REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

The Role of Risk-Reducing Surgery in Hereditary Breast and Ovarian Cancer

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Hereditary breast and ovarian cancer is a syndrome that involves an increased predisposition to breast cancer, ovarian cancer, or both and an autosomal dominant pattern of transmission. The numbers of breast-cancer diagnoses, the ages of patients at diagnosis, and the occurrence of ovarian cancer in addition to breast cancer vary among families with hereditary breast and ovarian cancer syndrome. The likelihood of detecting an underlying disease-causing mutation is highest in the most severely affected families, especially those with ovarian cancer. Disease-causing mutations in *BRCA1* and *BRCA2*, the genes most often associated with hereditary breast and ovarian cancer syndrome, are identified in only a minority of families with suspected hereditary breast and ovarian cancer syndrome.

Risk-reducing mastectomy and risk-reducing salpingo-oophorectomy are options for the primary prevention of breast and ovarian cancers, and they have been shown in multiple studies to have efficacy. However, these procedures, which have profound effects on a woman's body, are associated with complex and emotionally charged decision making.

In this review, we address issues related to the care of women in families with hereditary breast and ovarian cancer syndrome who have not had cancer. We discuss risk assessment for breast and ovarian cancers according to the woman's age, the efficacy of risk-reducing surgery, the complications and psychosocial effects of these procedures, alternative strategies for risk management, and the best ways to facilitate individual decision making.

GENETIC FACTORS AND RISK ASSESSMENT

BREAST AND OVARIAN CANCER AMONG CARRIERS OF PATHOGENIC VARIANTS (MUTATIONS)

There is a considerable range in the published estimates of cancer risks among carriers of *BRCA1* or *BRCA2* mutations because of variations in study designs, analyses, and populations studied (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Figure 1 shows average cumulative risks of breast and ovarian cancer among *BRCA1* and *BRCA2* mutation carriers[1,2] (and Antoniou A: personal communication). The data in Figure 1 are from 2785 families, 537 of which carried *BRCA1* or *BRCA2* mutations and were identified through population-based studies. In this review, the term "ovarian cancer" refers to cancer arising in the ovaries, fallopian tubes, and peritoneal cavity. Among *BRCA1* carriers, the average cumulative risk of breast cancer by 80 years of age is 67% and the average cumulative risk of ovarian cancer is 45%. Among *BRCA2* car-

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riers, these average cumulative risks are 66% and 12%, respectively. After a first breast cancer, *BRCA1* and *BRCA2* carriers also have a substantial risk of contralateral breast cancer (Table S2 in the Supplementary Appendix).[3]

The types of breast cancer that occur in *BRCA1* carriers differ considerably from those that occur in *BRCA2* carriers. More than 75% of breast cancers that develop in *BRCA1* carriers are estrogen-receptor (ER)–negative, high-grade cancers, and 69% are ER-negative, progesterone-receptor–negative, and human epidermal growth factor receptor 2–negative, or "triple-negative," breast cancers.[4] In contrast, breast cancers in *BRCA2* carriers mirror those seen in the general population (77% are ER-positive and only 16% are triple-negative breast cancers).[4] Ovarian cancer typically occurs earlier and with greater frequency among *BRCA1* carriers than among *BRCA2* carriers (Fig. 1), and serous ovarian cancers predominate in both types of carriers.[4] Histologic types of ovarian cancer occurring in carriers of other genes that may predispose to the disease are currently not well defined (Table S3 in the Supplementary Appendix).

The likelihood that breast or ovarian cancer will develop in a mutation carrier is influenced by multiple factors. Even among families with mutations in the same gene, there is considerable variability in the risk of cancer.[5] The observed risk of breast or ovarian cancer is higher among carriers with a positive family history than among those with no family history, presumably because of an underlying polygenic predisposition, multifactorial predisposition, or both. Defining genetic and nongenetic modifiers of risk is the subject of ongoing research.[6,7]

A woman's age is highly relevant to her risk of breast or ovarian cancer. An unaffected 30-year-old *BRCA2* carrier has a 66% cumulative risk of breast cancer developing by 80 years of age and a 12.2% cumulative risk of ovarian cancer developing by that age. In contrast, an unaffected 60-year-old *BRCA2* carrier has a 48% cumulative risk of breast cancer developing by 80 years of age and a 3.9% cumulative risk of ovarian cancer developing by that age. Thus, counseling on "lifetime" risk must factor in the woman's current age (Table S4 in the Supplementary Appendix). We generally estimate a woman's risk over the next 10 years, given the rapid advances in management options for hereditary breast and ovarian cancer syndrome, or, if the risk remaining over her expected life span is more relevant, we estimate that risk.

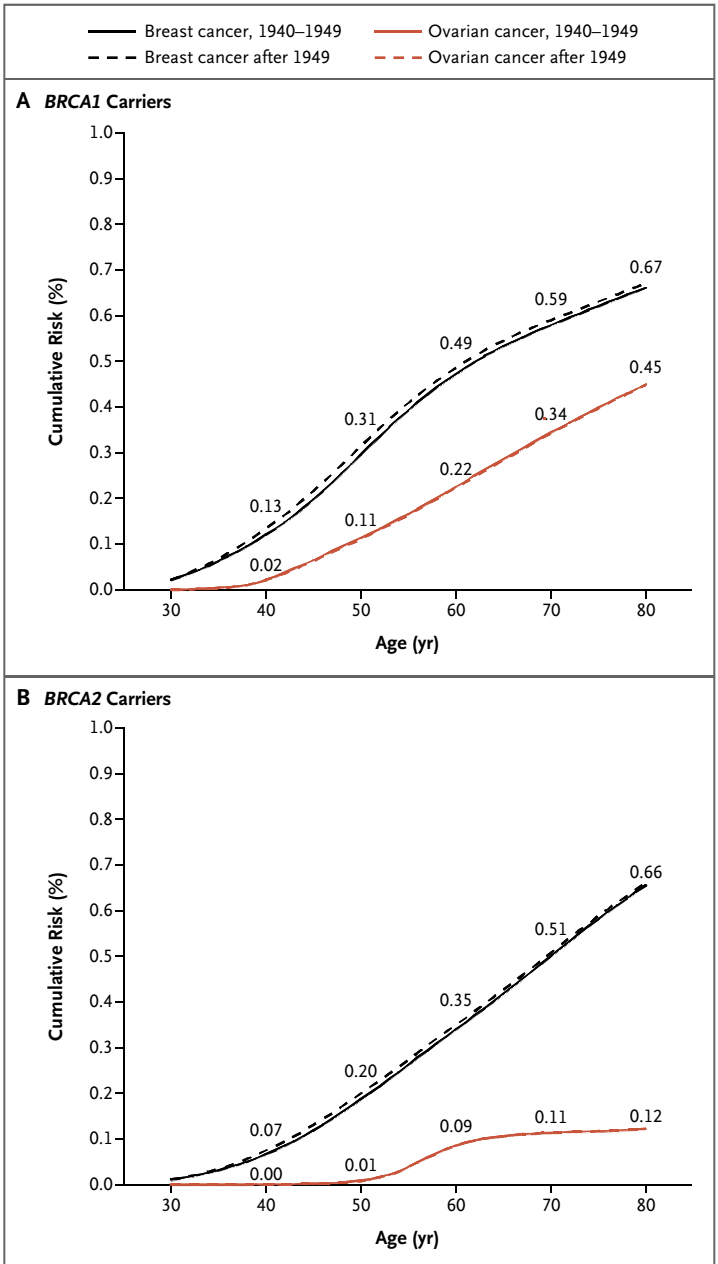

Figure 1. Cumulative Risk of Breast and Ovarian Cancer.

Shown are the cumulative risks of breast cancer and ovarian cancer among *BRCA1* carriers (Panel A) and *BRCA2* carriers (Panel B) in the 1940–1949 cohort and the cohort beginning in 1950 (Table S9 in the Supplementary Appendix). The numeric values shown are from the birth cohort beginning in 1950 (Table S9 in the Supplementary Appendix). Data are from the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm[1,2] (and Antoniou A: personal communication).

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Table 1. Bilateral Risk-Reducing Mastectomy (BRRM).*

Study and Focus	Design	Eligibility	Participants	Follow-up	Outcomes
				yr	
Cancer risk reduction					
Mayo Clinic; Hartmann et al.[22]	Retrospective cohort	Women with high familial risk of breast cancer	214 with BRRM, 403 sisters without BRRM	14	3 breast cancers in BRRM group, 38 breast cancers in no-BRRM group; hazard ratio for development of breast cancer, 0.08 (95% CI, 0.02–0.33)
Mayo Clinic; Hartmann et al.[23]	Subcohort of carriers identified among original 214 women with BRRM	*BRCA1* or *BRCA2* carriers	18 with BRRM	13.4	0 breast cancers in BRRM group†‡
Rotterdam; Meijers-Heijboer et al.[24]	Prospective cohort	*BRCA1* or *BRCA2* carriers	76 with BRRM, 63 without BRRM	2.9	0 breast cancers in BRRM group, 8 breast cancers in no-BRRM group†
Rotterdam; Heemskerk-Gerritsen et al.[25]	Prospective cohort	*BRCA1* or *BRCA2* carriers and noncarriers with hereditary risk of breast cancer	177 with BRRM	4.5	1 breast cancer in BRRM group‡
PROSE Study Group; Rebbeck et al.[26]	Retrospective cohort	*BRCA1* or *BRCA2* carriers	102 with BRRM, 378 without BRRM	6.4	2 breast cancers in BRRM group, 184 breast cancers in no-BRRM group; hazard ratio for development of breast cancer, 0.05–0.09 (95% CI, 0.01–0.38)
PROSE; Domchek et al.[27]	Prospective cohort	*BRCA1* or *BRCA2* carriers	247 with BRRM, 1372 without BRRM	3	0 breast cancers in BRRM group, 98 breast cancers in no-BRRM group†
Multicenter European collaboration; Evans et al.[28]	Ascertainment both retrospective and prospective; follow-up prospective	Women with a lifetime risk of breast cancer >25%	314 with BRRM	NR	0 breast cancers in women with BRRM; authors estimated that 21 breast cancers would have occurred in these women from person-years at-risk analysis based on mutation status or family history†§
Denmark; Skytte et al.[29]	Retrospective national cohort	*BRCA1* or *BRCA2* carriers	96 with BRRM, 211 without BRRM	NR	3 breast cancers in BRRM group, 16 breast cancers in no-BRRM group; hazard ratio for development of breast cancer, 0.39 (95% CI, 0.12–1.36); P=0.14
Psychosocial effects					
Mayo Clinic; Frost et al.[30]	Retrospective cohort; data from patient questionnaire	Women with family history of breast cancer who had BRRM, 1960–1993	609 eligible, 572 responded	14.5	Satisfaction: 70% satisfied, 11% neutral, 19% dissatisfied; 74% had decreased concern about breast-cancer risk; percentages of women who reported favorable effects, no change, or negative effects, respectively, in the following quality-of-life measures were: emotional stability: 23%, 68%, and 9%, stress: 28%, 58%, and 14%, self-esteem: 13%, 69%, and 18%, satisfaction with sexual relationships: 4%, 73%, and 23%, feelings of femininity: 8%, 67%, and 25%, and physical appearance: 16%, 48%, and 36%

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University of Sydney; Heiniger et al.[31]	Prospective cohort; data from patient questionnaires at baseline and 3-yr follow-up	Women with high familial risk of breast cancer	17 with BRRM, 39 matched controls	3	BRRM group had significant reduction in perceived risk of breast cancer and cancer-related anxiety; no change from baseline in measures of general anxiety, depression, body image, and sexual activity
Karolinska Institutet; Brandberg et al.[32]	Prospective study; data from patient questionnaire at baseline and 1 yr postoperatively	Women at high risk for breast cancer considering BRRM, 1997–2005	Of 90 consecutive women, 65 completed questionnaire 1 yr after surgery (58% *BRCA* carriers, 42% other high-risk patients)	1	Measures of anxiety decreased significantly; preoperatively to 1 yr postoperatively, no change on measures of physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health; percentages of women who reported favorable effects or negative effects, respectively, in the following quality-of-life measures were: overall "satisfaction in life": 61% and 13%, femininity: 27% and 27%, and intimate situations: 16% and 46%; with respect to body image, women who reported that they were, respectively, "not at all," "a little," "quite a bit," or "very much" self-conscious were 52%, 40%, 8%, and 0%, less physically attractive: 60%, 29%, 11%, and 0%, dissatisfied with their appearance: 83%, 17%, 0%, and 0%, less feminine: 65%, 30%, 5% and 0%, avoiding people: 98%, 2%, 0%, and 0%, feeling that their body was less whole: 71%, 29%, 0%, and 0%, dissatisfied with their body: 74%, 21%, 5%, and 0%, and dissatisfied with their scar: 56%, 33%, 9%, and 2%; women who reported that they were, respectively, "not at all," "a little," quite a bit," or "very much" having difficulty seeing themselves naked were 76%, 19%, 3%, and 2%, and less sexually attractive: 52%, 38%, 8%, and 2%
Cancer Research Campaign, London; Hatcher et al.[33]	Prospective study; data from patient interviews and questionnaires before surgery and 18 mo after surgery in BRRM group and at baseline and 18 mo follow-up in no-BRRM group	Women with high familial risk of breast cancer or other high-risk features	79 with BRRM, 64 without BRRM		In the BRRM group, 60% reported psychological distress before surgery and 29% reported psychological distress 18 mo after surgery ($P<0.001$), and in the no-BRRM group, 57% reported psychological distress before surgery and 41% reported psychological distress 18 mo after surgery ($P=0.11$); a significantly larger proportion of women in the no-surgery group were prone to anxiety; sexual pleasure was unchanged in both groups from baseline to 18 mo; women who chose surgery had more diagnostic tests and perceived a greater risk of breast cancer

* CI denotes confidence interval, NA not available, NR not reported, and PROSE Prevention and Observation of Surgical Endpoints.
† If there were no cancer events in the BRRM group, hazard ratios could not be estimated.
‡ There was no comparison group, so hazard ratios could not be estimated.
§ The expected number was based on an analysis of person-years at risk according to mutation status or family history.

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BREAST CANCER IN MALE *BRCA1* AND *BRCA2* CARRIERS

By 70 years of age, the cumulative risk of breast cancer is approximately 1% among men with *BRCA1* mutations and approximately 7% among men with *BRCA2* mutations[8] (Table S5 in the Supplementary Appendix). The lifetime risk in the general male population is 0.1%.[9]

HEREDITARY BREAST AND OVARIAN CANCER DUE TO GENES OTHER THAN *BRCA1* AND *BRCA2*

Numerous additional genes have been identified in which mutations have been found to confer a predisposition or are suspected of conferring a predisposition to breast or ovarian cancer (Tables S3 and S6 in the Supplementary Appendix). Data are very limited on gene-specific penetrance and the cancer spectrum for some variants and genes.[10] One cannot assume that the cancer spectrum and risks among the carriers of these mutations are similar to those among *BRCA1* and *BRCA2* carriers. In providing estimates of cancer risk to carriers of such mutations, if published data are lacking, it may be most appropriate to cite estimates that would be provided for persons who are not carriers. A study involving women who were tested for suspected *BRCA1* or *BRCA2* mutations and in which no other genes were tested showed no increased risk of ovarian cancer.[11] It should be noted that recently discovered but uncommon mutations in genes such as *BRIP1* confer an increased risk of ovarian cancer.[12]

HEREDITARY BREAST AND OVARIAN CANCER WITHOUT AN IDENTIFIED GENETIC CAUSE

Given that panel testing of dozens of genes can be performed simultaneously, it is noteworthy that 64.1 to 86.5% of persons with a suspected hereditary predisposition to breast and ovarian cancer have not been found to have a mutation that is probably pathogenic (Table S7 in the Supplementary Appendix). For these patients, we recommend integrating estimates of cancer risks according to family history with other clinical factors.

Some tools that are used to estimate the probability of *BRCA1* and *BRCA2* mutations are also designed to estimate cancer risks, regardless of gene status.[13-15] These tools are the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) (ccge.medschl.cam.ac.uk/boadicea/), BRCAPro, and the International Breast Cancer Intervention Study (Tyrer–Cuzick model) (www.cancertechnology.co.uk/ibis-software-tyrer-cuzick-model).

In addition, the tables created by Claus et al.[16] can be used to calculate age-specific risks of breast cancer on the basis of family history alone. The Breast Cancer Risk Assessment Tool (BCRAT) (also called the Gail model) (www.cancer.gov/bcrisktool/)[17] is not recommended for calculating the risk of breast cancer among women in very-high-risk families because it incorporates only breast-cancer events in mothers, sisters, and daughters and thus does not take into consideration the family history of ovarian cancer, paternal history of cancer, and history of breast cancer in more distant maternal relatives.

BILATERAL RISK-REDUCING MASTECTOMY

REDUCTION IN CANCER RISK

After the initial identification of hereditary breast and ovarian cancer syndrome in 1971,[18] some surgeons performed prophylactic removal of breast or ovarian tissue in women from families with suspected hereditary breast and ovarian cancer syndrome. However, there was skepticism in the medical community about the efficacy of these procedures. Case reports described the development of breast cancer on the chest wall after prophylactic mastectomy[19] and intraabdominal carcinoma after prophylactic oophorectomy.[20] When clinical testing to detect *BRCA1* and *BRCA2* mutations became available in the 1990s, mutation carriers could be identified, but there was no proof of the efficacy of preventive strategies. The first guideline for the care of persons with hereditary breast and ovarian cancer syndrome, published in 1997, stated that there was "insufficient evidence to recommend for or against prophylactic mastectomy [or] oophorectomy."[21]

From 1999 through 2004, the results of four retrospective and prospective observational studies were published. These studies compared breast-cancer outcomes in women who underwent prophylactic mastectomy with outcomes in women at similar risk who did not undergo surgery (Table 1).[22-29] Four studies showed a reduction of 90% or more in the risk of subsequent breast cancer among women who underwent prophylactic mastectomy. Updated reports and additional studies have confirmed these initial results; only

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one small study[29] did not show a significant reduction in the risk of subsequent breast cancer after bilateral mastectomy (Table 1).[22-29] Current position statements on indications for risk-reducing mastectomy and types of procedures used are described in the text box.[34-43]

PSYCHOSOCIAL EFFECTS

In a large study of psychosocial effects after bilateral risk-reducing mastectomy, 572 women completed a study-specific questionnaire a median of 14.5 years after the procedure (Table 1).[30-33] A total of 74% had a reduction in concern about breast cancer, 86% had favorable or unchanged levels of stress, and 70% were satisfied with their decision to undergo surgery. Among women who were dissatisfied with the decision, complications associated with breast implants and physician advice to undergo the mastectomy were cited as the two primary reasons for their dissatisfaction.

Hatcher et al. conducted a prospective study involving 143 women who were at high risk for breast cancer; 79 chose mastectomy and 64 chose surveillance.[33] The perceived risk of breast cancer was higher among women who chose surgery than among women who chose surveillance, and this perception was often inaccurate. Measures of psychological distress such as depression and anxiety decreased significantly in the surgery group but were unchanged in the surveillance group. The reported degree of sexual pleasure did not change significantly over time in either group. Additional studies are summarized in Table 1.

RISK-REDUCING SALPINGO-OOPHORECTOMY

OVARIAN CANCER

Pathological and molecular advances have revealed that most pelvic high-grade serous cancers, previously attributed to an ovarian origin, are probably implants from cancer originating in the fimbria of the fallopian tube.[44] Seven efficacy studies of risk-reducing salpingo-oophorectomy for prevention of ovarian cancer and one meta-analysis showed a significant risk reduction of approximately 80% among *BRCA1* and *BRCA2* carriers (Table 2).[27,45-51] Follow-up times were relatively short, averaging approximately 4 years.

Current guidelines recommend risk-reducing salpingo-oophorectomy for both *BRCA1* and *BRCA2* carriers between the ages of 35 and 40 years who have completed their childbearing.[34,41] However, given the differences between *BRCA1* and *BRCA2* carriers with respect to age at diagnosis of ovarian cancer (Fig. 1), we think that the procedure can be delayed until approximately 45 years of age in *BRCA2* carriers, since their risk of ovarian cancer by 50 years of age is only 1%.

A common question is whether hysterectomy should be performed with salpingo-oophorectomy. Although hysterectomy is not thought to be justified for cancer prevention, it can simplify later hormonal therapy in women who will receive tamoxifen for reduction of the risk of breast cancer or estrogen for menopausal symptoms, since both of these agents are associated with an increased risk of endometrial cancer.

SALPINGECTOMY ALONE

The discovery that many pelvic serous cancers originate in the fallopian tubes raises the question of whether bilateral salpingectomy with delayed oophorectomy may be an option for premenopausal women who want to delay surgical menopause. Anecdotal reports indicate that this option is being used occasionally.[57] However, data regarding the efficacy of this investigational approach are lacking.[57,58]

BREAST CANCER

Beyond its use for the prevention of ovarian cancer, salpingo-oophorectomy has been evaluated in observational studies for its effect on breast-cancer risk. In studies in which breast cancer is the end point of interest, women with prior breast cancer should be excluded to avoid biases that would favor either the surgical or nonsurgical group.[59] Table 2[27,46,48,52-55] lists seven studies of salpingo-oophorectomy and breast-cancer risk among *BRCA1* and *BRCA2* carriers; these studies excluded women with previous breast cancer. Five showed a significant reduction in risk of approximately 50% when the operation was performed in women before menopause.[27,46,48,52,53]

A recent nationwide Dutch study examined this question with the use of additional criteria to minimize potential bias. This study excluded women with prior breast or ovarian cancer, considered risk-reducing mastectomy to be a censoring event, and allocated person-time before surgery to the group that did not undergo surgery. The investigators reported no effect of salpingo-oophorectomy on the later risk of breast cancer.[55]

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Box 1. Overview of Key Positions Regarding Risk-Reducing Surgery in Women with Hereditary Breast and Ovarian Cancer Syndrome.

The following position statements pertain to women without prior breast or ovarian cancer. These statements acknowledge that bilateral risk-reducing mastectomy and salpingo-oophorectomy have potential adverse effects, and multidisciplinary consultations before surgery are recommended to ensure informed decision making by the patient.

Bilateral Mastectomy

NCCN (National Comprehensive Cancer Network; www.nccn.org): "Risk-reducing mastectomy . . . provides a high degree of protection against breast cancer in women with a *BRCA1/2* mutation." Discuss risk-reducing mastectomy on a case-by-case basis, with a review of the potential adverse effects of the procedure. Risk-reducing mastectomy is also an option for patients with the Li–Fraumeni syndrome and the Cowden syndrome. Consensus recommendations are not provided for carriers of mutations in other genes.[34]

USPSTF (U.S. Preventive Services Task Force): "Among high-risk women and mutation carriers, risk-reducing mastectomy [as compared with no surgery] decreased breast cancer by 85 to 100% and breast-cancer mortality by 81 to 100%."[35]

Society of Surgical Oncology: Indications for bilateral prophylactic mastectomy include mutations in *BRCA1*, *BRCA2*, or other strongly predisposing breast-cancer susceptibility genes or, in the absence of data on mutations, a hereditary breast-cancer syndrome.[36]

NICE (National Institute for Health and Care Excellence; United Kingdom): "Bilateral risk-reducing mastectomy is appropriate only for a small proportion of women who are from high-risk families and should be managed by a multidisciplinary team . . . . Bilateral mastectomy should be raised as a risk-reducing strategy option with all women at high risk."[37]

Additional international guidelines have been summarized by Easton et al.[10]

Comments on the procedure: No mastectomy can remove all breast tissue, which is widely distributed on the chest wall. Several mastectomy approaches have been used for prophylaxis. A total (simple) mastectomy removes more than 95% of breast tissue, including the overlying skin and nipple–areolar complex. In a classic subcutaneous mastectomy, the skin and nipple–areolar complex are preserved, and varying amounts of glandular tissue may be left below the areola. The use of this procedure for prophylaxis has been criticized because of the possible retention of excess at-risk tissue in the skin flaps and below the areola. Most surgical oncologists recommend a skin-sparing mastectomy for prophylaxis; this preserves the natural skin of the breast. A recent technique called "nipple-sparing" or "total skin-sparing" mastectomy also preserves the overlying skin of the nipple–areola complex. The underlying glandular tissue at risk is removed, and immediate reconstruction is performed. Cosmesis is enhanced by preserving the nipple skin.[38,39] More than 90% of women who undergo bilateral risk-reducing mastectomy elect immediate breast reconstruction, usually with implants. Complications may be immediate or delayed. In a prospective cohort of 112 consecutive women who underwent risk-reducing mastectomy followed by immediate breast reconstruction and were followed for 2.8 years, 10% had bleeding, 9% infection, and 14% capsular contracture. A total of 33% of women required reoperation.[40]

Bilateral Salpingo-Oophorectomy

NCCN: "Recommend risk-reducing salpingo-oophorectomy (ideally in consultation with a gynecologic oncologist) typically between 35 and 40 years, and upon completion of child bearing."[34]

USPSTF: "Risk-reducing salpingo-oophorectomy decreased breast cancer incidence by 37 to 100%, ovarian cancer by 69 to 100%, and all-cause mortality by 55 to 100%."[35]

Society of Gynecologic Oncology: "The most proven method for the prevention of ovarian cancer in women who carry a deleterious *BRCA1* or *BRCA2* mutation is risk-reducing salpingo-oophorectomy. Prospective studies have reported a 70% to 85% reduction in ovarian cancer . . . risk-reducing salpingo-oophorectomy between the ages of 35 and 40 years is recommended for risk reduction in women at increased genetic risk of ovarian cancer. The age [at which risk-reducing salpingo-oophorectomy is performed] may also be individualized according to the earliest age of onset in the family and personal choices."[41]

Comments on the procedure: The procedure, usually performed laparoscopically, should include visual assessment of the abdomen and pelvis, a pelvic washing, and total bilateral salpingo-oophorectomy, including ligation of the ovarian artery and vein approximately 2 cm proximal to the ovary and tube to ensure removal of all tissue. Because of the possibility of occult cancer, including serous tubal in situ carcinoma, meticulous processing of the surgical specimen is necessary according to the SEE-FIM protocol (protocol for sectioning and extensively examining the fimbriated end).[41-43]

Salpingectomy Alone

NCCN: "Salpingectomy [alone] is not the standard of care and is discouraged outside a clinical trial. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer."[34]

Society of Gynecologic Oncology: "Salpingectomy can be considered at the completion of childbearing in women at increased genetic risk of ovarian cancer who do not agree to salpingo-oophorectomy. However, this is not a substitute for oophorectomy, which should still be performed as soon as the woman is willing to accept menopause, preferably by the age of 40 years."[41]

At this time, some caution may be warranted in counseling that reduction in the risk of breast cancer is a definite benefit of salpingo-oophorectomy that is performed before menopause, although most published data show reduced risk.

MORTALITY

In the Prevention and Observation of Surgical Endpoints (PROSE) multicenter prospective cohort study, which involved 2482 *BRCA1* and *BRCA2* carriers, investigators studied the effects of risk-reducing salpingo-oophorectomy on mortality.[27] The median follow-up was 3.7 years in the group of patients who underwent surgery and 4.3 years in the group of patients who did not undergo surgery. The surgical group had lower all-cause mortality (hazard ratio, 0.40; 95% confidence interval [CI], 0.26 to 0.61), breast cancer–specific mortality (hazard ratio, 0.44; 95% CI, 0.26 to 0.76), and ovarian cancer–specific mortality (hazard ratio, 0.21; 95% CI, 0.06 to 0.80). Table 2[27,48,51,56] lists other studies that ex-

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amined mortality after risk-reducing salpingo-oophorectomy.

HORMONE-REPLACEMENT THERAPY AFTER RISK-REDUCING SALPINGO-OOPHORECTOMY

Use of hormone-replacement therapy does not appear to negate the benefits of salpingo-oophorectomy in *BRCA1* and *BRCA2* carriers. In a prospective cohort study involving *BRCA1* and *BRCA2* carriers with no prior cancer history, investigators examined the effect of hormone-replacement therapy on breast-cancer risk reduction among women who had undergone salpingo-oophorectomy.[60] Women who had not undergone surgery and did not receive hormone-replacement therapy were controls. Women who received short-term hormone-replacement therapy after salpingo-oophorectomy still had a reduction in breast-cancer risk: among 62 women who underwent surgery without hormone-replacement therapy, the hazard ratio was 0.38 (95% CI, 0.09 to 1.59), and among 93 women who underwent surgery with hormone-replacement therapy, the hazard ratio was 0.37 (95% CI, 0.14 to 0.96).[60] In this study, the sample size did not permit analysis of the duration of hormone use. However, the authors indicated that many high-risk women who receive hormone-replacement therapy after salpingo-oophorectomy do so only until the age of natural menopause, which usually occurs at approximately 50 years of age.

HEALTH CONSIDERATIONS RELATED TO PREMATURE SURGICAL MENOPAUSE

The long-term side effects of premature menopause, which have been well-characterized in the general population, include an increased risk of osteoporosis and cardiovascular disease and possible cognitive decline in later life.[56] Data from long-term follow-up studies involving large populations of *BRCA1* and *BRCA2* carriers who have undergone salpingo-oophorectomy are lacking. Common side effects in *BRCA1* and *BRCA2* carriers are vasomotor symptoms, reduced libido, vaginal dryness, and dyspareunia.[61] These symptoms may not be fully relieved by estrogen therapy.[61]

Favorable effects of salpingo-oophorectomy include significantly reduced cancer-related worry in approximately 80% of *BRCA1* and *BRCA2* carriers and 95% satisfaction with their decision to undergo surgery.[62] Women who are considering surgery should be informed about the expected effects of salpingo-oophorectomy and management options for symptoms.

ALTERNATIVES TO RISK-REDUCING SURGERY

RISK-REDUCING MEDICATIONS

Breast Cancer

Placebo-controlled prevention trials involving women with varying degrees of increased risk of breast cancer have shown a reduced risk of ER-positive breast cancer with the use of selective estrogen-receptor modulators and aromatase inhibitors.[35] Currently, data on the use of tamoxifen for primary prevention of breast cancer in *BRCA1* and *BRCA2* carriers are very limited. To our knowledge, the only prospective data derive from the National Surgical Adjuvant Breast and Bowel Project P1 trial, in which mutation status was determined in the 288 women in whom breast cancer developed.[63] Only 8 *BRCA1* carriers and 11 *BRCA2* carriers were identified. The hazard ratios for the development of breast cancer among women who received tamoxifen were 1.67 (95% CI, 0.32 to 10.7) among *BRCA1* carriers and 0.38 (95% CI, 0.06 to 1.56) among *BRCA2* carriers. Although these results are limited by small sample sizes, they are consistent with an effect in *BRCA2* carriers; approximately 77% of breast cancers in *BRCA2* carriers are ER-positive.[4] Because of small sample sizes, these results are uninformative for *BRCA1* carriers.

The major question is whether tamoxifen can provide primary prevention of breast cancer in *BRCA1* carriers, in whom 75 to 80% of breast cancers are ER-negative.[4] Investigators have performed observational studies, as a surrogate for primary prevention trials, involving *BRCA1* and *BRCA2* carriers, some of whom had received tamoxifen for their first breast cancer. These researchers studied the effect of tamoxifen on the risk of cancer in the contralateral breast.[64] With these retrospective data, the ER status of the first breast cancer is often unknown, and it is likely that tamoxifen would be administered infrequently for an ER-negative primary breast cancer. However, in one study involving 76 *BRCA1* carriers who received tamoxifen and were known to have an ER-negative first breast cancer, the hazard ratio for an event in the contralateral breast was 0.33 (95% CI, 0.13 to 0.79).[64] Of note,

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Table 2. Trials of Risk-Reducing Salpingo-Oophorectomy (RRSO) in *BRCA1* and *BRCA2* Carriers.

Study and Focus	Design	Patients		Follow-up	Ovarian Cancers		Hazard Ratio (95% CI)		
		RRSO	No RRSO		RRSO	No RRSO	*BRCA1* and *BRCA2*	*BRCA1* Only	*BRCA2* Only
		number			*number*				
Ovarian-cancer risk reduction									
Kauff et al.[45]	Prospective unmatched cohort	98	72	Mean, 24.2 mo	1	5	0.15 (0.02–1.31)	NR	NR
Rebbeck et al.[46]	Retrospective cohort, prospective follow-up	259	292	Mean, RRSO, 8.2 yr, no RRSO, 8.9 yr	2*	58	0.04 (0.01–0.16)	NR	NR
Finch et al.[47]	Retrospective cohort	1041	779	Mean, 3.5 yr	7†	32	0.20 (0.07–0.58)	NR	NR
Domchek et al.[48]	Prospective matched cohort	155	271	Mean, RRSO, 3.1 yr, no RRSO, 2.1 yr	2	16	0.11 (0.03–0.47)	NR	NR
Kauff et al.[49]	Prospective unmatched cohort	509	283	Median, RRSO, 34–40 mo, no RRSO, 38 mo	3	12	0.12 (0.03–0.41)	0.15 (0.04–0.56)	NA‡
Rebbeck et al.[50]	Meta-analysis	1555	1285	NR	NR	NR	0.21 (0.12–0.39)	NR	NR
Domchek et al.[27]§	Prospective unmatched cohort	465	1092	3 yr	6¶	63	0.28 (0.12–0.69)	0.31 (0.12–0.82)	NA‡
Finch et al.[51]§	Prospective unmatched cohort	1602	1334	Mean, 5.6 yr	32‖	108	0.20 (0.13–0.30)	NR	NR
Breast-cancer risk reduction									
Rebbeck et al.[52]	Retrospective cohort, prospective follow-up unmatched cohort	43	79	Mean, RRSO, 9.6 yr, no RRSO, 8.1 yr; mean age at start of follow-up, RRSO, 39 yr (range, 22–63), no RRSO, 35 yr (range, 17–65)			NR	0.53 (0.33–0.84)	NR
Rebbeck et al.[46]	Retrospective cohort, prospective follow-up	99	142	Mean, RRSO, 8.2 yr, no RRSO, 8.9 yr; mean age at start of follow-up, RRSO, 40 yr (range, 21–66), no RRSO, 39 yr (range, 19–70)			0.47 (0.29–0.77)	NR	NR
Kramer et al.[53]	Prospective unmatched cohort	33	65	Mean, 16.5 yr			NR	0.38 (0.15–0.97)	NR
Domchek et al.[48]	Prospective matched cohort	155	271	Mean, RRSO, 3.1 yr, no RRSO, 2.1 yr; mean age in yr (±SD) at start of follow-up, RRSO, 45±8.5, no RRSO, 43±10.0			0.36 (0.20–0.67)	NR	NR

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Domchek et al.[27]**	Prospective unmatched cohort‡	336	1034	3 yr; mean age at start of follow-up, RRSO, 44 yr (range, 21–79), no RRSO, 36 yr (range, 18–90)	0.54 (0.37–0.79)	0.63 (0.41–0.96)	0.36 (0.16–0.82)
Mavaddat et al.[54]**	Prospective unmatched cohort‡	309	679	Median, 2 yr; mean, 3 yr	0.62 (0.35–1.09)	0.52 (0.24–1.13)	0.79 (0.35–1.80)
Heemskerk-Gerritsen et al.[55]	Retrospective unmatched cohort, prospective follow-up	346	476	Median, 2.7–4.6 yr; median age at start of follow-up, RRSO, 44 yr (range, 30–66), no RRSO, 33 yr (range, 30–66)	1.09 (0.67–1.77)	1.21 (0.72–2.06)	0.45 (0.17–1.66)
Mortality ††							
Domchek et al.[48]	Two cohorts, one age-matched and one unmatched	155 matched; 183 unmatched	271 matched; 460 unmatched	Mean, RRSO, 3.1 yr, no RRSO, 2.1 yr	0.24 (0.08–71); 0.47 (0.15–1.46)	NR	NR
Finch et al.[51]	Prospective unmatched cohort	905	1334§	Mean, 5.6 yr; mean age at start of follow-up, RRSO, 50.5 yr (range, 30–88), no RRSO, 42.4 yr (range, 30–86)	0.23 (0.13–0.39)	0.21 (0.12–0.37)	0.67 (0.08–5.35)
Domchek et al.[27]	Prospective unmatched cohort	336	1034	3 yr; mean age at start of follow-up, RRSO, 44 yr (range, 21–79), no RRSO, 36 yr (range, 18–90)	0.40 (0.26–0.61)	0.38 (0.24–0.62)	0.52 (0.22–1.23)
Rocca et al.[56]	Cohort of women in Olmsted County, MN (not selected for BRCA-positive status); case:control	1091	2383	Median, RRSO, 25 yr, no RRSO, 26 yr	1.67 (1.16–2.40)	NR	NR

* Another 6 ovarian cancers were diagnosed incidentally at RRSO.
† Another 11 ovarian cancers were diagnosed incidentally at RRSO.
‡ The hazard ratio could not be assessed because there were no post-RRSO events.
§ All data shown are from the group with no prior breast cancer.
¶ Another 9 ovarian cancers were diagnosed incidentally at RRSO.
‖ Another 46 ovarian cancers were diagnosed incidentally at RRSO.
** Some overlap of cases between the study by Domchek et al.[27] and the study by Mavaddat et al.[54] was noted.
†† Hazard ratios in studies of mortality were for an increase in all-cause mortality to age 70 yr.

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the majority of that entire *BRCA1* group (1583 patients) received chemotherapy, and chemotherapy is known to reduce the risk of cancer in the contralateral breast among women younger than 50 years of age.[65]

Currently, we think that the data are inadequate to support the use of tamoxifen for primary prevention of breast cancer in *BRCA1* carriers. However, given the predominance of ER-positive disease that develops in *BRCA2* carriers, tamoxifen is an option for this group.

Ovarian Cancer

Data from randomized, controlled trials of oral contraceptives for the prevention of ovarian cancer are lacking. Observational studies have shown associations between the use of oral contraceptives and a reduced risk of ovarian cancer among *BRCA1* and *BRCA2* carriers, with odds ratios suggesting a 40 to 50% reduction in risk.[66]

There is concern about a possible increase in the risk of breast cancer among women with a high risk of ovarian cancer who have taken oral contraceptives. Data on this issue have been inconsistent.[34] However, two meta-analyses showed no significant association between the use of oral contraceptives and the risk of breast cancer among high-risk women.[66,67]

SCREENING

Breast Cancer

Since only a minority of *BRCA1* and *BRCA2* carriers opt for risk-reducing mastectomy (Table S8 in the Supplementary Appendix), effective surveillance for breast cancer in *BRCA1* and *BRCA2* carriers is vital. Data showing that screening mammography reduces mortality among high-risk women are lacking[68]; rather, studies of mammography have shown higher rates of node-positive disease and interval cancers among high-risk women than among women with normal risk.[68] Breast magnetic resonance imaging (MRI) is an important additional screening tool in high-risk women.

Prospective studies have shown MRI to have approximately twice the sensitivity of mammography, with slightly reduced specificity,[69] and a possible earlier stage distribution.[70] Data from randomized trials comparing mammography with and without MRI are lacking, so the quality of data on important end points, including mortality, is limited. A national MRI-based screening study involving *BRCA1* carriers in Norway showed that 68 breast cancers developed in 802 *BRCA1* carriers over a mean of 4.2 years. The mean tumor size was 1.4 cm, and 85% of the cancers were node-negative. Despite these favorable features, the 5- and 10-year survival rates were lower than anticipated; these findings are consistent with the aggressive phenotype of *BRCA1*-associated breast cancer.[71] Current screening guidelines are listed in Table 3.

Ovarian Cancer

Although research continues to close in on improved screening approaches,[72] especially in high-risk women, data to show improved survival with screening for ovarian cancer in any population are lacking. The NCCN does not consider screening for ovarian cancer to be a reasonable substitute for salpingo-oophorectomy in women with hereditary breast and ovarian cancer syndrome.[34] A woman who declines salpingo-oophorectomy can undergo screening with the use of serum measurement of CA-125 and transvaginal ultrasonography every 6 to 12 months, starting at age 30 to 35 years or 5 to 10 years before the earliest diagnosis of ovarian cancer in the family.[34]

DECISION MAKING

High-risk women who do not have cancer seek guidance from a variety of health care professionals. We recommend consultation with specialists who have expertise in genetics; among these specialists, genetic counselors can serve a pivotal role.[73] Given the complex issues and multifaceted effect of decisions, consultations should provide both medical information and emotional support. Estimates of cancer risk should include the risk of a first breast cancer, contralateral breast cancer, ovarian cancer, and other possible cancers. Risk estimates should be based on the woman's current age and should be projected over the next 10 years. Residual lifetime risks can also be provided. The likely disease course associated with a given cancer (e.g., ovarian cancer or triple-negative breast cancer) should be described.

Decisions include not only which intervention or interventions to pursue but when to implement them. Timing will depend on the ages at diagnosis of cancer in a woman's family and her reproductive plans. For example, the use of risk-

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Table 3. Suggested Approaches to Care of Patients with Hereditary Breast and Ovarian Cancer Syndrome.*

Focus and Approach	*BRCA1* Carriers	*BRCA2* Carriers	No Mutation Detected in Known Predisposing Genes
Breast cancer in women			
Surveillance	NCCN[34] guidelines recommend breast "awareness" starting at age 18 yr; clinical breast examination, every 6–12 mo, starting at age 25 yr; ages 25–29 yr: annual MRI (preferred) or mammography if MRI unavailable; ages 30–75 yr: annual mammography and MRI; >75 yr: individualized care	NCCN[34] guidelines recommend breast "awareness" starting at age 18 yr; clinical breast examination, every 6–12 mo, starting at age 25 yr; ages 25–29 yr: annual MRI (preferred) or mammography if MRI unavailable; ages 30–75 yr: annual mammography and MRI; >75 yr: individualized care	Annual breast MRI with mammography recommended for lifetime risk >20–25%, starting 5–10 yr before youngest age of diagnosis of breast cancer in family
Risk-reducing medication†	Inadequate data to support its use	Option, given anticipated 50% risk reduction in ER-positive breast cancers[63]	Option, given anticipated 50% risk reduction in ER-positive breast cancers[35]
Risk-reducing mastectomy	Given the often aggressive high-grade, ER-negative nature of breast cancers and uncertain benefit of chemoprevention, surgical prevention may be given higher priority than surveillance	Option for women who prefer surgical risk reduction rather than surveillance and chemoprevention	Consider on a case-by-case basis, informed by risk estimates
Ovarian cancer			
Surveillance	NCCN guidelines do not endorse routine screening with transvaginal ultrasonography and measurement of serum CA-125 levels. Not to be considered a reasonable substitute for risk-reducing salpingo-oophorectomy in *BRCA1* and *BRCA2* carriers. In women who delay risk-reducing salpingo-oophorectomy, these approaches may be considered, starting at age 30–35 yr[34]	NCCN guidelines do not endorse routine screening with transvaginal ultrasonography and measurement of serum CA-125 levels. Not to be considered a reasonable substitute for risk-reducing salpingo-oophorectomy in *BRCA1* and *BRCA2* carriers. In women who delay risk-reducing salpingo-oophorectomy, these approaches may be considered, starting at age 30–35 yr[34]	Not indicated
Risk-reducing medication	No prospective trials; observational studies of oral contraceptives are consistent with 40–50% reduction in risk[68,69]	No prospective trials; observational studies of oral contraceptives are consistent with 40–50% reduction in risk[68,69]	Oral contraceptives may reduce risk; may be relevant in families with ovarian-cancer history
Risk-reducing salpingo-oophorectomy	Recommended by age 40 yr	Recommended by age 45–50 yr	Consider on a case-by-case basis, informed by risk estimates and new genetic information
Breast cancer in men			No evidence of increased risk
Surveillance	NCCN guidelines recommend training in breast self-examination and initiation of annual clinical breast examinations starting at age 35 yr[34]	NCCN guidelines recommend training in breast self-examination and initiation of annual clinical breast examinations starting at age 35 yr[34]	Not indicated
Risk-reducing mastectomy	Given that risk of male breast cancer among *BRCA1* carriers is lower than that among average-risk women, risk-reducing mastectomy is not recommended	Given that risk of male breast cancer among *BRCA2* carriers is lower than that among average-risk women, risk-reducing mastectomy is not recommended	Not indicated

* The suggested approaches are those of the authors unless otherwise indicated. ER denotes estrogen receptor, and MRI magnetic resonance imaging.
† Risk-reducing medications are tamoxifen for premenopausal women and tamoxifen or an aromatase inhibitor for postmenopausal women.

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reducing medications such as tamoxifen during pregnancy and lactation is not recommended.

To enhance decision making, providers must ask about a woman's primary concerns and goals. Many women have determined their preferred course of management before consulting a care provider.[74] However, other women need more time to weigh their choices. Studies have shown that numerical risk is only one determinant of patient preferences; other less quantifiable influences include experiences with cancer diagnoses and deaths in the family,[75] whether a woman has children, a woman's level of risk aversion,[74] and generalized anxiety and depression. The ways in which women make such complex decisions is not well understood.[76] One qualitative study showed that some women were disappointed with providers who did not give sufficient direction, whereas other women found their provider or providers too directive.[30,76] Clearly, physicians and counselors need to ask how much advice a woman prefers at a given time.

In conclusion, women from families with hereditary breast and ovarian cancer syndrome face substantial risks of breast and ovarian cancer. Although risk-reducing surgeries (mastectomy and salpingo-oophorectomy) provide considerable benefits in terms of cancer prevention, they can be associated with adverse physical and psychosexual effects. A discussion of management options, including surgery, risk-reducing medications, and surveillance, should include information about the different types of breast cancer that develop in *BRCA1* and *BRCA2* carriers, and patients should be informed that these carriers have various levels of risk of breast and ovarian cancers and various ages at diagnosis. Women with mutations in rarer genes, or those in whom no mutations are detected, must make decisions on the basis of even less information. These decisions are complex, and patients require information in an understandable format, as well as adequate time and emotional support to think through their options.

Additional research is needed to devise improved approaches for women with hereditary breast and ovarian cancer syndrome. Prospective data on how to help women evaluate their options and make decisions are lacking. Prospective data on surveillance strategies and the short-term and longer-term psychosocial and medical effects of various approaches are needed. Although large studies — some with more than 10 years of follow-up — have consistently shown the efficacy of risk-reducing mastectomy, longer follow-up is needed in studies of the efficacy and side effects of salpingo-oophorectomy. Some questions remain about the extent of reduction in breast-cancer risk from salpingo-oophorectomy among premenopausal women according to mutation carrier status. Data to evaluate the effect of salpingectomy alone with delayed oophorectomy are needed. Ideally, approaches for the care of women with *BRCA1* or *BRCA2* mutations should be tailored according to the gene, given the differing outcomes in the two groups. Data regarding outcomes in *BRCA1* versus *BRCA2* carriers are often lacking, as are data on women with strong family histories but no *BRCA1* or *BRCA2* mutations or women with DNA variants in rare genes.

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