman, 1997\textsuperscript{14}</td>
<td>Population-based 54 male breast cancer patients from Southern California analyzed for BRCA1/BRCA2 mutation</td>
<td>54</td>
<td>2/54 (4%) – BRCA2, no BRCA1</td>
<td></td>
</tr>
<tr>
<td>Thorlacius, 1997\textsuperscript{15}</td>
<td>1182 Icelander tested for BRCA2 mutation</td>
<td>520 – random population, 632 – female breast cancer patients (FBC), 30 – male breast cancer (MBC) patients</td>
<td>BRCA2 mutation detected in: 3/520 (0.6%) of random population 49/632 (7.7%) of FBC 12/30 (40%) of MBC</td>
<td></td>
</tr>
<tr>
<td>Haraldsson, 1998 Sweden\textsuperscript{65}</td>
<td>34 male breast cancer patients tested for BRCA2 mutation and AR gene</td>
<td>34</td>
<td>7/34 (21%) – BRCA2, no AR gene</td>
<td>Nearly 1/5 of all MBC in Sweden are due to BRCA2 gene mutation</td>
</tr>
<tr>
<td>Csokay, 1999 Hungary\textsuperscript{66}</td>
<td>18 male breast cancer patients and 3 gynaecomastia patients analyzed for BRCA1/BRCA2</td>
<td>18</td>
<td>6/18 (33%) – BRCA2 mutation, no BRCA1 mutation</td>
<td></td>
</tr>
<tr>
<td>Sverdlov et al., 2000\textsuperscript{67}</td>
<td>31 Jewish Israeli male breast cancer patient were analyzed for BRCA mutation (11 from high risk families, 20 from unselected for family history)</td>
<td>31</td>
<td>2/31 (6%) one patient with BRCA1 and BRCA2 each.</td>
<td>Both patients are from high risk group</td>
</tr>
<tr>
<td>Kwiatkowska, 2000 Poland\textsuperscript{68}</td>
<td>37 MBC analyzed for BRCA2 and AR gene</td>
<td>37</td>
<td>4/37 (11%) – BRCA2 mutation, no AR gene detected</td>
<td></td>
</tr>
<tr>
<td>Basham, 2001 UK\textsuperscript{69}</td>
<td>Population-based 94 MBC patients screened for BRCA1/BRCA2</td>
<td>94</td>
<td>5/94 (8%) – BRCA2, no BRCA1</td>
<td></td>
</tr>
<tr>
<td>Frank et al., 2002\textsuperscript{16}</td>
<td>76 male breast cancer patients analyzed for BRCA1/BRCA2 mutation</td>
<td>76</td>
<td>14 patients (18%) – BRCA2 mutation, 8 patients (11%) – BRCA1 mutation</td>
<td></td>
</tr>
<tr>
<td>Ottini, 2003 Italy\textsuperscript{70}</td>
<td>Population-based 25 MBC patients tested for BRCA mutation</td>
<td>25</td>
<td>4/25 (16%) BRCA2 mutated (3 BRCA2 and 1 BRCA1)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{1} H.B. Mohamad, J.P. Apffelstaedt / The Breast 17 (2008) 441–450
Several family-based studies have examined the association of BRCA mutations and the risk of pancreatic cancer. Most of the series showed an increased risk to develop pancreatic cancer in individuals with BRCA mutations or individuals at high risk of having a BRCA mutation. The relative risk (RR) increase was between 2.26 and 5.9 compared to the general population. Brose et al. in a clinic-based population study, analyzed 483 individuals from 147 families with documented BRCA1 mutation carriers for estimation of their cancer risk. The cumulative age-adjusted lifetime risk of pancreatic cancer was 3.6% (95% CI = 1.9%–5.3%), three times the estimated 1.3% population risk. Asperan et al. studied 1811 individuals from 139 BRCA2 families in The Netherlands. Of 441 individuals tested for BRCA2 mutations, 303 were identified as carrier. The RR for each cancer site was determined by comparing observed numbers with those expected, based on Dutch cancer incidence rates. They observed a six-fold increased risk for pancreatic cancer. Interestingly, the risk increase was independent of age (below or above 65 years old), but restricted to males.

Three other series report the prevalence of deleterious BRCA2 mutations in unselected series of patients with pancreatic cancer, BRCA2 mutation carrier status in these series increased the risk to develop pancreatic cancer. The prevalence of BRCA2 mutations was between 17.2% and 27% (Table 4).

Colorectal cancer

In 1994, the Breast Cancer Linkage Consortium reported that the risk of colorectal cancer in BRCA1 mutation carriers was significantly increased (RR = 4.11). The same consortium found no risk increase in BRCA2 mutation carriers (RR = 1.43).
Two further studies analyzed portions of the Breast Cancer Linkage Consortium data to further describe the risks of cancers in BRCA1 mutation carriers. Brose et al. found the cumulative age-adjusted risk of colon cancer in BRCA1 mutation carriers (11%, 95% CI = 8.2%–13.9%) two-fold increased relative to the general population of 5.6%. These data are clinically relevant, because estimates based on families ascertained for linkage studies may overestimate cancer risk in mutation carriers.

Thompson and Easton also reported a two-fold increase in colon cancer risk (RR = 2.03) but a statistically significantly decreased risk of rectal cancer (RR = 0.23) when BRCA1 mutation carriers were compared to those without such a mutation. No statistically significantly increased risk after combining the rectal and colon cancers in BRCA1 mutation carriers compared with those without such a mutation (RR = 1.25). Moreover, no excess risk of colorectal cancer was observed in men (RR = 0.93).

Risch et al. studied 515 women with ovarian cancer and identified an increased RR of colorectal cancer in male and female first-degree relatives of BRCA2 mutation carriers but not for relatives of BRCA1 mutation carriers (for BRCA1 mutation carriers, RR = 0.70, 95% CI = 0.17–2.8; for BRCA2 mutation carriers, RR = 2.5, 95% CI = 1.0–6.3), compared with those without such mutations in a family member. Neill and colleagues, reporting on BRCA1 and BRCA2 mutation carriers, found a non-significant increase of colon cancer risk. Kirchhoff et al. identified 6 BRCA carriers (1.02%) in 586 colorectal patients. The RR when compared to healthy group was only 0.50. Struwing et al. also did not find an association of BRCA mutations with the risk of colorectal cancer.

**Other cancers**

Only two epidemiologic studies have assessed the risk of developing leukemia for subjects with a high probability of carrying a BRCA mutation. Both studies showed a significantly increased risk. Risch et al. showed the RR to be 2.6 for first degree relatives of BRCA1 mutation carriers with ovarian cancer. The RR was slightly lower (2.31) in Evans et al.’s series. However, Friedenson in a meta-analysis found that clinically significant BRCA mutation increased risks up to nearly 2000-fold for certain hematological malignancies, in particular mantle cell lymphomas, acute myeloid leukemias, acute lymphocytic leukemias, chronic lymphocytic leukemias and prolymphocytic leukemias.

Several epidemiologic studies report an increased risk for gastric cancer in BRCA mutation carriers. Brose et al. showed the highest RR of 6.9 in families with a BRCA1 mutation carrier. Before that, Risch et al. also observed RR of 6.2 in 1st degree relatives of BRCA1 mutation: the BCLC study identified a statistically increased in BRCA2 mutation carriers (RR = 2.59). Bermejo and Hemminki noted that gastric cancer before age 70 years was twice as frequent in families with breast and ovarian cancers as in the general population and postulated an association of BRCA1/BRC2 mutation with risk of stomach cancer at population level.

For the risk of malignant melanoma, only the BCLC 1999 study observed an elevation with RR of 2.58. In contrast to that, a cohort study by Asperen et al., demonstrated a significantly decreased risk of melanoma. In a recent study of 385 patients with uveal melanoma, no pathogenic BRCA2 mutation was detected.

Whether there is an increased risk of cancer of the liver, bones and brain is difficult to say as these organs are a common site for metastases. The BCLC observed a RR increase of 4.18 for liver cancer. Thompson et al. showed RR of 4.06, but at the same time noted that there was no evidence of an increased risk of other cancers than pancreas and prostate in men (carrier RR = 2.10; non-carrier RR = 3.36). Similar to BCLC studies, Asperen et al. found an increased risk for liver cancer. However, only two of five liver cancers were confirmed by histopathology as primary liver malignancies.

**Risk management strategies**

Although the sites that show increased risk for cancer vary among studied populations, there seems to be a generally increased risk of breast, prostatic, pancreatic, gastric and hematological malignancies.

**Breast cancer**

In contrast to female BRCA mutation carriers, we are not aware of any publications reporting on screening or prophylactic surgery in male BRCA mutation carriers, regardless of the presence of family history. Instead, cancer risk counseling and heightened surveillance are recommended for male breast cancer risk management. For men who are at risk and have gynaecomastia and male patients with BRCA mutations, screening mammography has been recommended. An algorithm has been suggested by Munn for asymptomatic males with a high risk of developing breast cancer; it recommends screening mammography after age of 40 years old.

**Prostate cancer**

The Association Française d’Urologie (AFU) recommends prostate cancer screening by PSA assay (prostate specific antigen) and digital rectal examination annually between the ages of 50 and 75 years, and from the age of 45 years in men with a family or ethnic risk. Similarly, The American Cancer Society (ACS) recommends that the prostate-specific antigen test (PSA) and digital rectal examination (DRE) to be offered annually to men at high risk starting at age 40 with high risk defined as having multiple relatives with prostate cancer. Another publication from the United States recommends prostate cancer screening for male carriers of BRCA mutations by digital examination and serum prostate-specific antigen level annually beginning at age 50 years. It is our opinion that BRCA mutation carriers...
should be treated as high risk for prostate cancer and screening should start as per the recommendations of the AFU and ACS at age 40.

Information concerning the limits, benefits and risks of screening and the available treatment options must be given before performing these examinations.49,50

Pancreatic cancer

To date, no known screening method is sensitive and specific enough to screen the asymptomatic general population. Experts suggest that surveillance is warranted in high risk populations, such as those with a family history of pancreatic cancer or melanoma or person with Peutz-Jeghers syndrome, but optimal screening methods are uncertain.52–57

Brentnall53 has suggested an algorithm for surveillance of those at high risk for pancreatic cancer, beginning 10 years before the earliest diagnosis of pancreatic carcinoma in the patient’s family or 50 years of age, whichever comes first. Most authors agree endoscopic ultrasound (EUS) as initial screening investigation in asymptomatic high risk patients.53,55,56 The annual EUS examination should be performed and interpreted by an individual who is an expert in EUS and diseases of the pancreas. If the EUS finding is abnormal, ERCP will be performed. If the patient is symptomatic or has a history of pancreatitis, alcohol abuse, or cholelithiasis, which can influence the EUS findings, ERCP should be performed in addition to the EUS. Total pancreatectomy would be considered if suspicious changes are detected on ERCP.53 Such surveillance is best performed at

<table>
<thead>
<tr>
<th>Authors</th>
<th>Base of study</th>
<th>Number of individuals studied</th>
<th>Incidence of BRCA mutation carrier in cancer patients</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goggins et al., 199645</td>
<td>Unselected patients of adenocarcinomas of the pancreas screened for BRCA2 alteration</td>
<td>41 patients</td>
<td>15 (27%) had allelic loss at the BRCA2 locus. Of that, 4 (9.8%) had abnormalities in the second allele upon screening of the entire BRCA2 gene by in vitro synthesized protein assay</td>
<td>Data support an important role for BRCA2 germ line mutations in a subpopulation of families with familial pancreatic cancer</td>
</tr>
<tr>
<td>Murphy et al., 200237</td>
<td>Pancreatic cancer patient enrolled for mutations test in four tumor suppressor candidate genes: (a) MAP2K4; (b) MADH4; (c) ACVR1B; and (d) BRCA2 by direct sequencing of constitutional DNA</td>
<td>29 patients whom were selected from kindred in which three or more family members were affected with pancreatic cancer, at least two of which were first-degree relatives</td>
<td>Five BRCA2 gene mutations (5 of 29, 17.2%) that are believed to be deleterious and one point mutation (M192T) unreported previously. No mutation was detected in other 3 tumor suppressor genes</td>
<td>The presence of a founder BRCA2 mutation was not associated with the risk of colorectal cancer (RR = 0.50, 95% confidence interval = 0.22–1.14)</td>
</tr>
<tr>
<td>Hahn et al., 200336</td>
<td>26 family of at least two 1st degree relatives had pancreatic ca tested for BRCA2 (familial pancreatic cancer)</td>
<td>64 patients (37 male, 27 female)</td>
<td>19% of the families had either a frameshift mutation or an unclassified variant of BRCA2</td>
<td>No significant risk</td>
</tr>
<tr>
<td>Kirchhoff et al., 200440</td>
<td>Screened 586 unselected Ashkenazi Jewish patients with colorectal cancer for the three common founder mutations in BRCA1 and BRCA2</td>
<td>586 patients</td>
<td>Six out of 586 carriers identified (1.02%). After adjusting for age at diagnosis and sex by use of logistic regression analysis, the incidence of carriers in this group was compared with that of 5012 Ashkenazi Jewish control subjects without a known history of colorectal cancer</td>
<td>Preliminary results show elevated rates of BRCA “Ashkenazi mutations” in Ashkenazi CRC patients, suggesting their involvement in CRC carcinogenesis</td>
</tr>
<tr>
<td>Niell et al., 200439</td>
<td>Population-based study in Northern Israel. 1002 patients with colorectal cancer</td>
<td>1002 patients with colorectal cancer x 1038 healthy subjects</td>
<td>24 (2.4%) patients and 20 (1.9%) healthy subjects carried one of the three Ashkenazi Jew founder mutations (odd ratio = 1.24)</td>
<td>This frequency is similar to the estimated normal Ashkenazi population frequency, thus suggesting that these specific mutations do not contribute to CRC predisposition</td>
</tr>
<tr>
<td>Drucker et al., 200053</td>
<td>136 consecutive Israeli Jewish patients with sporadic CRC were screened for BRCA “Ashkenazi mutations”</td>
<td>136</td>
<td>Three Ashkenazi carriers out of 87 Ashkenazi patients tested, 3.5%</td>
<td>No significant risk</td>
</tr>
<tr>
<td>Chen-Shtoyerman et al., 200174</td>
<td>225 unselected Ashkenazi Jewish CRC patients were tested for the presence of the three common Jewish BRCA1/BRCA2 germ line mutations</td>
<td>225</td>
<td>A total of four carriers were found: 4/225 (1.78%)</td>
<td>No significant risk</td>
</tr>
</tbody>
</table>

**Table 4**

Studies of patients with cancers other than prostate and male breast cancer for incidence of BRCA mutation

<table>
<thead>
<tr>
<th>Authors</th>
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<td>Unselected patients of adenocarcinomas of the pancreas screened for BRCA2 alteration</td>
<td>41 patients</td>
<td>15 (27%) had allelic loss at the BRCA2 locus. Of that, 4 (9.8%) had abnormalities in the second allele upon screening of the entire BRCA2 gene by in vitro synthesized protein assay</td>
<td>Data support an important role for BRCA2 germ line mutations in a subpopulation of families with familial pancreatic cancer</td>
</tr>
<tr>
<td>Murphy et al., 200237</td>
<td>Pancreatic cancer patient enrolled for mutations test in four tumor suppressor candidate genes: (a) MAP2K4; (b) MADH4; (c) ACVR1B; and (d) BRCA2 by direct sequencing of constitutional DNA</td>
<td>29 patients whom were selected from kindred in which three or more family members were affected with pancreatic cancer, at least two of which were first-degree relatives</td>
<td>Five BRCA2 gene mutations (5 of 29, 17.2%) that are believed to be deleterious and one point mutation (M192T) unreported previously. No mutation was detected in other 3 tumor suppressor genes</td>
<td>The presence of a founder BRCA2 mutation was not associated with the risk of colorectal cancer (RR = 0.50, 95% confidence interval = 0.22–1.14)</td>
</tr>
<tr>
<td>Hahn et al., 200336</td>
<td>26 family of at least two 1st degree relatives had pancreatic ca tested for BRCA2 (familial pancreatic cancer)</td>
<td>64 patients (37 male, 27 female)</td>
<td>19% of the families had either a frameshift mutation or an unclassified variant of BRCA2</td>
<td>No significant risk</td>
</tr>
<tr>
<td>Kirchhoff et al., 200440</td>
<td>Screened 586 unselected Ashkenazi Jewish patients with colorectal cancer for the three common founder mutations in BRCA1 and BRCA2</td>
<td>586 patients</td>
<td>Six out of 586 carriers identified (1.02%). After adjusting for age at diagnosis and sex by use of logistic regression analysis, the incidence of carriers in this group was compared with that of 5012 Ashkenazi Jewish control subjects without a known history of colorectal cancer</td>
<td>Preliminary results show elevated rates of BRCA “Ashkenazi mutations” in Ashkenazi CRC patients, suggesting their involvement in CRC carcinogenesis</td>
</tr>
<tr>
<td>Niell et al., 200439</td>
<td>Population-based study in Northern Israel. 1002 patients with colorectal cancer</td>
<td>1002 patients with colorectal cancer x 1038 healthy subjects</td>
<td>24 (2.4%) patients and 20 (1.9%) healthy subjects carried one of the three Ashkenazi Jew founder mutations (odd ratio = 1.24)</td>
<td>This frequency is similar to the estimated normal Ashkenazi population frequency, thus suggesting that these specific mutations do not contribute to CRC predisposition</td>
</tr>
<tr>
<td>Drucker et al., 200053</td>
<td>136 consecutive Israeli Jewish patients with sporadic CRC were screened for BRCA “Ashkenazi mutations”</td>
<td>136</td>
<td>Three Ashkenazi carriers out of 87 Ashkenazi patients tested, 3.5%</td>
<td>No significant risk</td>
</tr>
<tr>
<td>Chen-Shtoyerman et al., 200174</td>
<td>225 unselected Ashkenazi Jewish CRC patients were tested for the presence of the three common Jewish BRCA1/BRCA2 germ line mutations</td>
<td>225</td>
<td>A total of four carriers were found: 4/225 (1.78%)</td>
<td>No significant risk</td>
</tr>
</tbody>
</table>
a center specializing in the endoscopy and pancreatic pathology.

Other center required pathological result suggesting neoplasmia before offered surgery.66

American Gastroenterology Association recommends spiral computerized tomography (CT) as initial screening investigation. If the CT results are non-diagnostic, EUS and measurement of serum CA 19-9 should be done.57 In certain high risk subsets of patients, annual testing of serum CA 19-9 in conjunction with EUS may improve detection rates. Parker et al.58 suggested an annual measurement of the CA 19-9 level and EUS as primary screening investigation. If a patient is found to have a CA 19-9 level near or greater than 37 U/mL or experiences a dramatic increase in the level during a 1-year period, ERCP is suggested.

Our opinion is that, male carriers of BRCA mutation with no family history of pancreatic cancer should have surveillance for pancreatic cancer at the age of 50 years old at a center with experience in dealing with pancreatic cancer and precursor lesions.

Gastric cancer

To our knowledge, there were no screening guidelines for gastric cancer in terms of when to start screening, the interval time for subsequent investigation and what investigation will be used. However, Japan had started on mass screening program for gastric cancer as early as 1956 using fluorography of the stomach.59 Screening was offered to all residents above 40 years old.60 Since 1996, conventional gastric barium X-ray was replaced by endoscopic examination which led to an increased cancer detection rate and a decreased in the gastric cancer related mortality rate.60

Endoscopy with biopsy mapping of the gastric mucosa was performed to look for multifocal gastric metaplasia in patients who are asymptomatic but at high risk of developing gastric carcinoma. If multifocal atrophic gastritis is found, repeat surveillance every 1–3 years should be considered. If a dysplastic lesion is located on endoscopy, resection of the lesion is recommended, and annual or biannual endoscopic surveillance is reasonable.61 Our opinion is that, the male BRCA mutation carriers should have surveillance for gastric cancer at the age of 40 years old at a gastroenterology center. Given the low 5-year survival rate in gastric cancer patients, preventive measures should be emphasized including avoidance of the use of tobacco, to eat a well-balanced diet, and to be treated for “premalignant” conditions such as Barrett’s esophagus, atrophic gastritis, or H. pylori colonization.61

Colorectal cancer

Currently, available guidelines for the care of BRCA1/BRCA2 mutation carriers recommend informing the mutation carrier of a possible increased risk for colorectal cancer and encouraging the individual to follow screening guidelines for the general population.62

Adults at average risk should begin colorectal cancer screening at age 50, utilizing one of the following five options for screening: (1) annual fecal occult blood test (FOBT); (2) flexible sigmoidoscopy every 5 years; (3) annual FOBT plus flexible sigmoidoscopy every 5 years; (4) double contrast barium enema (DCBE) every 5 years; or (5) colonoscopy every 10 years.50,63 Direct and indirect evidence indicates that all the tests are effective, but they differ in their sensitivity, specificity, cost, and safety. The available evidence does not currently support choosing one test over another.63 Combining flexible sigmoidoscopy with FOBT can increase the benefits beyond those of either test alone, more so in the instance of adding flexible sigmoidoscopy every 5 years to annual FOBT. Thus, the ACS guidelines state that if either test is chosen, combining the two represents a better option.50

Conclusion

Male carriers of BRCA mutation were shown having increased risk to develop breast, prostate, pancreatic, stomach and hematological cancers and therefore were encouraged to be counseled regarding screening for these cancers. Beside that, the possibility of an increased risk of other malignancies should be discussed. Patients also must be made aware of self-examination techniques and signs and symptoms of cancer. More than that, health counseling towards healthy lifestyle including guidance about smoking cessation, diet, physical activity is as important as undergoing various screening tests.

Conflict of interest statement

None declared.

Authors’ contribution

HBM searched for the literatures, analyzed and drafted the manuscript. JPA conceived of the study, and participated in its design and coordination. Both authors read and approved the final manuscript.

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