Review

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Evidence-based management options for women at increased breast/ovarian cancer risk

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Recent developments in our ability to predict breast cancer risk necessitates primary care physicians learn to evaluate breast cancer risk and its importance in shaping decisions concerning surveillance and risk reduction measures. This article reviews the current opinion on risk assessment and management of women with an increased risk of breast/ovarian cancer. Management options are given for women at slightly, moderately and highly elevated breast cancer risk, as well as for *BRCA1/2* carriers, based on currently available evidence.
Key words: *BRCA1*, *BRCA2*, familial risk, hereditary breast cancer, ovarian cancer, prophylactic surgery

Introduction

Approximately 15–20% of all breast cancers occur within the context of familial breast cancer. Recent advances in molecular genetics allow us to identify individuals at risk, and new developments in the clinical management of familial breast/ovarian cancer have brought this new field to the attention of a wide range of health care professionals.

Population-based breast cancer screening with mammography among women from 50 to 70 years of age has been performed for many years and has been shown to reduce breast cancer mortality by up to 35%. However, for women at increased breast cancer risk no randomized trials have been conducted and the best surveillance strategy remains unknown. In addition, a number of interventions have been developed in recent years to reduce the risk of breast and ovarian cancer. There is emerging evidence that chemoprevention with selective estrogen receptor modulators may reduce the incidence of breast cancer in healthy women at increased risk for breast cancer. But the most effective class of endocrine agent, the optimal duration or the age at which chemoprevention should begin have not yet been defined. Recent studies have shown substantial benefit of surgical interventions, such as prophylactic mastectomy and/or oophorectomy, for a select group of moderate to high-risk women. Since surgical interventions are irreversible and have far-reaching repercussions, a thorough overview with respect to their advantages and limitations is needed in order to take an appropriate decision.

In recent years, many professional groups, including the Swiss Institutes for Applied Cancer Research Network for Cancer Predisposition Testing and Counseling [1], have developed specialized multidisciplinary programs for familial cancer. In order to provide optimal care, breast cancer risk needs to be assessed as precisely as possible and appropriate decisions concerning surveillance and risk reduction measures have to be taken based on evidence. This review aims to summarize the currently available evidence concerning surveillance and risk reduction measures for women at increased breast/ovarian cancer risk.

Risk assessment

Breast cancer risk needs to be assessed as precisely as possible to enable appropriate decisions to be taken concerning surveillance and risk reduction measures. Claus and Gail are two models for predicting breast cancer risk which are widely used in research studies and clinical counseling [2, 3]. Both have their limitations and the risk estimated from these two models may differ for an individual patient. However, these models provide the best methods currently available for individual risk assessment. Neither the Gail nor the Claus model were designed to estimate the probability of a patient carrying a *BRCA* mutation, but other models have been designed for that purpose.

Risk assessment models

The Claus model. The Claus model [2] projects the probability of developing breast cancer for women with a family history of breast cancer using empirical data from the Cancer and Steroid Hormone (CASH) study. This model is based on assumptions of the prevalence of high-penetrance genes for susceptibility to breast cancer. The risk estimate is based on the following:

- a woman's current age;
- the number of first- and second-degree relatives with breast cancer;
- the age of cancer onset in first- and second-degree relatives.

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This model provides cumulative risk estimates for several different family history configurations but does not take other risk factors associated with lifestyle and environmental factors into account.

The maximum number of affected family members this model can accommodate is two. Therefore it may underestimate the breast cancer risk for women with three or more affected family members. Pedigree data are not taken into account and important genetic information conveyed by the presence of unaffected family members is minimized.

The Gail model. The Gail model [3] projects the probability of developing both invasive and noninvasive breast cancer based on some of the known risk factors for breast cancer. The Gail model predicts the cumulative risk of breast cancer by decade up to 90 years of age. It is based on the major predictors of risk identified in the Breast Cancer Detection Demonstration Project, a large mammographic screening project in the 1970s. Utilized risk factors are as follows:

- current age;
- age at menarche;
- age at first live birth;
- number of previous breast biopsies;
- presence of atypical hyperplasia;
- number of first-degree relatives with breast cancer.

To calculate breast cancer risk with the Gail model, a woman's risk factors are translated into an overall risk score by multiplying her relative risks from several categories. The risk score is then multiplied by an adjusted population risk of breast cancer to determine the individual risk of breast cancer. The Gail model does not consider second-degree relatives, paternal relatives, age of onset of breast cancer in the affected relative or cases of ovarian cancer in the family and thus may overestimate the risk in women whose first-degree relatives had breast cancer at an old age and underestimate the risk in women whose first-degree relatives had breast cancer at a young age.

Because the Gail model includes only first-degree relatives in its risk calculation and does not consider second-degree relatives, paternal relatives, age of onset of breast cancer in the affected relative or cases of ovarian cancer, it is *not* an appropriate model for women with a family history of multiple relatives with breast cancer which is suggestive of an inherited breast cancer predisposition. The Gail model has been validated in four populations [4–7] as a predictor of breast cancer risk in women who adhere to regular mammography screening. Some of these studies indicate that the model overestimates risk in women who do not undergo mammographic screening regularly.

Models for predicting likelihood of BRCA1 or BRCA2 mutations. Several studies have assessed the frequency of *BRCA1* or *BRCA2* mutations in women with breast or ovarian cancer. There have been population-based studies as well as studies from clinical referral centers.

Personal characteristics associated with an increased likelihood of *BRCA1* or *BRCA2* mutations are as follows:

- breast cancer diagnosed <40 years of age;
- bilateral breast cancer, especially at a young age;
- a history of both breast and ovarian cancer.

Family history characteristics associated with an increased likelihood of *BRCA1* or *BRCA2* mutations [8] are as follows:

- two or more family members <50 years of age with breast cancer;
- both breast and ovarian cancer in the family;
- male breast cancer;
- one or more family members <50 years of age with breast cancer and with Ashkenazi Jewish background;
- ovarian cancer and Ashkenazi Jewish background.

In one multicenter study [9], the likelihood of finding a *BRCA1* or *BRCA2* mutation was >50% if a breast cancer-affected individual was <50 years of age and had at least one first- or second-degree relative with breast or ovarian cancer or if a patient had bilateral breast cancer, both breast and ovarian cancer or a diagnosis of breast cancer <40 years of age and relatives with both breast and ovarian cancer.

In a German referral clinic, families were evaluated for *BRCA1* mutation if three or more family members developed breast or ovarian cancer with at least two of the affected family members being <60 years of age. A mutation was found in 33% of families with both breast and ovarian cancers and 17% of the families with breast cancer only. A referral clinic in Pennsylvania found *BRCA1* mutations in 40% of families with breast and/or ovarian cancer but only in 7% of families with breast cancer only.

These studies indicate that among women with personal or family history characteristics suggesting an increased risk of breast cancer, a *BRCA1* or *BRCA2* mutation is more likely to be found if the family history includes the following:

- members with both breast and ovarian cancer;
- two or more primary breast or ovarian cancers;
- multiple breast cancers occurring at an early age.

Statistical models based on these data have been developed to estimate an individual's probability using personal and family history characteristics. Computer programs have been developed from these models to estimate probabilities based on data entered by a health professional. One of these, BRCAPRO, is now available via the Internet (http:// astor.som.jhmi.edu/brcapro). One of the major differences between this model and those cited above is its ability to consider the structure of the family pedigree including both affected and unaffected family members, in estimating the probability of a *BRCA1* or *BRCA2* mutation. BRCAPRO also includes data regarding age at onset of ovarian and breast cancer, presence of bilateral and male breast cancer and Ashkenazi Jewish heritage in the probability computation. All models are based on prevalence, penetrance and mutation frequency data derived from persons who participated in research studies of *BRCA1* and *BRCA2* or who chose to be clinically tested. Most of the persons tested were affected with cancer. Like the models cited above, these data are thus likely to be subject to selection biases with the estimated probabilities depending

significantly on the *BRCA1* and *BRCA2* penetrance estimates chosen. The BRCAPRO model has recently been validated as an accurate counseling tool for determining the probability of carrying mutations of *BRCA1* or *BRCA2* [10].

Other breast cancer susceptibility genes that have to be taken into account when assessing inherited breast cancer. Although mutations in several genes confer an increased breast cancer risk, *BRCA1*, *BRCA2* and *TP53* appear to be the most relevant in clinical practice. Estimates of the proportion of inherited breast cancers due to *BRCA1* and *BRCA2* mutations range from 30% in clinical-based families to 84% in the Breast Cancer Linkage Consortium [11–13]. *TP53* and *PTEN* each account for <1% of cases [14, 15]. Heterozygous *ATM* mutation carriers have an increased risk of breast cancer but the magnitude of risk is not quantified [16]. Other genetic conditions with associated breast cancer risk include Muir Torre syndrome with *MLH1* mutations and Peutz Jeghers syndrome with *LKB1/STKII* mutations.

Surveillance

Breast self-examination

The increased risk of early onset breast cancer and reports of the failure of mammography to detect breast cancer in carriers of *BRCA1* mutations may make breast awareness of greater value in high-risk women than in average-risk women.

Clinical breast examination

Clinical breast examination detects palpable breast cancers. It can detect cancers that are not detectable by mammography or interval cancers between regular mammographic screenings. The National Breast and Cervical Screening Program recently reported the results of 753081 clinical breast examinations provided during the period from 1995 to 1998 to low-income women. A breast cancer detection rate of 5.1% was observed for an abnormal clinical breast examination with a normal mammogram [17]. The Canadian National Breast Screening Study, a randomized study to evaluate the effect of mammography over clinical breast examination, reported after 13 years of follow-up similar death rates in the combined mammography and clinical breast examination arm compared with the clinical breast examination only arm [18]. In the Breast Cancer Detection Demonstration Project, 6.2% of tumors were detected by clinical examination alone (National Cancer Institute and American Cancer Society, 1979). Clinical examination may be an important adjunct in screening for breast cancer in young, high-risk women for whom there is some doubt about the sensitivity of mammography.

Mammographic screening

A limited number of studies describing the experiences and results of surveillance in women with familial breast cancer have been published [19–23]. A recent study suggested that tumors in *BRCA* carriers have the same radiological appearance as in non-carriers [24], which suggests that yearly screening may be effective. However, a study by Brekelmans et al. [25] observed a substantial risk of interval cancers in *BRCA* mutation carriers undergoing annual mammographic screening, which suggests that current recommendations of yearly mammographies beginning between 25 and 35 years of age may be insufficient in this very high-risk group. This may be due to highly proliferative cancers, because 70% of *BRCA1*-associated breast cancers are grade 3 lesions [26]. Moreover, in the group of proven *BRCA* carriers and women under the age of 40, 56% and 62% of mammographically detected breast cancers, respectively, were node positive, compared with an expected rate of around 31% in this age group [27, 28]. Although several studies have shown that 60–90% of breast cancers diagnosed in young women are evident mammographically [29], breast density is known to be higher in young women and thus may hamper effective mammographic screening [30, 31].

Ovarian cancer surveillance

Screening strategies using ultrasound and measurements of serum CA125 levels may detect ovarian cancer before the onset of clinical symptoms. However, screening for ovarian cancer has not been shown to reduce mortality in unselected patients nor is it clear what the optimal frequency of screening is (NIH Consensus Development Panel on Ovarian Cancer 1995 [32]).

Transvaginal ultrasound enables the assessment of ovarian size and morphology. Ovarian enlargement and solid and cystic morphology may give rise to an index of suspicion for neoplasia. Ovarian tumors are characterized by a lower than average impedance to blood flow, which may be detected by color flow Doppler. The sensitivity and specificity of this technique has been reported to be 98.4% and 99.8%, respectively [33]. The addition of transvaginal ultrasound to CA125 measurements increases specificity to 100% and gives a positive predictive value of 27% [34, 35]. However, normal physiological changes in the premenopausal ovary near the time of ovulation have low impedance flow characteristics similar to those seen in malignancy [36]. Therefore transvaginal ultrasound should be timed to avoid ovulation in order to reduce the frequency of false-positive results.

Data are limited with regard to the benefit of pelvic ultrasound in screening women with an inherited risk of ovarian cancer. One study examined 1601 women with a family history of ovarian cancer with pelvic ultrasound; of these scans 3.8% were found to be abnormal. Only three of 61 women with abnormal scans had ovarian cancer, two with stage I and one with stage III ovarian cancer [37]. The NIH Consensus Statement on Ovarian Cancer recommended that women with a *BRCA* mutation-associated risk of ovarian cancer undergo transvaginal ultrasound and serum CA125 measurement every 6–12 months commencing at 35 years of age [32]. The Cancer Genetics Studies Consortium task force has recommended that female carriers of a *BRCA1* high-risk mutation undergo 6–12 monthly screening using transvaginal ultrasound and serum CA125 measurement beginning at 25–35 years of age [38].

Risk reduction measures

Chemoprevention

Tamoxifen, a selective estrogen receptor modulator, was the first drug shown to reduce the incidence of breast cancer in healthy women. The breast cancer prevention trial randomly assigned more than 13000 women with a 5-year risk of breast cancer of at least 1.7% in the Gail model to 5 years of tamoxifen 20 mg or placebo [39]. After a median follow-up of 4 years, tamoxifen had reduced the incidence of estrogen receptor-positive (ER^+) breast cancers by 49% compared with placebo. In contrast, two European trials did not find tamoxifen protective [40, 41]. The difference in results may be related to differences in the design of the studies and the populations included [42]. A subgroup analysis of the P-1 trial showed that tamoxifen reduces the breast cancer incidence among healthy *BRCA2* carriers by 62% similar to the reduction in incidence of ER^+ breast cancer among all women in the breast cancer prevention trial, but tamoxifen use beginning at ≥35 years of age did not reduce breast cancer risk among healthy *BRCA1* carriers [43].

A recently published retrospective study among select women with *BRCA* mutations who received adjuvant therapy with tamoxifen has documented a reduction in risk of contralateral breast cancer among *BRCA* carriers [44]. This study examined the effect of tamoxifen in two groups of patients with either a *BRCA1* or a *BRCA2* mutation; namely, in 209 and 374 women with bilateral and unilateral breast cancer, respectively. Tamoxifen protected against contralateral breast cancer and the risk reduction was 75% for women who used tamoxifen for 2–4 years. Moreover, the protective effect of tamoxifen appeared to be independent from oophorectomy. However, a recent paper by Li et al. [45] argues that the incidence of contralateral ER^- breast tumors may even be increased with adjuvant tamoxifen therapy. This may be an important finding with respect to chemoprevention in *BRCA1* carriers as up to 80% of *BRCA1*-related tumors are ER^- [46].

Tamoxifen has side-effects such as venous thromboembolism, endometrial cancer and cataracts. Although tamoxifen maintains bone density in postmenopausal women [47], it may result in bone loss in premenopausal women. Raloxifene, a selective estrogen-receptor modulator, has been approved in the USA for the prevention and treatment of osteoporosis in postmenopausal women. The effect of raloxifene on the risk of breast cancer has been monitored in several ongoing placebo-controlled trials directed at osteoporosis and other endpoints. The multiple outcomes of the raloxifene (MORE) trial randomly assigned 7705 women with osteoporosis to raloxifene 120 mg daily or placebo [48]. After 40 months of follow-up, raloxifene was found to have reduced the annual odds of breast cancer by 65% and reduced the risk of invasive breast cancer. At the present time, the trial of tamoxifen and raloxifene (STAR) evaluates whether raloxifene is effective in reducing the risk of breast cancer in postmenopausal women and will provide comparative information on the side-effects of these two drugs. However, the most effective class of endocrine agent, the optimal duration or the age at which to begin chemoprevention have not yet been defined for women at increased breast cancer risk. Therefore, chemoprevention should only be performed within the context of well designed clinical trials.

Prophylactic mastectomy

Carriers of *BRCA* mutations have an increased risk of both breast and ovarian cancer. For *BRCA* mutation carriers, the risk of contralateral cancer after breast cancer may exceed 5% per year, and in non-carriers at or below the age of 50 years with at least one similarly affected first-degree relative or relative with ovarian cancer, the rate is estimated to be 2.8% per year [49].

Efficacy. Until very recently there were no prospective trials of prophylactic mastectomy or oophorectomy for the reduction of breast or ovarian cancer mortality. Therefore, two groups have developed theoretical models to facilitate clinical decision making in these women. Schrag et al. [49] and Grann et al. [50] modeled the effect of prophylactic mastectomy and oophorectomy on the life expectancy of *BRCA* carriers to facilitate clinical decision making. Statistical models estimate that a 30-year-old woman who carries a *BRCA* mutation may gain 3–5 years of life expectancy from prophylactic mastectomy and 0.5–1.5 years of life expectancy from prophylactic oophorectomy depending on her cumulative risk of cancer. Estimates of the mean or median age of onset for breast cancer range from 38 to 43 years of age in *BRCA1* [51, 52] mutation carriers and from 41 to 45 years of age in *BRCA2* mutation carriers [9]. Therefore, gains of life expectancy decline with age at the time of prophylactic surgery and are minimal for 60-year-old women. This suggests that the greatest benefit of prophylactic mastectomy may be expected in a young carrier.

Meijers-Heijboer et al. [53] conducted the first prospective study of 139 women with *BRCA1* and *BRCA2* mutations. Seventy-six women chose to undergo prophylactic bilateral mastectomy to reduce their breast cancer risk and 63 women were followed according to a surveillance protocol consisting of a monthly breast self-examination, a semi-annual breast examination by a health care professional and annual mammography. From 1995 annual magnetic resonance imaging (MRI) was offered. No breast cancers were observed in the 76 women who underwent bilateral prophylactic mastectomy, whereas eight breast cancers were detected in the surveillance group. The observed cancer incidence was consistent with the number expected from estimates of the penetrance of *BRCA1* and *BRCA2* mutations. This study supports the retrospective report by Hartmann et al. [54], that prophylactic bilateral mastectomy has an efficacy of 90% in women classified as having a high breast cancer risk based on family history.

Two large retrospective case series on the use of prophylactic mastectomy for familial breast cancer risk have been reported in the literature [54, 55]. The best available evidence concerning efficacy comes from a cohort analysis of 639 women with a family history of breast cancer who had bilateral subcutaneous mastectomy (90%) or total mastectomy (10%) at the Mayo Clinic from 1960 to 1993 [54]. Approximately two-thirds of the women

were classified as high risk on the basis that they possessed some of the features of autosomal dominant breast–ovarian cancer syndrome. One-third were defined as moderate risk including all women with a family history of breast cancer that did not meet the more stringent high-risk criteria. Even with the most conservative estimate of breast cancer incidence, prophylactic mastectomy resulted in a 90% reduction of breast cancer incidence. Similar estimates were derived for the moderate risk group. In a recent update of the Mayo Clinic study, 26 of 214 high-risk women have been identified as *BRCA1* or *BRCA2* mutation carriers and none of them has developed breast cancer after a median of 13.4 years of follow-up [56].

However, breast cancer may occur after prophylactic simple mastectomy [57], which is usually of the subcutaneous form. Breast tissue may be present in the axilla and abdominal wall [58]. Historically the surgical options for women who elected to undergo prophylactic mastectomy have included subcutaneous mastectomy (usually includes an inframammary incision with removal of the breast tissue, leaving the overlying skin, nipple and areola in place) and total mastectomy where as much breast tissue as possible is removed by excising an ellipse of skin (including the nipple and areola and underlying breast tissue down to the fascial plane overlying the chest wall). In subcutaneous mastectomy the nipple areola complex is partially preserved and this tissue remains at risk for malignant transformation and the spared nipple areola complex is insensate, because the underlying breast tissue bearing the nerve branches undergoes scarring and retraction. More recently skin sparing techniques with immediate breast reconstruction have been further refined in the management of breast cancer and have been adopted for prophylactic mastectomy [59]. Breast tissue and the areolar complex are removed in skin sparing mastectomy but the inframammary fold and the breast skin are preserved. At the present time, many experts recommend total mastectomy because this method removes as much tissue at risk as possible.

Psychosocial consequences. Few studies with a small number of patients have specifically addressed the psychosocial sequelae of prophylactic mastectomy in high-risk women. Twenty-six Swedish women were studied prospectively to determine the psychiatric and psychosocial outcomes of subcutaneous mastectomy with immediate reconstruction [60]. Only one of these women had surgery for familial breast cancer. At 8 weeks and 1 year after surgery, the majority of women were satisfied with their surgery, but a considerable proportion reported feelings of depression and some impact on their sexuality. In a small qualitative study of 10 women who underwent cutaneous prophylactic mastectomy with immediate reconstruction no adverse psychological sequelae were described [61].

Prophylactic oophorectomy

In recent times laparoscopic-assisted surgery has been used to perform prophylactic oophorectomy on women with family histories of ovarian cancer. Prophylactic oophorectomy is most commonly prescribed as a strategy to reduce ovarian cancer. Surgical complications specifically attributable to prophylactic oophorectomy are not well described. Possible non-fatal complications of prophylactic oophorectomy include infection, bleeding and urinary tract and bowel injury [62].

Unfortunately, the occurrence of peritoneal cancer, or as it is sometimes called ‘papillary serous carcinoma of the peritoneum’, after prophylactic oophorectomy has been well described [63]. There are two hypotheses about the origin of peritoneal cancer after oophorectomy: (i) the tumor develops from an occult primary ovarian focus with subsequent spread through the peritoneum, or (ii) it is a *de novo* disease originating from the peritoneal mesothelium, which has a common origin with the Mullerian duct epithelium from which epithelial cancer develops. Recent molecular evidence suggests that peritoneal cancer may be multifocal with a polyclonal origin, supporting the second hypothesis [64]. Two retrospective studies by Struewing et al. [65] and Piver et al. [63] documented 44 and 324 patients, respectively, who underwent prophylactic oophorectomy because of a family history of ovarian cancer. These studies describe an incidence of two and six peritoneal cancers, respectively, between 1 and 27 years of age after prophylactic oophorectomy.

Efficacy. The effectiveness of prophylactic oophorectomy in known *BRCA1* and *BRCA2* carriers has also been studied in the two decision models of Grann et al. [50] and Schrag et al. [49]. They assumed that prophylactic oophorectomy has an efficacy of 50% in carriers. The estimated penetrance of ovarian cancer in carriers in the high-risk group was higher in the Grann model but both studies found that prophylactic oophorectomy in a 30-year-old carrier resulted in 1.7 to 2.8 additional years of survival. In the Grann model, quality-of-life analysis resulted in 0.5 additional life years. In both models the benefits were lower with increasing age at prophylactic oophorectomy and with lower ovarian cancer penetrance estimates. The optimal timing for prophylactic oophorectomy has not yet been determined. This is important, because loss of fertility, potential risk of cardiovascular disease, osteoporosis and premature menopausal symptoms must be balanced against an age-adjusted risk of ovarian cancer. In hereditary ovarian cancer [66, 67] the mean age of onset has been reported to be 48–51 years in several series. These figures have led some to suggest that prophylactic oophorectomy could be deferred to a later age to minimize the negative side-effects of premature loss of ovarian function. However, because ovarian cancer has been reported in *BRCA1* mutation carriers in their thirties, an NIH Consensus Development Panel on ovarian cancer [32] recommended that prophylactic oophorectomy should be performed after childbearing has been completed or after 35 years of age.

New data from two large studies recently published in the *New England Journal of Medicine* show that the benefit from prophylactic oophorectomy is substantial for both breast and ovarian cancer risk. A prospective follow-up study by Kauf et al. [68] of 170 women with *BRCA1* or *BRCA2* mutations choosing to undergo either surveillance or salpingo-oophorectomy demonstrated that after a mean follow-up of 24.2 months, bilateral oophorectomy resulted in an ovarian cancer risk reduction of 85% and a breast cancer risk reduction of 68%. An accompany-

ing article reporting the results of a multicenter retrospective analysis of 551 women carrying mutations in either *BRCA1* or *BRCA2* from Rebbeck et al. [69] showed a risk reduction for coelomic epithelial cancer of 96% and for breast cancer of 53% after bilateral prophylactic oophorectomy. These results confirm previous reports [65, 70] that the risk of breast cancer is substantially reduced after prophylactic oophorectomy. Moreover, the study by Rebbeck et al. [69] supports the practice of performing prophylactic oophorectomy in *BRCA1* or *BRCA2* carriers as soon as possible after childbearing is completed because of a mean age at diagnosis of ovarian cancer of 50.8 (range 30–73 years). In addition, the use of hormonal replacement therapy did not abolish the beneficial effect of oophorectomy on breast cancer risk. Although opinions on the use of hormonal replacement therapy after prophylactic oophorectomy are divided, this finding together with quality of life issues may facilitate the decision to use estrogens in premenopausal women, making prophylactic oophorectomy more acceptable for these women. In 2001, two studies were published concerning fallopian tube carcinomas [71, 72], which suggested that the procedure of choice in *BRCA* mutation carriers is bilateral salpingoophorectomy possibly with hysterectomy.

In summary, because effective risk reduction measures such as salpingo-oophorectomy are now available for healthy women with *BRCA1* or *BRCA2* mutations, many experts feel that attitudes towards genetic testing for hereditary breast and ovarian cancer syndromes should be changed and individuals at risk encouraged to undergo genetic testing.

Endocrine changes. Apart from the loss of fertility with the onset of postmenopausal symptoms, oophorectomy causes other physiological changes in premenopausal women. It is associated with adverse changes in lipid profile [73] and confers an approximately two-fold increase in coronary artery disease risk [74]. Oophorectomized women have an increased incidence of osteoporosis [75]. These symptoms may be reduced by the use of hormonal replacement therapy. However, the use of exogenous estrogen is of particular concern in women with an increased breast cancer risk due to a hereditary susceptibility. Data on adverse effects concerning the breast cancer risk in young *BRCA* mutation carriers is pending.

Psychosocial considerations. Several authors have investigated the effect of oophorectomy on sexuality and mood. Nathorst-Boos et al. [76] examined the effect of hysterectomy with and without bilateral oophorectomy on sexual function and psychological status and androgen levels in 101 Swedish women. Only half of the women were given hormonal replacement therapy. Oophorectomized women reported lower libido and sexual dissatisfaction regardless of the use of hormonal replacement therapy (HRT) and levels of circulating androgens. General psychological well-being was lowest in the oophorectomy groups, but the use of HRT negated this difference. In a retrospective study, Dennerstein et al. [77] found high levels of sexual dysfunction in a sample of 89 women interviewed up to 5 years after hysterectomy and prophylactic ovariectomy. In contrast, Everson et al. [78] were unable to demonstrate an adverse psychological effect of menopause in a small sample of women with bilateral oophorectomies who were studied prospectively in the healthy women study.

Lifestyle modifications

A number of studies have identified potentially modifiable non-genetic risk factors for breast cancer, such as reproductive factors, hormonal replacement therapy, hormonal contraception, increased dietary fat intake [79, 80], body weight, physical activity [81], alcohol intake [82] and decreased antioxidant vitamin intake.

Body weight. The relationship between body mass index and breast cancer risk changes with age during a woman's lifetime. Whereas a higher body mass index is associated with protection against premenopausal breast cancer [83, 84], an increased risk of breast cancer with higher body mass index was observed among postmenopausal women [85].

Dietary factors. The potential role of dietary factors in breast cancer has been difficult to establish. Many case–control studies have examined the association, and in contrast to cohort studies, have tended to favor at least a weak association between dietary fat and breast cancer [86]. A recent case–control study conducted in Indonesia, a country with a low overall fat intake, observed a strong dose–response trend between dietary fat intake and likelihood of breast cancer, especially during premarital years [87]. Concerning the intake of vitamins, in a large prospective cohort study a protective association for vitamin C intake from foods for premenopausal breast cancer among women with a family history was observed [88].

Phytoestrogens are plant-derived compounds with estrogen agonist and antagonist effects that have been linked to a low risk of breast cancer in some observational reports [89]. Studies to determine whether phytoestrogens promote the risk of breast cancer or not are underway.

Physical activity. A large prospective cohort study indicated that leisure time physical activity during adulthood was associated with decreased breast cancer risk [90]. In a study that focused on postmenopausal breast cancer, cumulative exercise patterns from menarche onwards showed an impressive lowering of risk. Interestingly, the protective influence of exercise was most pronounced among women who had avoided substantial weight gain during adulthood [91]. Despite evidence to support a link between physical activity and breast cancer, a definitive association has not yet been established.

No data are available so far on the effect of body weight, diet and physical activity for carriers of *BRCA* mutations.

Use of oral contraceptives. A small study reported that long-term oral contraceptive use before a full-term pregnancy may increase breast cancer risk in *BRCA1* and *BRCA2* carriers [92]. However,

Table 1. Level of evidence ratings

Level of evidence	
I	Evidence obtained from a systematic review of all relevant randomized controlled trials
II	Evidence obtained from at least one randomized controlled trial
III-1	Evidence obtained from well-designed pseudorandomized controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomized (cohort studies), case–control studies or interrupted time-series with a control group
III-3	Evidence obtained from comparative studies with historical controls, two or more single-arm studies or interrupted time-series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre- and post-test
V	Expert opinion (clinical experience of respected authorities or reports of expert committees), no published evidence

a case–control study demonstrated that the use of oral contraceptives by *BRCA1* mutation carriers decreases the risk of ovarian cancer by 50% [93]. A recently published historical cohort study [94] of 426 families of breast cancer probands suggests that women who have ever used formulations of oral contraceptives during or prior to 1975 with a first-degree relative with breast cancer may be at particularly high risk of breast cancer. *BRCA1* and *BRCA2* mutation screening among high-risk families in this study is currently being undertaken to determine the association of breast cancer with oral contraceptive use in these families. These findings suggest that the impact of oral contraceptive use on breast and ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers needs to be examined more closely before any firm recommendations on their use in women with these mutations can be made.

Use of HRT. Observational studies have suggested that postmenopausal HRT halves the risk of coronary heart disease and osteoporosis but increases the risk of breast cancer by 30–40% [95]. However, the reduction in the risk of coronary heart disease could not be demonstrated in a recently published placebo-controlled randomized trial with HRT for secondary prevention of heart disease in postmenopausal women [96], nor was the progression of established coronary atherosclerosis affected by estrogen (plus or minus medroxyprogesterone acetate) [97]. Moreover, the cumulative effect of HRT on breast cancer risk has raised concerns about the practice of prescribing HRT for 10 years or longer. In a meta-analysis of 51 case–control and cohort studies of 52705 women with breast cancer and 198411 women without breast cancer, short-term use of HRT (<5 years) was not associated with breast cancer risk [98], but a 35% increase in breast cancer risk was seen in women using estrogen replacement therapy for 5 years or longer. Because the risk of osteoporosis may also be lowered through the use of other drugs, most experts feel that the use of HRT in postmenopausal women needs to be re-examined.

The balance between risks and benefits may shift significantly for women with a substantially increased risk of breast cancer. Although the relative risk associated with HRT does not appear to be higher in women with a family history of breast cancer, the absolute benefit of HRT measured as the net increase in life expectancy falls according to decision analysis as the risk of breast cancer increases [99]. In one of the models, HRT no longer increased life expectancy in women with a lifetime breast cancer risk above 30%. Although the number of postmenopausal women with such a high breast cancer risk is small, assessment of breast cancer risk provides valuable information for making decisions about HRT. With respect to ovarian cancer risk, a new 14-year study of more than 211000 postmenopausal women showed that women who take estrogens for ≥10 years [100] doubled their risk of dying of ovarian cancer, compared with those who did not take the hormone.

Levels of evidence

A five-point rating system has been used to identify evidence for key recommendations. Because, as in many other areas of medicine, clinicians in cancer genetics have to make management decisions in the absence of sound evidence, recommendations based on clinical experience of respected authorities or reports of expert committees have been included. At the same time, these expert opinion-based recommendations represent areas in need of high-quality research in the field (Table 1).

Recommendations for individuals at, or slightly above, average risk for breast cancer. Risk category: lifetime risk of 12–15%. Family history:

- no confirmed family history of breast cancer;
- one first-degree relative diagnosed with breast cancer at ≥50 years of age;
- one second-degree relative diagnosed with breast cancer at any age;
- two first- or second-degree relatives diagnosed with breast cancer at ≥50 years of age.

Recommended model for risk calculation: Gail.

Management options for individuals at, or slightly above, average risk for breast cancer (Table 2).

Table 2. Management options: slightly above average risk for breast cancer

	Level of evidence
Monthly breast self-examination	V
Advise to visit general primary care physician promptly if any breast changes are noticed	V
Clinical breast examination every year	II
Mammography every second year after 50 years of age	I
Regular exercise	III-2[a]
At least five servings of fruit or vegetables daily and a fat intake ≤60 g daily	V[a]
Avoidance of smoking	V[a]
Not being overweight	V[a]

[a]Counseling regarding possible health benefits of a low-fat, high-fiber diet with an intake of at least five servings of fruit and vegetables daily, regular exercise and avoidance of carcinogens, such as cigarette smoking, is encouraged. Although dietary and exercise measures are unproven means to reduce breast cancer risk, they have a broad range of other health benefits. Moreover, lifestyle modifications give individuals with an increased breast cancer risk the opportunity to take active steps to promote their health. However, sufficient explanation should be given concerning the uncertainty of benefits in cancer risk reduction to permit latitude for individual choice.

Recommendations for individuals at moderately increased risk for breast cancer. Risk category: lifetime risk of 15–29%.
Family history:

- One or two first-degree relatives diagnosed with breast cancer at <50 years of age (without the additional features of the potentially high-risk group described below).
- Two first- or second-degree relatives on the same side of the family diagnosed with breast or ovarian cancer at <50 years of age (without the additional features of the potentially high-risk group described below).

Recommended models for risk calculation: Claus and Gail.

Management options for individuals at moderately increased risk for breast cancer (Table 3).

Recommendations for individuals at highly increased risk for breast cancer due to a known BRCA mutation or with a family history suggestive of hereditary breast or ovarian cancer but no detectable mutation or no genetic testing. Risk category: lifetime risk of 30–80%.

Personal characteristics associated with an increased likelihood of *BRCA1* or *BRCA2* mutations are as follows:

- breast cancer diagnosed at an early age;
- bilateral breast cancer;
- a history of both breast and ovarian cancer.

Family history characteristics associated with an increased likelihood of *BRCA1* or *BRCA2* mutations [8] are as follows:

- two or more family members <50 years of age with breast cancer;

Table 3. Management options: moderately increased risk for breast cancer

	Level of evidence
Monthly breast self-examination	V
Advise to visit general primary care physician promptly f any breast changes are noticed	V
Clinical breast examination every 6 months	II
Mammography every year from the age of 40 years; additional surveillance, such as mammograms at a younger age or more frequent mammograms, should be considered on an individual basis, as evidence for the optimal strategy in this group does not currently exist	I
Participation in clinical trials for the chemoprevention of breast cancer should be discussed	
Regular exercise	III-2[a]
At least five servings of fruit or vegetables daily and a fat intake ≤60 g daily	V[a]
Avoidance of smoking	V[a]
Not being overweight	V[a]

[a]Counseling regarding possible health benefits of a low-fat, high-fiber diet with an intake of at least five servings of fruit and vegetables daily, regular exercise and avoidance of carcinogens, such as cigarette smoking, is encouraged. Although dietary and exercise measures are unproven means to reduce breast cancer risk, they have a broad range of other health benefits. Moreover, lifestyle modifications give individuals with an increased breast cancer risk the opportunity to take active steps to promote their health. However, sufficient explanation should be given concerning the uncertainty of benefits in cancer risk reduction to permit latitude for individual choice.

- both breast and ovarian cancer in the family;
- male breast cancer;
- one or more family members <50 years of age with breast cancer and Ashkenazi Jewish background.

Recommended model for calculation of *BRCA* mutation probability: BRCAPro and Myriad.
Recommended model for risk calculation without genetic testing or without detectable *BRCA* mutation: Claus.

Management options for individuals at highly increased risk for breast cancer due to a known BRCA mutation or with a family history suggestive of hereditary breast and/or ovarian cancer with no detectable mutation or no genetic testing (Table 4).

Table 4. Management options: highly increased risk for breast cancer

	Level of evidence
Monthly breast self examination	V
Advise to visit general primary care physician promptly if any breast changes are noticed	V
Clinical breast examination every 6 months	V
Annual mammographic screening with ultrasound from the age of 30 years or at least 5 years earlier than the age at diagnosis of the youngest breast cancer case in the family	III
Participation in screening studies should be encouraged	
Participation in trials for chemoprevention of breast cancer should be discussed	
Annual transvaginal pelvic ultrasound with Doppler color measurements and CA125 measurement, commencing at 35 years of age or at least 5 years earlier than the age at diagnosis of the youngest ovarian cancer case in the family	V
For women shown by genetic testing to carry a high-risk mutation, consideration should be given to prophylactic surgery, such as bilateral mastectomy or salpingo-oophorectomy	III-2
Regular exercise	III-2[a]
At least five servings of fruit or vegetables daily and a fat intake ≤60 g daily	V[a]
Avoidance of smoking	V[a]
Avoid long-term use of hormonal replacement therapy	III-2
Not being overweight	V[a]

[a]Counseling regarding possible health benefits of a low-fat, high-fiber diet with at least an intake of five servings of fruit and vegetables daily, regular exercise and avoidance of carcinogens, such as cigarette smoking, is encouraged. Although dietary and exercise measures are unproven means to reduce breast cancer risk, they have a broad range of other health benefits. Moreover, lifestyle modifications give individuals with an increased breast cancer risk the opportunity to take active steps to promote their health. However, sufficient explanation should be given concerning the uncertainty of benefits in cancer risk reduction to permit latitude for individual choice.

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