BRCA susceptibility genes – A Review of current conservative management of *BRCA* mutation carriers

H. Levavi, *M.D.*; **G. Sabah,** *M.D.*

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Rabin Medical Center, Petah Tiqva. Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv (Israel)

Summary

Three options for the management of a patient carrying a deleterious mutation in the *BRCA* gene exist: close surveillance, chemoprevention and prophylactic surgical procedures. We aimed at reviewing the current knowledge on the conservative management of patients who are found to be carriers of the *BRCA* susceptibility genes.

Recent literature in the English language was reviewed for publications containing the conservative management of *BRCA* mutation-carriers.

Close surveillance for the breasts includes breast self-examination, clinical examination by a specialist and breast imaging techniques – mammography and magnetic resonance imaging. Ovarian surveillance includes pelvic examination, transvaginal ultrasonography and blood CA-125 measurements. Age at beginning of examinations and their frequency are discussed.

Chemoprevention includes tamoxifen and oral contraceptives for breast and ovarian cancer prevention, respectively.

Key words: BRCA mutation; Breast cancer; Ovarian cancer; Chemoprevention; Mammography.

Introduction

Heavy history of breast and ovarian cancer in several members of the same family belong to familial cancer syndromes, introduced by Lynch and Krush [1]. Linkage analysis studies and later actual cloning of the *BRCA* genes responsible for many of these hereditary cancers [2, 3] have introduced the issue of genetic testing and counseling for women carrying *BRCA* mutations. The management of these high-risk women is a frequent problem raised by patients and their caregivers.

Women who test positive for a *BRCA1/2* mutation can pursue more aggressive cancer surveillance and prevention regimens. Three options for the management of a patient carrying a deleterious mutation in the *BRCA* gene exist: Close surveillance, chemoprevention and prophylactic surgical procedures.

In this review we will discuss the current surveillance and chemoprevention managements and recommendations available for women carrying *BRCA* mutations.

Close Surveillance - Breast

For the early detection of breast cancer, breast self-examination, clinical examination by a specialist and imaging methods are available. The efficacy of breast self-examination in reducing breast cancer mortality has never been established. In fact, a recent study in China has found that teaching a general population of women breast self-examination (BSE) does not appear to decrease the number of deaths from breast cancer. On the other hand, intensive teaching of BSE was found to increase the rate of benign breast biopsies, potentially adding to health care costs without benefits [4].

The efficacy in reducing breast cancer mortality by clinical breast examination by a specialist has also not been established.

Lack of performance standards and quality-assurance practices and low efficacy in 40-49 year-old women in small, localized tumors are among the reasons for that. The same arguments apply for screening mammography in *BRCA* carriers. There is a lower sensitivity in detecting small tumors in *BRCA* carriers. The efficacy in reducing mortality in *BRCA* carriers and the efficacy in reducing mortality in women younger than 40 have also not been established. Furthermore, the age at first screening and intervals, thereafter have not yet been decided.

Concerns about the accuracy of mammography in the detection of hereditary breast cancer have been raised. In one study, only six of 13 small tumors (46%) in *BRCA*1 carriers were mammographically detectable, compared with 96 of 108 (89%) in non-carriers ($p < 0.001$) [5].

Stoutjesdijk *et al.* [6], compared magnetic resonance imaging (MRI) with mammography to determine which is more sensitive and whether MRI could play a role in the early detection of breast cancer for a cohort of women at risk for early onset familial breast cancer. Patients' lifetime risk of breast cancer had to exceed 15% based on family history of breast or ovarian cancer or the presence of a germline mutation in the *BRCA*1 or *BRCA*2 gene. No personal history of breast cancer was included. Receiver operator characteristic curves were generated for MRI and mammography, and the area under each curve (AUC) was assessed for the entire cohort of 179 women. They found that the AUC for mammography was 0.74 (95% confidence interval [CI] = 0.68 to 0.79), and the AUC for MRI was 0.99 (95% CI = 0.98 to 1.0). The authors concluded that MRI was more accurate than mammography in annual breast cancer surveillance of women with a hereditary risk of breast cancer [6].

Similar conclusions were drawn by Kuhl *et al.,* who found that the accuracy of MR imaging is significantly higher than that of conventional imaging in screening high-risk women. They also added that difficulties can be caused by an atypical manifestation of hereditary breast cancers at both conventional and MR imaging and by contrast material enhancement associated with hormonal stimulation [7].

More intriguing is the concern for a higher cancer risk occurring following mammography in *BRCA* carriers. It is known that relatively low doses of X-rays cause single- and double-strand breaks in DNA. While normal women have DNA repair systems that adequately reverse the DNA damage that occurs, women with *BRCA*1/2 gene defects will be less able to repair radiation damage to their DNA leading to a presumed higher risk of breast cancer at an earlier age [8].

Close Surveillance - Ovary

Surveillance as a method for early detection of ovarian cancer is a crucial problem. Given that the ovaries are intraabdominal organs, most ovarian cancers are diagnosed at an advanced stage, hence the dismal survival prospects. Screening for ovarian cancer, practically, does not exist. Neither CA-125 nor ultrasound have proven to be sensitive means of detecting Stage I and Stage II ovarian cancers. Nevertheless, several researchers have begun to produce results with regular ovarian screening [9]. A statement issued by the NIH concerning CA-125 blood level measurements, pelvic examination and transvaginal ultrasonography, stated "There are no data demonstrating that screening these high-risk women reduces their mortality from ovarian cancer. Nonetheless, [the above screening measures] are recommended..." [10].

While the limitations are well accepted, for the time being, and until better screening methods are developed, these clinical procedures are still recommended by many [11].

Chemoprevention - Breast

Chemoprevention effect of *tamoxifen* in *BRCA*-mutation carriers is controversial. Narod *et al.* [12] performed a retrospective, case-controlled study to evaluate the effect of *tamoxifen* on preventing the development of contralateral breast cancer in 209 confirmed *BRCA* carriers with a diagnosis of bilateral breast cancer and an age-matched control group of 384 *BRCA* carriers with unilateral breast cancer. In a multivariate analysis, *tamoxifen* used in women after breast cancer was found to decrease contralateral breast cancer by 50%. The risk decreased with longer duration of use: the OR for less than two years' use was 0.47 (0.23–0.99) and for two to four years' use 0.25 (0.07–0.91). The protective effect of *tamoxifen* was greater in carriers of *BRCA1* mutations (OR 0.38, CI 0.19–0.74) compared to *BRCA2* mutations (OR 0.63, CI 0.20–1.5). These results seem to be in contradiction with the fact that *BRCA1*-associated tumors are more estrogen-receptor negative than positive [13]. However, several facts support the suggestion that estrogen plays an important role in tumor development: prophylactic oophorectomy, especially in younger age, significantly reduces the risk of breast cancer in *BRCA* mutation carriers [14]. Pregnancy, a high circulating estrogen concentration period in a woman's life, confers a higher risk of developing breast cancer in *BRCA* mutation carriers. Johannsson *et al.* [15] reported a greater than expected number of pregnancy-related breast cancers (i.e., those diagnosed during or within 1 year of pregnancy) among carriers of *BRCA1* and *BRCA2* mutations (10 pregnancy-related breast cancers were found vs 2.7 expected). In another study [16] the authors found that carriers of *BRCA* mutations who have children are significantly more likely to develop breast cancer by age 40 than carriers who are nulliparous. Each pregnancy was found to be associated with an increased cancer risk, and an early first pregnancy did not confer protection for carriers of *BRCA1* or *BRCA2* mutations. All these facts corroborate for a role of estrogen in the development of breast cancer in *BRCA* mutation carriers.

Several other studies evaluated the effect of *tamoxifen* in reducing the risk of breast cancer in *BRCA* carriers: The Royal Marsden Hospital Trial [17] enrolled only women with first-degree relatives with breast cancer and who may, therefore, have had hereditary breast cancer. Results did not show a reduction in breast cancer incidence with *tamoxifen.*

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial P-1, analyzed the effect of *tamoxifen* in reducing primary breast cancers in *BRCA* carriers [18]. No benefit for *tamoxifen* use was observed in women who were found to be *BRCA1* mutation carriers. However, an estimated 62% reduction in breast cancer incidence with *tamoxifen* use was observed for women who were found to be *BRCA2* mutation carriers, of whom 76% had estrogen-receptor positive tumors.

In a recent study, Duffi and Nixon [19] combined the estrogen-receptor specific effects of *tamoxifen* from randomized preventive or therapeutic trials with the estrogen receptor status of tumors in *BRCA*1 and *BRCA*2 mutation positive women from published tumor surveys to obtain estimates of the likely effect of *tamoxifen* administration in mutation carriers. They showed an estimated reduction in risk of breast cancer from administration of *tamoxifen* in *BRCA*1 mutation-positive women of 13% (RR = 0.87, 95% CI = 0.68-1.11). The corresponding estimated reduction in *BRCA*2 mutation-positive women was 27% (RR = 0.73, 95% CI = 0.59-0.90). They concluded that the benefit of prophylactic use of tamoxifen in *BRCA*1 mutation carriers is likely to be modest, and the effect in *BRCA*2 mutation carriers is somewhat greater [19].

Chemoprevention – Ovary

Ovarian cancer risk is reduced in women in the general population who have used oral contraceptives (high-dose pills as well as the new generation of lower-dose pills) as compared to women who have never used them, by a third to 40%. Protection persists for 10-15 years after oral contraceptives have been discontinued.

The role of oral contraceptives in the chemoprevention of *BRCA*-related ovarian cancer is still controversial.

In *BRCA*1 or *BRCA*2 carriers the use of oral contraceptives for six or more years was associated with a 60% reduction in the risk of ovarian cancer. The risk decreased with increasing duration of use [20].

An ongoing concern is whether there is an increased risk of breast cancer with current or previous oral contraceptive use in the general population. A recent large case-control study [21] examined the question in 4,575 American women with breast cancer and 4,682 matched controls. Results showed absolutely no increase in the risk of breast cancer for current oral contraceptive users (adjusted OR 1.0; 95% CI = 0.8 to 1.3) or for previous users (0.9; 0.8 to 1.0).

However, some researchers have expressed their concern against the use of oral contraceptives in *BRCA* mutation carriers. Estrogenic stimulation activates the *BRCA* gene and causes a burst in the activity of DNA repair enzymes. A woman with impaired *BRCA* gene function would have difficulty repairing or removing cells containing DNA damaged by oxidized products of oral contraceptives. Oral contraceptives would act as tumor promoters by stimulating these damaged (initiated) cells. Hence, the position is cautious against the use of oral contraceptives in these patients [22].

Modan *et al.* [23], in a study on behalf of the National Israeli Study of Ovarian Cancer found that if a woman has a founder mutation in *BRCA* genes, oral contraceptives will not reduce her risk of developing ovarian cancer. They claim that the increased risk found for breast cancer in high-risk families warns high-risk women to avoid oral contraceptives and to abandon the strategy of using them for protection from ovarian cancer.

In a more recent study, Narod and colleagues [24] examined the history of oral contraceptive use among 1,311 women with *BRCA*1 or *BRCA*2 mutations that had breast cancer and 1,311 mutation carriers without breast cancer. Among BRCA1 mutation carriers, those who used oral contraceptives for five or more years had a 33% increase in the risk of breast cancer, compared with women who had never used oral contraceptives (OR = 1.33, 95% CI = 1.11 to 1.60). Among women with *BRCA*2 mutations they did not find any increase in breast cancer risk (OR = 0.94, 95% CI = 0.72 to 1.24). The risk for breast cancer was also elevated in women carrying *BRCA*1 mutations who used oral contraceptives before age 30, (OR = 1.29, 95% CI = 1.09 to 1.52), women who were diagnosed with breast cancer before age 40 (OR = 1.38, 95% CI = 1.11 to 1.72), and women who first used oral contraceptives before 1975 (OR = 1.42, 95% CI = 1.17 to1.75). The authors conclude that oral contraceptive use after the age of 30 is not likely to increase the risk of breast cancer in women carrying *BRCA*1 mutations and that it can be used safely to reduce the risk of ovarian cancer.

More studies should be done to confirm the limited data on *BRCA*2 mutation carriers.

To summarize the conservative management of *BRCA* mutation carriers, Eisen *et al.* [25] outlined their surveillance-management recommendations for *BRCA* mutation carriers as follows: for breast cancer surveillance, beginning at age 25, monthly breast self-examination, clinical breast examination every six months, and mammography every six to 12 months (or MRI – annually, in a research protocol). Patients should also consider *tamoxifen* trials. For ovarian cancer surveillance annual or semi-annual gynecological examination, transvaginal sonography and serum CA-125 should be carried out starting at 25 to 35 years. For ovarian chemoprevention they recommended oral contraceptives until childbearing is complete, then prophylactic oophorectomy with hormone replacement or SERM therapy.

References

[1] Lynch H., Krush A.: "Carcinoma of the breast and ovary in three families". *Surg. Gynecol. Obstet.,* 1971, *133,* 644.
[2] Miki Y., Swensen J., Shattuck-Edens D. *et al.*: "A strong candidate for the breast and ovarian cancer susceptibility gene *BRCA*1". *Science*, 1994, *266*, 66.
[3] Wooster R., Bignell G., Lancaster J. *et al.*: "Identification of the breast cancer susceptibility gene *BRCA*2". *Nature*, 1995, *378,* 789.
[4] Thomas D., Gao D., Ray R. *et al.*: "Randomized trial of breast self-examination in Shanghai: final results". *J. Natl. Cancer Inst.,* 2002, *94*, 1445.
[5] Goffin J., Chappuis P.O., Wong N., Foulkes W.D.: "Magnetic resonance imaging and mammography in women with a high hereditary risk of breast cancer". *J. Natl. Cancer Inst.,* 2001, *93,* 1754 [letter].
[6] Stoutjesdijk M.J., Boetes C., Jager G.J. *et al.*: "Magnetic Resonance Imaging and Mammography in women with a hereditary risk of breast cancer". *J. Natl. Cancer Inst.,* 2001, *93*, 1095.
[7] Kuhl C.K., Schmutzler R.K., Leutner C.C. *et al.*: "Breast MR imaging screening in 192 women proved or suspected to be carriers of a breast cancer susceptibility gene: preliminary results". *Radiology,* 2000, *215*, 267.
[8] Sharan S.K., Morimatsu M., Albrecht U. *et al.*: "Embryonic lethality and radiation hypersensitivity mediated by Rad51 in mice lacking *BRCA*2". *Nature,* 1997, *386*, 804.
[9] Menon U., Jacobs I.: "Screening for ovarian cancer". *Best Practice & Research Clinic Obstet. Gynecol.,* 2002, *16,* 469.
[10] NIH Consensus Panel on Ovarian Cancer: "Ovarian cancer. Screening, treatment and follow-up". *J. Amer. Med. Assoc.,* 1995, *273*, 491.
[11] Burke W., Daly M., Garber J. *et al.*: "Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. Cancer Genetics Studies Consortium". *J. Amer. Med. Assoc.*, 1997, *277*, 997.
[12] Narod S.A., Brunet J-S., Ghadirian P., Robson M., Heimdal K., Neuhausen S.L. *et al.*: "Tamoxifen and risk of contralateral breast cancer in *BRCA*1 and *BRCA*2 mutation carriers: a case-control study". *Lancet*, 2000, *356,* 1876.
[13] Lakhani S.R., van de Vijver M.J., Jacquemier J. *et al.*: "The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, Her-2 and p53 in patients with mutations in *BRCA*1 and *BRCA*2". *J. Clin. Oncol.,* 2002, *20*, 2310.
[14] Rebbeck T.R., Lynch H.T., Neuhausen S.L. *et al.*: "Prophylactic oophorectomy in carriers of *BRCA*1 or *BRCA*2 mutations". *N. Engl. J. Med.,* 2002, *346,* 1616.
[15] Johannsson O., Loman N., Borg A., Olsson H.: "Pregnancy-associated breast cancer in *BRCA*1 and *BRCA*2 germline mutation carriers". *Lancet*, 1998, *352*, 1359.
[16] Jernstrom H., Lerman C., Ghadirian P., et al.:. "Pregnancy and risk of early breast cancer in carriers of BRCA1 and BRCA2". Lancet, 1999, 354, 1846-50.
[17] Powles T., Eeles R., Ashley S. *et al.*: "Interim analysis of the incident breast cancer in the Royal Marsden Hospital tamoxifen randomized prevention trial". *Lancet,* 1998, *362,* 98.
[18] King M.C., Wieand S., Hale K. *et al.*: "Tamoxifen and breast cancer incidence among women with inherited mutations in *BRCA*1 and *BRCA*2: National Surgical Adjuvant Breast and Bowel Project NSABP-P1) Breast Cancer Prevention Trial". *J. Amer. Med. Assoc.*, 2001, *286*, 2251.
[19] Duffi S.W., Nixon R.M.: "Estimates of the likely prophylactic effect of tamoxifen in women with high risk *BRCA*1 and *BRCA*2 mutations". *Brit. J. Cancer*, 2002, *86,* 218.
[20] Narod S.A., Risch H., Moslehi R. *et al.*: "Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group". *N. Engl. J. Med.,* 1998, *339*, 424.
[21] Marchbanks P.A., McDonald J.A., Wilson H.G. *et al.*: "Oral contraceptives and the risk of breast cancer". *N. Engl. J. Med.,* 2002, *346,* 2025.
[22] Grabrick D.M., Hartmann L.C., Cerhan J.R. *et al.*: "Risk of breast cancer with oral contraceptive use in women with a family history of breast cancer". *J. Amer. Med. Assoc.*, 2000, *284,* 1791.
[23] Modan B., Hartge P., Hirsh-Yechezkel G. *et al.*: "Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a *BRCA*1 Or *BRCA*2 mutation". *N. Engl. J. Med.,* 2001, *345*, 235.
[24] Narod S.A., Dubé M-P., Klijn J. *et al.*: "Oral contraceptives and the risk of breast cancer in *BRCA*1 and *BRCA*2 mutation carriers". *J. Natl. Cancer Inst.,* 2002, *94,* 1773.
[25] Eisen A., Rebbeck T.R., Wood W.C., Weber B.L.: "Prophylactic surgery in women with a hereditary predisposition to breast and ovarian cancer". *J. Clin. Oncol.,* 2000, *18,* 1980.

Address reprint requests to:
H. LEVAVI, M.D.
Div. of Gyn. Onc. Dept. Ob/Gyn.
Rabin Medical Center
Petah Tiqva, 49100
(Israel)