Clinical Implications of Genetic Testing for BRCA1 and BRCA2 Mutations in Austria

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Abstract

Objectives: To describe the experience of genetic testing in Austrian women with a BRCA1 or BRCA2 mutation, in terms of preventive measures taken and incident cancers diagnosed.

Methods: We collected clinical information on 246 Austrian women with a BRCA1 or BRCA2 mutation tested between 1995 and 2012, and followed 182 of them for an average of 6.5 years.

Results: Of the 90 women who were cancer-free at baseline, 21.4% underwent preventive bilateral mastectomy (PBM), 46.1% had preventive bilateral salpingo-oophrectomy, and one took tamoxifen. 58.8% of the at-risk women underwent at least one screening breast MRI. Of the 85 women with breast cancer, 69.4% had a unilateral mastectomy or lumpectomy and 30.6% had a contralateral mastectomy. In the follow-up period, 14 new invasive breast cancers (six first primary and eight contralateral), one DCIS case, two incident ovarian cancer cases, and one peritoneal cancer were diagnosed.

Conclusions: In Austria, the majority of healthy women with a BRCA1 or BRCA2 mutation opt for preventive oophorectomy and MRI screening to manage their breast cancer risk; few have preventive mastectomy or take tamoxifen.

Keywords: BRCA1, BRCA2, breast cancer, prevention, risk

INTRODUCTION

Genetic testing for BRCA1 and BRCA2 began in Austria in 1995 and since then, 3,753 women have been tested and 863 mutation carriers have been identified (23%). The principal goals of genetic testing are to prevent new primary cancers and cancer recurrences among women with a mutation, and to detect incident cancers at an early stage. The lifetime breast cancer risk for BRCA1 carriers varies by mutation and ranges from 50% to 85%.[1-5] The lifetime risk of ovarian cancer is approximately 40% for BRCA1 carriers and 20% for BRCA2 carriers.[1,2] Several strategies are available to manage these risks: MRI screening allows to detect breast cancer earlier,[6] but has yet to demonstrate a mortality reduction beyond that of conventional mammography.[7] Prophylactic bilateral mastectomy (PBM) reduces the risk of breast cancer by 90% [8] and prophylactic bilateral salpingo-oophorectomy (PBSO) decreases breast cancer risk by 50% and ovarian cancer risk by 80%.[9,10] In addition, tamoxifen reduces the risk of contralateral breast cancer by 50%.[11] For breast cancer patients with a BRCA1 mutation bilateral mastectomy and PBSO are both associated with improved survival (submitted).[12-14] These options are all available for Austrian mutation carriers and treatment costs are covered by the national health insurance program. We estimated the frequencies of preventive options among Austrian mutation carriers and compared them with other countries to evaluate the impact of our genetic testing program.

MATERIALS AND METHODS

Subjects and Methods

Genetic testing: In Austria, genetic testing is conducted by sequencing and Multiplex-ligation Assays (MLPA) at a single reference laboratory. Women are offered free testing if their

familial history fulfills one of the following criteria: a) three cases of breast cancer below age 60; b) two cases of breast cancer below age 50; c) one case of breast cancer below age 35; d) one breast cancer case below age 50 and e) one case of ovarian cancer at any age; f) two cases of ovarian cancer at any age; g) male and female breast cancer. From 1995 to 2012, 3631 women were tested and 825 were found to carry a BRCA1 mutation (n = 561), a BRCA2 mutation (n = 257), or both mutations (n = 7).

Follow up study: A baseline questionnaire was sent to 407 women with BRCA1 or BRCA2 mutations. 246 women returned the questionnaire (60.4%). The responding women had been tested between 1995 and 2012 and represent 29.8% of all carrier women identified. On average 1.4 years had elapsed from the date of genetic testing until the date of completion of the baseline questionnaire. Responders did not significantly differ from the overall population in socio-economic and demographic respects (data not shown). They belong to 177 different families living throughout Austria. All 246 women were invited to complete a follow-up questionnaire a minimum of one year following the baseline questionnaire. At least one follow-up questionnaire was received from 182 of the women (73%). In total, the 182 women contributed 1179 person-years of follow-up from the date of the baseline questionnaire (mean, 6.5 years, range 0.4 to 17.5 years). Of the 182 women, 85 had been diagnosed with breast cancer and 17 women with ovarian cancer prior to the baseline questionnaire. 10 women had developed both cancers while 90 women remained cancer free.

Statistical Analyses

Cancer incidence: To estimate the risk of first primary breast cancer, we included women without breast cancer at baseline and followed them until either the development of breast cancer, PBM or the date of the last questionnaire. To estimate the risk of contralateral breast

cancer, we included women who had breast cancer at baseline and followed them until the development of contralateral breast cancer, PBM or the date of the last questionnaire. To estimate the risk of ovarian cancer, we included women without a history of ovarian cancer at baseline and followed them until the development of ovarian cancer, a PBSO or the date of the last questionnaire. For each analysis, we estimated the annual cancer risk.

RESULTS

Distribution of mutations: Of the 246 responding women from 177 families, 182 had a BRCA1 while 64 had a BRCA2 mutation, three had a mutation in both genes. The distribution of mutations is provided in table 1. 23 mutations were seen in more than one family and these 23 accounted for 70% of all families with a mutation and 83% of all 246 mutation carriers. The three most common mutations were seen in 21 (C61G), 14 (3137delTTCCA), and 10 families (5382insC).

Treatment of Breast Cancer: Of the 85 women with breast cancer, 84 underwent unilateral mastectomy or lumpectomy and one had bilateral mastectomy as initial treatment. 25 of the women had a contralateral mastectomy at a later date (30%). 57 women with breast cancer had a PBSO (67%) and 60 of 83 breast cancer patients received chemotherapy (72%). Of the women with a contralateral breast intact, eight developed a contralateral breast cancer (annual risk 2.3%).

Preventive measures: 182 eligible women completed at least one follow-up questionnaire. On average, 7.8 years had passed from the date of receiving the genetic test result to the date of most recent questionnaire. Based on the questionnaires we found that of 90 women without a

history of breast or ovarian cancer at baseline, 17 had a PBM (21.1%), one woman had taken tamoxifen for chemoprevention, while 41 (45.6%) had undergone PBSO.

Cancer Incidence: 90 unaffected carriers who had not undergone prophylactic surgery were followed for a total of 452 person-years for incident breast cancer. After a mean follow-up of 5.2 years, six new cases of invasive breast cancer developed, which corresponds to a 1.1% (95% CI 0.3% to 2.9%) annual average risk for BRCA1 mutation carriers and a 2.7% (95% CI 0.3% to 9.3%) risk for BRCA2 mutation carriers. 75 BRCA1 carriers underwent PBSO (60%) and among them one developed peritoneal cancer. Furthermore, two melanomas, two colon cancers, one vaginal cancer, one lung cancer, one basal cell carcinoma, one thyroid cancer, one stomach cancer and one lymphoma were detected.

DISCUSSION

In this study, we estimate that without PBM, the annual incidence rate for breast cancer among Austrian BRCA1 mutation carriers is approximately 1.1% from age 25 to age 70. This rate is lower than among Norwegian (2.0%) Polish (1.7%) and North Americans (2.4%) carriers,[15] but the number of incident cases in our study is too small to allow age-specific comparisons. The annual risk for BRCA2 carriers is larger (2.7%), but is based on only two carriers who developed breast cancer during the follow-up.

Of the 246 women 205 (82.7%) had a mutation that was seen more than once. The most prevalent mutation (C61G) is common in Slavic populations.[16] The second most common mutation 3137delTTCA is an Austrian founder mutation.[17] The 5382insC mutation is found in Slavic families and in Ashkenazi Jewish women and is the most common mutation seen in Poland,[16] Belarus,[18] Lithuania,[19] and Russia.[20] The ten most common

mutations account for 48%, and 23 recurrent mutations cover 75% of the families. Based on this distribution, we propose a multiplex assays including 23 alleles which would have a 70 % sensitivity for identifying Austrian carriers. This approach is particularly interesting since a high proportion of carriers lack a family history which would qualify them for genetic testing.[21,22]

To date, we have tested 3753 Austrian women, which represents 0.12% of the female Austrian population above age 25 and have identified 863 carriers; assuming an underlying carrier rate of one in 300, this represents 9% of the estimated 10,000 female mutation carriers above age 25 in Austria.

The majority of carriers who were healthy at baseline underwent MRI screening and PBSO. 19 had PBM (mean age of 40.4). Fewer than 50% of unaffected carriers in Austria underwent PBSO, which is lower than in North America and in other western European countries.[23] It is important to understand why women do not undergo oophorectomy, and to ensure that patients have access to the information on the risks and benefits of the procedure. One possible reason for the low uptake of prophylactic surgery is the current legislation, which prohibits directive counseling in Austria. Since almost all Austrians are insured and are entitled to free prophylactic surgery, inadequate access to care cannot explain this discrepancy.

Breast cancer patients were more likely to undergo oophorectomy (67%) than healthy carriers (46%). We have recently shown that among breast cancer patients with a BRCA mutation, cancer survival is improved by prophylactic surgery.[12-14] In Austria, 30% of carriers with breast cancer eventually had a contralateral mastectomy. Narod *et al* have recently proposed that all BRCA1 carriers with breast cancer were candidates for chemotherapy.[24] Nevertheless, in Austria, 28% of women with breast cancer and a BRCA

mutation did not receive chemotherapy, it is important that the reasons behind these choices be explored.

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Table 1: Distribution of BRCA1 and BRCA2 mutations in Austria

Distribution of BRCA1 mutations in Austria

Mutation	Frequency	Percent
C61G	21	16.3
3137delTTCA	14	10.9
5382insC	10	7.8
Q563X	9	7.0
R1347G	8	6.2
Q1395X	5	3.9
W321X	4	3.1
R1751X	4	3.1
185delAG	4	3.1
795delT	3	2.3
3819del5	3	2.3
3600del11	3	2.3
IVS16+3G>C	2	1.6
3875del4	2	1.6
2798delGAAA	2	1.6
Other single mutations	35	27.1
Total	165	100.0

Distribution of BRCA2 mutations in Austria

Mutation	Frequency	Percent
8983-1G>A (IVS21-1G>A)	6	13.0
8592G-A (W2788X)	6	13.0
4088delA	5	10.9
8074delT	3	6.5
886del GT	2	4.3
4143delT	2	4.3
4075delGT	2	4.3
2041insA	2	4.3
Other single mutations	18	39.1
Total	46	100.0