Review article
UDC: 616.036.22:614.44

Mirjana BRANKOVIĆ-MAGIĆ
Radmila JANKOVIĆ
Siniša RADULOVIĆ

INSTITUTE FOR ONCOLOGY AND RADIOLOGY OF SERBIA, BELGRADE, YUGOSLAVIA

Breast cancer susceptibility genes: Options for those carrying BRCA1 mutations

KEYWORDS: Breast Neoplasms; Genetic Techniques; Genes, BRCA1; Mutation

ABSTRACT

The discovery of the association between breast and ovarian cancer and the BRCA genes and the development of methods for genetic testing made it possible to screen women for genetic predisposition to develop hereditary breast cancer (HBC). Parallelly, prevention strategies, including clinical, surgical and medical interventions become available in order to reduce cancer risk. In a meantime, we became aware of limitations of genetic testing from the aspect of BRCA gene penetrance, negative result interpretation etc. All of these, together with data that invasive prevention strategies such as prophylactic surgery demonstrate better results in risk reduction than regimens including self and clinical-examination, face BRCA mutation carriers with difficult choice for risk reduction options. Therefore, the patients at high risk of HBC can best make informed decisions when guided by a multidisciplinary genetic counseling team.

Address correspondence to:
Mirjana Branković-Magić, Ph.D., Institute for Oncology and Radiology of Serbia, Pasterova 14, 11 000 Belgrade, Yugoslavia, Email: magicm@drenik.net

The manuscript was received: 16.10. 2002.

Accepted for publication: 21.10. 2002.

INTRODUCTION

Minorities of breast cancer patients are present with a striking family history, suggestive of Mendelian inheritance. Term hereditary cancer defined cancers associated with specific germ line genetic mutations, inherited as a Mendelian trait, whether through an oncogene, a tumor suppressor gene, or a DNA mismatch repair gene. Hereditary breast cancer accounts for 5 to 10 % of all breast cancers. In Yugoslavia estimated breast cancer incidence per 100 000 women is about 3890 cases (1). It means that hereditary breast cancer can be estimated at about 195 to 389 cases per 100 000 women. An additional 15% to 20% of breast cancer cases are concerned as familial breast describing cancers for which positive family history is evident, but they are not associated with known germ line mutations.

The most common variant of hereditary breast cancer (HBC) is hereditary breast and ovarian cancer (HBOC) syndrome.

The discovery of the association between breast and ovarian cancer and the genes BRCA1 and BRCA 2 made it possible to screen women for this genetic predisposition to develop either one or both of these diseases. Since BRCA1 and BRCA2 genes encode proteins that normally function to mediate integrity after DNA damage, they are classified as tumor suppressor genes. When mutations in these genes occur, they disrupt their normal functions in regulating cell turnover and DNA integrity, on that way increasing the risk of cancer. Escalating risk associated with BRCA1 and BRCA2 is the consequence of inheritance of one mutated allele, usually in autosomal-dominant manner. The offspring of mutation carriers have a 50% chance of inheriting a mutant allele from either parent.

BRCA1 gene is located on chromosome 17q21. It is composed of 24 exons. Exon 1 is noncoding and exon 11 is unusually large. BRCA1 gene encodes 1863 amino acid protein with a "zinc-finger" motif suggesting that it may function as a transcription factor (2). Mutations are located throughout BRCA1 gene with little evidence for clustering or "hot spots". More than 340 different mutations, most of them capable of disrupting BRCA1's tumor suppressor function, have been reported scattered along the gene.

About half of all hereditary breast cancer are attributed to mutations in BRCA1 gene (3). A woman with such a mutation has a 56% to 87% lifetime risk of developing breast cancer (4), although some new studies suggested lower risk.

Because major clinical benefit may accrue through identifying clinical risk indicators of the hereditary cancer phenotype it is necessary to paid attention on:

- Onset at an usually early age - for mutated BRCA1 carriers, the disease tends to have strikingly early age of onset, with 50% of cases diagnosed by age 41 (4);
- Bilateral development;
- Development more than 1 primary cancer in a patient or a family member;
- Family history of high rates of the same type of cancer;
- Breast cancer development in a male patient or relative.

To all of this, data can be added about family member harboring BRCA1 or BRCA2 mutations, as well as about ethnicity since it has been shown that some ethnically isolated populations such as Ashkenazi Jewish women, have a higher risk of harboring BRCA1 and BRCA2 mutations (5).

Pathobiology of hereditary breast cancer

Growing data about different pathobiologic characteristics between BRCA1 and BRCA2-related hereditary breast cancers, as well as in BRCA1/BRCA2 breast cancer compared with nonhereditary breast cancer with the consequent influence on the course of disease, enforce the need for hereditary breast cancer identification. When compared with nonhereditary breast cancer, invasive BRCA1-related hereditary breast cancer has a lower diploidy rate and strikingly higher proliferation rate; they are estrogen and

progesterone receptor negative and p53 positive. BRCA1-related cancers are frequently ductally invasive, high-grade carcinomas with an abundant lymphocyte infiltration (6). It seems that BRCA1 hereditary breast cancer shows predominantly deviant phenotype. But despite adverse prognostic features, BRCA-related HBC patients have paradoxically lower recurrence rates than other HBC patients (7). Using microarray technology, Hedenfalk et al. demonstrated that gene expression of tumors with BRCA1 and BRCA2 mutations and sporadic tumors differ significantly from each other indicating that a heritable mutation influences the gene expression profile of cancer (8). But, despite to established data, there is no any specific prognostic marker or therapeutic approach to hereditary breast cancer. Concerning BRCA-related cancer, when disease occurs, its course is very similar to nonhereditary ones and the mutated BRCA1 carriers fared no worse than breast cancer patients at large (9).

GENETIC SUSCEPTIBILITY TESTING

Hereditary breast and/or ovarian cancer belong to the group of hereditary syndromes with high probability of linkage to known cancer susceptibility genes (BRCA1/BRCA2) (Group 2). Medical benefit of the identification of a heterozygote (carrier) is presumed, but not established for BRCA genes, in part because of their limited penetrance. The penetrance for breast cancer in BRCA1 or BRCA2 mutation ranges from approximately 70% to 85%. In any case, the BRCA1 and BRCA2 genetic tests were among the first genetic tests to become widely available, due to high incidence and high mortality of breast cancer in Western countries. Identification of BRCA1 and BRCA2 mutations can provide valuable information about lifestyle choices and prevention strategies. But, the majority of alterations detected in BRCA1 alone, together with the high cost of complete BRCA1/BRCA2 gene sequencing and with very low incidence of BRCA1/2 mutation in the general population, directed genetic testing towards selected population. The American Society of Clinical Oncology (ASCO) has issued guidelines regarding testing for genetic susceptibility to cancer and recommends such testing when 3 conditions are met (10):

- The patient's family has a history of cancer, especially in cases of early-onset disease. Likelihood of positive test should be greater than 10%.
- The selected test can be interpreted satisfactorily.
- Test results will influence how the patient's cancer risk is managed.

BRCA-associated cancers are distinguished by their occurrence in multiple family members within a single lineage (11). Every woman with minimum two or more family members who developed breast cancer before the age of 50 years or ovarian cancer at any age should be considered for genetic testing (12,13).

BRCA testing is performed in a blood sample. The most appropriate test for mutated BRCA1/2 identification is a complete gene sequence analysis of the entire coding sequence and this remains the gold standard for mutation screening. Ideal situation is the possibility to test the patient with breast cancer the first. Besides complete BRCA gene sequencing the other options are possible in the certain situations:

- For BRCA testing of the relatives when a certain type of mutation is confirmed in an affected family member;
- For a specific examination of the mutations more commonly seen in usually isolated population (for example examination of the three founder mutations in women of Ashkenazi Jewish ancestry).

Mutation-negative results

Mutation-negative result must be accepted with precaution, since it has not the same implication if mutation has been or has not been detected in family. Patients with negative results for BRCA1 and BRCA2 mutations previously identified in their relatives can be reassured that they have not inherited the familial mutation and are therefore not at increased risk of breast cancer. When a patient tests are negative for BRCA mutations in the occasion when the mutation has not been previously detected in the family, the results must be interpreted with caution. For these patients, particularly for those with strong family history, remain at risk of carrying another genetic predisposition associated with mutation in cancer-causing gene that has yet to be discovered.

The patients who are mutation-negative must understand that they continue to carry a risk of sporadic cancer identical to that of the general population.

Mutation-positive results

The patients who test positive for BRCA mutations will require, besides pretest, also posttest genetic counseling. Implications for blood relatives, including if and how to inform them and whether they should be tested, must be considered. Mutated BRCA carriers face crucial clinical decisions regarding how best to manage their cancer risk.

INFORMED CONSENT FOR BRCA TESTING, GENETIC COUNSELING AND PREVENTION STRATEGIES

Before the peripheral blood collection that will be used for DNA isolation for germ line mutation testing, the patient must provide informed consent. Physicians who offer the option of genetic testing should do so in conjunction with patient education, counseling and support. This process deals with the task to enable the patient to be knowledgeable participant with understanding the disorder and implication of data regarding the cancer phenotype and its penetrance in the presence of cancer-causing genes. Genetic counseling team has at least to be composed of physician, genetic counselor, psychologist, and registered nurse. Pretest education should include the following information:

- A description of patient's risk status;
- An explanation of what it means to have an inherited susceptibility to cancer;
- An information about the meaning of testing outcomes - the results my be positive, negative or uninformative;
- An appraisal of the risks, benefits, and limitations of genetic testing;
- A discussion about cancer surveillance and the limitations of anticancer therapies;
- A review of the psychosocial issues related to genetic testing;
- An explanation of the alternatives to genetic testing;
- An information about the risk of passing a mutation to children;

Besides that, in Western countries a discussion about insurance, employment and confidentiality concerns is recommended. It is imperative that counseling be indirect allowing the patient full autonomy in deciding whether to be tested.

Posttest genetic counseling for mutation carriers must include a full explanation of a positive result accompanied by a description of surveillance and options for clinical management. The guidelines for follow-up care of individuals with BRCA1 and BRCA2 mutations have been issued by task force under the auspices of Cancer Genetics Studies Consortium, USA and include options for both surveillance and risk reduction (14). Very similar routine screening for BRCA mutation carriers recommended European experts.

Recommendations for the breast surveillance can be summarized as the following:

- A monthly breast self-examination that begins by age 18 to 21 years.

Although the efficacy of self-examination may be questionable, it may be of increased value in genetically susceptible women concerning their tendency to develop cancer at an age when mammograms are difficult to interpret.

- An annual or semiannual clinical breast examination, starting at age 25, along with an annual mammogram, starting at age 25-35.

There is some concern that early radiation connecting with mammography at early age might itself be carcinogenic, but the benefit of early cancer detection in high-risk women is likely to outweigh this risk.

Since mutated BRCA genes carriers are under the certain risk of ovarian

© 2002, Institute of Oncology Sremska Kamenica, Yugoslavia

cancer development (16% to 44% in life-time concerning BRCA1) (3), the recommendation concerning surveillance of the ovary is also offered. Early detection of ovarian cancer in BRCA1/BRCA2 mutation carriers presents more difficulties than surveillance for breast cancer, but a semiannual pelvic examination, starting at age 25 together with a semiannual transvaginal ultrasound with color Doppler and serum CA-125 measuring, also starting at age 25, are recommended. (14):

Patients with BRCA mutations also have an increased risk for colon cancer. Male BRCA1 mutation carriers have increased potential to develop prostate cancer.

Risk reduction recommendations for population at high risk for hereditary breast cancer includes general health guidelines such as low-fat, high-fiber diet rich in fresh fruit and vegetables, regular exercising and avoiding tobacco and alcohol use.

Besides that, 3 general directions of preventive strategy, alone or in combination, including chemprophylaxis, prophylactic mastectomy and prophylactic oophorectomy is optionally proposed. Much attention has been directed to those prevention possibilities in the past few years, but the implementation any of them is real dilemma for those carrying BRCA mutations.

Chemoprevention. Current chemoprevention for breast cancer involves tamoxifen and possibly raloxifene, which belong to a class of nonsteroidal antiestrogens known as selective estrogen receptor modulators. The possibility of chemoprophylaxis with tamoxifen (nolvadex) is raised on data concerning reduced rates of recurrent and contralateral disease in sporadic breast cancer patients (15). In 1998, after it was found that tamoxifen reduced by 47% the risk of breast cancer in women at high risk as judged by a family history of disease (16), its use was officially recommended. But, the use of tamoxifen in BRCA1 and BRCA2 mutation carriers, however, remains unclear. Chemoprevention with tamoxifen, and potentially with aromatase inhibitors offers less benefit to BRCA1 patients, minority of whom develop steroid receptor positive tumor - e.i. their tumors are hormone-independent. Nevertheless, study of Narod et al. showed that tamoxifen reduced the risk of contralateral breast cancer in women with pathogenic mutations in BRCA1/BRCA2 genes (17). But, it must be kept in mind that the tamoxifen side effects include an increased risk of endometrial cancer and thromboembolism. Because of that, besides tamoxifen, raloxifene, as a newer estrogen receptor modulator with different spectrum of tissue -specific estrogen receptor activity acting without risk of endometrial cancer is now examined. But even if chemoprevention is ultimately shown to be effective, this is a long-term and costly daily therapy and it is questionable how it will be accepted by women at high-risk of HBC.

Prophylactic mastectomy. Surgical intervention for BRCA mutation carriers is more invasive, but studies demonstrated its efficacy in reducing cancer risk. Prophylactic mastectomy is a drastic but effective option for women who are mutation carriers, as risk-reduction strategies and surveillance methods have not shown long-term effectiveness, especially in women with dense breast tissue. Hartman et al. found that prophylactic mastectomy may reduce the risk of breast cancer up to 90% in women at high risk in regard to family history (18), as well as in the BRCA1 and BRCA2 carriers (19). Similar results for BRCA1/2 mutation carriers have been reported by Meijers-Heijboer et al. (20). However, patients must be informed that neither prophylactic mastectomy, nor prophylactic oophorectomy provides absolute protection against disease. Cancer subsequent to mastectomy, mostly subcutaneous mastectomy, which is likely to have a higher failure rate, has been reported in 1% to 19% of high-risk breast cancer patients (21). Anyway, mutation carriers who undergo mastectomy should continue postoperative surveillance with mammograms and clinical breast examinations. In addition, women who is a candidate for prophylactic mastectomy has to be faced with the lost of secondary sex characteristic and mutilation in the situation of limited penetrance of BRCA genes.

Prophylactic oophorectomy. Because screening methods for ovarian cancer seldom detect the disease in its earliest stages, prophylactic oophorectomy is ordinarily offered to BRCA1 and BRCA2 mutation carriers who have completed their families. Further, women with BRCA1 mutations who underwent bilateral prophylactic oophorectomy had a significantly decreased risk of developing breast cancer, compared with women with the mutation who did not have the surgery (22). The likely mechanism is the reduction of ovarian hormone exposure. It seems that the use of hormone replacement therapy after the procedure do not appear to counteract the apparent protective effect of oophorectomy. Although promising, the results are not enough to recommend prophylactic oophorectomy to women with BRCA1 mutations. After the surgical procedure, women must still be counseled regarding the well-described occurrence of peritoneal cancer after oophorectomy. Although the patients undergo prophylactic oophorectomy faced to premature menopause, this procedure will be more applicable in future than prophylactic mastectomy, due to the lack of exterior mutilation.

Recent studies, bases on modeling systems demonstrates that BRCA1/2 mutation carriers can prolong their survival combining prophylactic surgeries or combining prophylactic surgery with chemoprevention (23).

It can be concluded that, since advantage has been made in identifying individuals at high risk of HBC, due to accessible genetic testing, as well as with in the development of prevention strategies, mutation carriers face difficult questions with regard to surveillance, risk management, and prophylactic surgery. Future research must further elucidate the mechanism of action of BRCA genes, the frequency and penetrance of the particular BRCA mutation, as well as to create more effective therapeutic modalities in order to reduce morbidity and mortality of HBC.

Acknowledgement:

This work was supported by grant provided by the Ministry of Sciences, Technology and Development of Serbia, "Clinical implications of molecular heterogeneity of solid tumors", No 1691.

REFERENCES

1. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2000: Cancer incidence, Mortality and Prevalence Worldwide. IARC CancerBase No. 5. Lyon, IARCPress, 2001.

2. Miki Y, Swensen J, Shattuck-Eldens D et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994; 266:66-71.

3. Ford D, Easton DF, Bishop DT et al. Risk of cancer in BRCA-1 mutation carriers. Lancet 1994; 343:692-95.

4. Couch FJ, DeShano ML, Blackwood MA et al. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. N Engl J Med 1997; 336:1409-15.

5. Offit K, Gilewski T, McGulre P et al. Germline BRCA1 185delAG mutations in Jewish women with breast cancer. Lancet 1996; 347:1643-45.

6. Marcus JN, Watson P, Page DL et al. Hereditary breast cancer: Pathobiology, prognosis, and BRCA1 and BRCA2 gene linkage. Cancer 1996; 77: 697-709

7. Marcus JN, Page DL, Watson P et al. BRCA1 and BRCA2 hereditary breast carcinoma phenotypes. Cancer 1997; 80:543-56.

8. Hedenfalk I, Duggan D, Chen Y et al. Gene expression profiles in hereditary breast cancer. N Eng J Med 2001; 344:539-48.

9. Raičević-Maravić L, Radulović S. Breast cancer susceptibility gene1- BRCA1. Archive of Oncology 2000; 8: 21-3.

10. Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptability, adopted on February 20, 1996. J Clin Oncol, 1996; 14:1730-36.

11. Fackenthal JD, Olopade OI. Inherited susceptibility to breast and ovarian cancer. Adv Oncol; 2000; 16:10-8.

12. Armstrong K, Eisen A, Weber B. Assessing the risk of breast cancer. N Engl J Med 2000: 342:564-71.

13. Raičević-Maravić L, Radulović S. Genetic testing for cancer susceptibility; point of view from a country with limited resources. J BUON 2000; 5:273-76.

14. Burke W, Daly M, Garber J et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. JAMA 1997; 277: 997-1003.

15. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. Lancet 1992; 339: 1-15.

©2002, Institute of Oncology Sremska Kamenica, Yugoslavia

16. Fisher B, Constantino JP, Wickerham DL et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998; 90:1371-88.

17. Narod SA, Brunet J-S, Ghadirian P et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Lancet 2000: 356:1876-81.

18. Hartman LC, Schaid DJ, Woods JE et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Eng J Med 1999; 340: 77-84.

19. Hartman LC, Sellers TA, Schaid DJ et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 carriers. J Natl Cancer Inst 2001: 93:1633-93.

20. Meijers-Heijboer H, van Gee B, van Putten WLJ et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2001; 345:159-64.

21. Pennisi VR, Capozzi A. Subcutaneous mastectomy data. Aestetic Plast Surg, 1989, 13, 15-21.

22. Rebbeck TR, Levin AM, Eisen A et al. Breast cancer risk after bilateral prophylactic oophorectomy in BRCA 1 mutation carriers. J Natl Cancer Inst 1999; 91:1475-79.

23. Grann VR, Jacobson JS, Thomasen D et al. Effect of prevention strategies on survival and quality-adjusted survival of women with BRCA1/2 mutations: an updated decision analysis. J Clin Oncol 2002; 20:2520-29.

© 2002, Institute of Oncology Sremska Kamenica, Yugoslavia