Cancer risks and management of BRCA1/2 carriers without cancer

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INTRODUCTION

Mutations in either of the breast cancer type 1 or 2 susceptibility genes (*BRCA1* and *BRCA2;* referred in this topic as *BRCA1/2*) account for the majority of hereditary breast and ovarian cancers with an identified pathogenic variant in a cancer susceptibility gene. Overall, pathogenic variants in these genes are implicated in about 15 percent of women with familial breast cancer and a similar proportion of all women with incident ovarian cancers [1,2].

Hereditary breast and ovarian cancer attributable to pathogenic variants in *BRCA1/2* is characterized by an autosomal-dominant pattern of inheritance, markedly increased susceptibility to breast and ovarian cancer, with an especially early onset of breast cancer, and an increased incidence of tumors of other organs, such as the fallopian tubes, prostate, male breast, and pancreas. This topic discusses the management of patients with pathogenic variants in *BRCA1/2.*

The selection of patients who should be offered genetic risk evaluation is discussed elsewhere. Management for individuals with well-defined, high-risk syndromes that are not due to *BRCA1/2* (eg, Li-Fraumeni syndrome and phosphatase and tensin homolog [PTEN] hamartoma tumor syndrome) is also discussed separately.

- (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes", section on 'Criteria for genetic risk evaluation'.)

- (See "Overview of hereditary breast and ovarian cancer syndromes".)

Finally, management of patients with germline *BRCA1/2* mutations and a diagnosis of cancer are discussed as follows:

- **Breast cancer**
  - (See "Contralateral prophylactic mastectomy", section on 'BRCA carriers'.)
  - (See "Breast cancer in men".)
  - (See "ER/PR negative, HER2-negative (triple-negative) breast cancer", section on 'Germline BRCA mutation'.)
  - (See "Overview of the approach to metastatic breast cancer", section on 'Special considerations'.)
- **Ovarian cancer**
  - (See "Approach to survivors of epithelial ovarian, fallopian tube, or peritoneal carcinoma", section on 'Breast cancer risk management in BRCA mutation carriers with EOC'.)
  - (See "Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-sensitive disease", section on 'PARP inhibition in BRCA carriers'.)
  - (See "Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-resistant disease", section on 'Patients with a BRCA mutation'.)

CLINICAL CHARACTERISTICS ASSOCIATED WITH BRCA1/2 PATHOGENIC VARIANTS

Most hereditary breast and ovarian cancers are due to highly penetrant germline *BRCA1/2* pathogenic variants, which are inherited in an autosomal-dominant fashion. The prevalence of germline *BRCA1/2* pathogenic variants is increased in certain ethnic or racial groups such as women of Ashkenazi Jewish ethnicity. (See 'Prevalence of BRCA1/2 pathogenic variants' below.)

In patients with *BRCA1/2* pathogenic variants, there are frequently several generations of women affected with breast cancer (often premenopausal), as well as, in some families, ovarian cancer. In addition, other *BRCA1/2*-associated malignancies such as prostate, male breast, and pancreatic cancer may be observed. Specific criteria for genetic evaluation in high-risk individuals are discussed separately. (See "Genetic testing and management of

individuals at risk of hereditary breast and ovarian cancer syndromes", section on 'Criteria for genetic risk evaluation'.)

PREVALENCE OF BRCA1/2 PATHOGENIC VARIANTS

The prevalence of *BRCA1/2* pathogenic variants varies based on a number of factors, including ethnicity and, for those with cancer, age at diagnosis. Several founder mutations (ie, particular *BRCA1/2* mutations occurring among defined ethnic groups or individuals from a specific geographic area) have been observed. Aside from Ashkenazi Jews, founder mutations have also been reported worldwide in populations from the Netherlands, Sweden, Hungary, Iceland, Italy, France, South Africa, Pakistan, Asia, and among French Canadians, Latinx, and African Americans [3-8].

- **Ashkenazi Jewish –** In an unselected non-Jewish population in the United States, the chance of having any pathogenic variant in *BRCA1/2* is about 1 in 400 [9]. By comparison, in Ashkenazi Jews unselected for personal/family cancer history (from Central or Eastern Europe), roughly 1 in 40 individuals (2.5 percent) has one of three founder mutations: 185delAG (also known as 187delAG or c.68_69delAG in *BRCA1*), 5382insC (also known as 5385insc or c.5266dupC in *BRCA1*), or 6174delT (c.5946delT) in *BRCA2* [10-13]. These three pathogenic variants account for about 90 percent of *BRCA1/2* mutations identified in this ethnic group [14-17].

- **Icelandic –** A founder mutation in *BRCA2*, 999del5, is present in approximately 8 percent of female breast cancer cases, 40 percent of male breast cancer cases, and 6 percent of ovarian cancer cases in Iceland [18,19]. It is present in 0.6 percent of the general Icelandic population [18]. Another founder mutation in *BRCA1*, G5193A, has also been identified, but the prevalence of this mutation is very low [19,20].

- **French Canadian –** At least three *BRCA1* and three *BRCA2* founder mutations account for about 75 to 85 percent of mutations present in French Canadians [21]. In an analysis of 1093 French Canadian women with noninvasive or invasive breast cancer, the prevalence of a founder mutation was 5.3 percent for women under age 50 years and 4.6 percent for women over age 50 with at least two affected first- or second-degree relatives with breast cancer [22]. The penetrance of *BRCA2* mutations is high relative to most other populations [21].

- **Latinx –** Nine pathogenic variants account for 53 percent of the *BRCA1/2* mutations identified in the Hispanic population in the United States, with the Ashkenazi Jewish founder mutation 185delAG (187delAG) being the most common [23].

- **African American –** Historically, the frequency of pathogenic *BRCA1/2* variants in patients of African American ancestry was reported to be low [24-28]. However, among 947 individuals of African descent referred for clinical molecular testing for suspicion of hereditary breast and ovarian cancer but who did not meet stringent high-risk criteria, 11.5 percent tested positive for a *BRCA1/2* mutation; among 1767 African individuals meeting stringent high-risk criteria, 29.4 percent tested positive for a *BRCA1/2* mutation, including 43 (2.4 percent) who had a large rearrangement [8]. Interestingly, several specific *BRCA1* large rearrangements were detected in this heterogeneous population of African ancestry, including a duplication of exons 18 to 19 in *BRCA1*.

CANCER RISKS IN BRCA1/2 CARRIERS

Patients with a pathogen*ic BRCA1/2* variant are at an increased risk of breast, ovarian, and other cancers. These risks are not isolated to women, but also affect male carriers. A 2022 international study of 3184 *BRCA1* carriers and 2157 *BRCA2* carriers reported on age-specific absolute risks for 22 cancer types.

The primary cancer risks are discussed below.

Breast and ovarian cancer — In clinical practice, it is difficult to provide highly individualized predictions about cancer risks. Therefore, we often provide patients with a range of risks and then tailor risk estimates to the implicated gene, their current age, breast cancer history, use of hormonal therapy, and oophorectomy status. Common genetic variations, called single-nucleotide polymorphisms (SNPs), may also contribute significantly to risk, particularly in *BRCA2* carriers; however, these are generally not assessed in routine clinical practice.

The range of risks that we quote is based on three meta-analyses [5,29,30] and two prospective studies [5,31].

We quote the range of lifetime breast cancer risk in *BRCA1* carriers to be between 57 and 72 percent, and between 45 and 69 percent in *BRCA2* carriers. We quote the lifetime risk for ovarian cancer to be between 39 and 59 percent for *BRCA1* carriers and 11 to 20 percent for *BRCA2* carriers. The risk of ovarian cancer under the age of 40 years, however, is low [5,29,31,32].

As an example of lifetime risk of breast and ovarian cancers, one contemporary prospective cohort study included 9856 patients with a pathogenic variant in *BRCA1/2* (approximately 60 and 40 percent for *BRCA1* and *BRCA2*, respectively) and reported the cumulative cancer risks to age 80 years as follows [31]:

- *BRCA1* mutation carriers

- Breast – 72 percent (95% CI 65 to 79 percent)
- Ovarian – 44 percent (95% CI 36 to 53 percent)

- *BRCA2* mutation carriers

  - Breast – 69 percent (95% CI 61 to 77 percent)
  - Ovarian – 17 percent (95% CI 11 to 25 percent)

Additionally, breast cancer incidence was noted to rise in early adulthood until 30 to 40 years for *BRCA1* carriers and until 40 to 50 years for *BRCA2* carriers, after which it plateaued at 20 to 30 per 1000 person-years until age 80.

The data from the prospective cohort study above represent cumulative cancer risk until age 80, which is the expected life expectancy of most healthy women in the United States. Note that previous key studies have generally estimated risk only to age 70 [5,29,30,32]. These data for breast and ovarian cancer, as well as for other cancers in *BRCA1/2* carriers, are summarized in the table (table 1).

As these figures demonstrate, the lifetime risk of breast cancer is generally somewhat higher with *BRCA1* than *BRCA2* mutations [29]. *BRCA1* carriers also have earlier-onset disease, particularly before age 50 [33-35]. The mean age of diagnosis of breast cancer is younger for *BRCA1* than *BRCA2* mutation carriers (43 versus 47 years in one study) [33]. *BRCA1* carriers are more likely to develop a triple-negative breast cancer than *BRCA2* carriers or those who are *BRCA1/2* mutation negative [36,37].

Ductal carcinoma in situ (DCIS) is also considered a component of the *BRCA1/2* clinical spectrum [38-41]. DCIS occurs at an earlier age in *BRCA1/2* carriers than in noncarriers. For example, in one study, *BRCA1/2* carriers with DCIS were more than 12 years younger than those with DCIS in the general population [38].

Male breast cancer — Male *BRCA1/2* carriers have increased susceptibility to breast cancer, and the risk is higher with *BRCA2* versus *BRCA1* mutations [42,43]. In men with a *BRCA2* gene mutation, one study found the lifetime risk of breast cancer to age 80 to be approximately 3.8 percent as compared with men with a *BRCA1* mutation, whose risk is approximately 0.4 percent [44]. Other studies have reported the lifetime risks in *BRCA2* carriers to be approximately 7 to 8 percent [42,43]. The lifetime risk of breast cancer for men in the general population is approximately 0.1 percent [45]. In a study including 97 male *BRCA1/2* mutation carriers with breast cancer, the median age at diagnosis was 64 (range, 24 to 87), and three men developed contralateral cancers [42]. (See "Breast cancer in men".)

Other gynecologic malignancies

- **Fallopian tube –** At least 50 percent of serous cancers diagnosed in *BRCA1/2* carriers are of distal fallopian tube origin [46-48]. The lifetime risk of developing fallopian tube carcinoma in *BRCA1/2* mutation carriers is estimated to be 0.6 percent [48], while the general population risk is 0.2 percent [49]. This risk may be an underestimate, given that many high-grade serous ovarian cancers appear to originate in the fallopian tubes [50,51]. Of note, the approach to treatment for ovarian versus fallopian tube carcinomas is identical. In addition, salpingectomy is recommended for all carriers who undergo risk-reducing bilateral salpingo-oophorectomy (rrBSO). (See 'Bilateral salpingo-oophorectomy' below.)

  In a retrospective review of 108 women with fallopian tube carcinoma, 33 (30.6 percent) carried a pathogenic mutation (*BRCA1,* 23 women; *BRCA2,* 10 women) [52]. The highest frequencies of pathogenic *BRCA1/2* variants were identified in women of Ashkenazi Jewish ancestry compared with women of other ancestries (55.6 versus 26.4 percent). In addition, carriers were more likely to be diagnosed before 60 years of age compared with women who did not carry a mutation (40.3 versus 17.4 percent).

- **Primary peritoneal** – The lifetime risk of developing peritoneal cancer in *BRCA1/2* carriers is estimated to be 1.3 percent. This estimate was derived from a retrospective review of 22 women of Ashkenazi Jewish ancestry affected with primary peritoneal carcinoma [48]. One of the three germline *BRCA1/2* founder mutations was identified in nine women (41 percent). The true incidence of primary peritoneal cancer is difficult to determine, and estimates are limited by the lack of precision in the assignment of site of origin for high-grade, metastatic, serous carcinomas at initial presentation. It is possible, for example, that some cancers classified as "primary peritoneal cancers" may have, in fact, been fallopian tube cancers that were missed.

- **Endometrial** – There are conflicting data on the risk of developing endometrial cancer in patients with pathogenic *BRCA* mutations [53-57]. One prospective study of 4456 *BRCA1/2* carriers found a small increased risk of endometrial cancer for both *BRCA1* (standardized incidence ratio [SIR] 1.91, 95% CI 1.06-3.19) and *BRCA2* (1.75, 95% CI 0.55-4.23) carriers, although the absolute risk was low [55]. The increased risk was found to be mostly attributable to tamoxifen use; the SIR for women who used tamoxifen was 4.14 (95% CI 1.92-7.87) and 1.67 for women who did not (95% CI 0.81-3.07). The ten-year cumulative risk among the women treated with tamoxifen was 2 percent. Similarly, a second prospective study found an increase in endometrial cancer risk (SIR of 3.5 among *BRCA1* carriers and 1.7 among *BRCA2* carriers), which persisted in an analysis that accounted for patients being on endocrine therapy [58].

  However, two large, prospective studies *of BRCA1/2* carriers found no increased risk of endometrial cancer after rrBSO, and results were unaffected by tamoxifen use [56,57].

Thus, at present, hysterectomy at the time of rrBSO is not recommended solely for prevention. (See 'Role for other prophylactic surgery?' below.)

- **Uterine papillary serous** – Several studies have suggested that uterine papillary serous or serous-like carcinoma (UPSC) is part of the *BRCA1/2* tumor spectrum, but the overall risk is very low. For example, one study of an unselected population of 151 women with UPSC found that seven women (4.6 percent) had mutations in *BRCA1*, *TP53,* and *CHEK2* [59]. Two percent of the subjects had a *BRCA1* mutation, which is higher than expected but still quite low.

In a subsequent study of 1083 *BRCA1/2* carriers undergoing rrBSO without hysterectomy, women with a *BRCA1* mutation experienced an increased incidence of serous endometrial cancer compared with what has historically been observed in the general population, though the absolute risk was still small (4 cases observed among 630 women with *BRCA1* mutations followed for a median of 5.1 years; observed-to-expected ratio 22.2, 95% CI 6.1-56.9) [56]. Women with *BRCA2* mutations did not experience a significantly higher incidence than the general population (1 case per 456 women; observed-to-expected ratio 6.4, 95% CI 0.2-35.5).

Pancreas — Many studies have confirmed an increased risk of pancreatic cancer in *BRCA1/2* mutation carriers [53,60-62]. The reported lifetime risk of pancreatic cancer to age 80 ranges between 1 and 3 percent for *BRCA1* carriers, and is slightly higher for *BRCA2* carriers, ranging between 2 and 5 percent [44,53,61].

In one study of 41 families with a known *BRCA1/2* mutation, the median age at diagnosis of pancreatic cancer was reported to be 59 (range, 45 to 80) in male and 68 (range, 38 to 87) in female *BRCA1* carriers, respectively. The median age at diagnosis of pancreatic cancer in *BRCA2* carriers was reported as 67 (range, 39 to 78) in men and 59 (range, 46 to 81) in women [63]. As in sporadic cases, survival in *BRCA1/2* mutation carriers is poor [64].

Prostate — Studies have shown that men with a *BRCA2* mutation have between a five- and ninefold increased risk of prostate cancer, estimated to translate to a risk of about 30 percent [44,60,65]. The risk of prostate cancer in men with a *BRCA1* mutation is less clear and data are mixed; for example, one study found the risk to be elevated by about 3.75-fold (translating to a risk of about 9 percent by age 65) [66], while a separate study did not find an increase among *BRCA1* carriers [44].

However, risk scores based on polygenic (single nucleotide polymorphism) testing, which are not routinely integrated into clinical care, have also been used to predict risks in *BRCA1/2* carriers [67]. Using the 50th percentile cutoff of polygenic risk score (PRS) distributions, the lifetime risk for *BRCA1* carriers is on the order of 15 to 20 percent, and 30 to 40 percent for *BRCA2* carriers. The absolute risk range to age 80 across the PRS distribution was wide: 7 to 26 percent for *BRCA1* and 19 to 61 percent for *BRCA2*. Note that the general population risk of

prostate cancer varies by race and ethnicity; therefore, absolute risk estimates are not necessarily reflective of these differences.

Given that a significant proportion of men in the general population have prostate cancer, many cases of which are found at autopsy, the baseline population risk is difficult to estimate. Determining the absolute risk in *BRCA1/2* carriers is similarly hard to pinpoint, and there is concern about whether the increased risks observed in carriers are the result of over-diagnosis. However, several studies have shown that prostate cancer in *BRCA1/2* carriers is more aggressive and has poorer survival outcomes relative to the general population [68-71].

Other solid tumors — Aside from the risks of breast, ovarian, prostate, and pancreatic cancers, risks of cancer at other sites in *BRCA1/2* carriers are based on low numbers of affected individuals, often with unconfirmed diagnoses, and findings have not been widely replicated. Thus, the clinical relevance of these data is uncertain, and the role of cancer screening and risk reduction options is undefined.

- **Colorectal** – Data regarding risk of colorectal cancer (CRC) in *BRCA1/2* carriers are inconsistent. Although some studies have reported an increased risk of CRC among *BRCA1* mutation carriers, other population-based series have not confirmed such an association. Further details are found elsewhere. (See "Colorectal cancer: Epidemiology, risk factors, and protective factors", section on 'Are patients with HBOC syndrome at risk?'.)

- **Melanoma and non-melanomatous skin cancers** – An association between *BRCA2* pathogenic variants and cutaneous melanoma has been described, but the risk is not well characterized [60,72,73]. No clear association with *BRCA1* has been noted.

  The risk of uveal melanoma, which is very rare, is increased in *BRCA2* carriers. For example, in a study of 222 *BRCA1/2* families, two *BRCA2* carriers developed this malignancy, which translated to a relative risk of 99.4 (95% CI 11.1-359.8) [74]. Because of the wide confidence interval, translation to an absolute risk is not possible. The risk of uveal melanoma in *BRCA1* carriers is not well described [75].

  Studies have not provided a definitive answer about whether the risk of non-melanoma skin cancer is elevated in *BRCA1/2* carriers [73].

- **Stomach and biliary** – An increased risk of biliary and gastric cancers in *BRCA1* and 2 carriers and esophageal cancers in *BRCA2* carriers has been described [44,76]. In a large international study the absolute risks of these cancers were low, for example in *BRCA2* carriers the risk of stomach cancer was 3.5 percent up to age 80 years [44]. In a study from Japan, however, the risk of gastric cancer in *BRCA1* and *BRCA2* carriers was about

19 to 20 percent up to age 85 [76]. This discrepancy may in part reflect the high risk of this malignancy in East Asian countries.

MANAGEMENT OF FEMALE BRCA1/2 CARRIERS WITHOUT CANCER

For women without a personal history of cancer in whom a *BRCA1/2* pathogenic variant is identified, national guidelines recommend risk-reducing bilateral salpingo-oophorectomy (rrBSO) once childbearing is complete, and between the ages of 35 and 40. As *BRCA2* carriers tend to develop ovarian cancer 8 to 10 years later than *BRCA1* carriers, delaying rrBSO until age 40 to 45 in *BRCA2* carriers can be considered. Studies show that rrBSO significantly reduces the risk of ovarian cancer and improves survival. (See 'Bilateral salpingo-oophorectomy' below.)

Specific recommendations for breast cancer risk management include intensive screening as well as consideration of hormonal and surgical forms of risk reduction. In addition to bilateral mastectomy, premenopausal women should be informed that obtaining rrBSO by the recommended age may reduce the risk of breast cancer. (See 'Risk-reducing surgery' below.)

Clinical decision-making around which strategies to pursue for cancer risk reduction (ie, surveillance, risk-reducing surgery, and/or chemoprevention) involves a trade-off between life expectancy and quality of life. Several studies have suggested that decision aids or data from models may help patients choose among different options [77-81], and most use decision analysis and the concept of time tradeoffs (ie, years of life saved by one strategy as compared with another). While useful from a clinical research standpoint, they are not often employed in clinical practice.

Counseling regarding modifiable lifestyle choices — Although several studies have reported associations between specific risk factors and breast/ovarian cancer risks in *BRCA1/2* carriers, a rigorous meta-analysis of 44 nonoverlapping studies assessing several hormonal and several exogenous risk factors found that the only factor to be clearly associated with breast cancer risk was age at first live birth [82].

Specifically, a meta-analysis of two cohort studies found that later age at first live birth for *BRCA1* carriers may be protective against breast cancer [82]. A reduced effect size (ES) was found when comparing women who had delivered their first child at age 30 years and older with women at age 25 to 29 years at the time of delivery (ES 0.69, 95% CI 0.48-99). However, there was no impact on age at first birth noted for *BRCA2* carriers (ES 1.02, 95% CI 0.64-1.63).

With respect to other risk factors, results from the meta-analysis showed that the following may have **possible** associations with cancer risks:

Increased breast cancer risk:

- Oral contraceptives (theoretic, both for *BRCA1* and *BRCA2*)
- Smoking (*BRCA2*)

Decreased breast cancer risk:

- Breastfeeding (*BRCA1*)
- Late age at menarche (*BRCA1*)

Decreased ovarian cancer risk:

- Breastfeeding (*BRCA1*)
- Tubal ligation (*BRCA1*)
- Oral contraceptive use (*BRCA1* and *BRCA2*)

In summary, while data are limited in *BRCA1/2* carriers, general information about specific risk factors may be useful for counseling individual women about their risk and modifiable lifestyle choices.

Risk-reducing surgery — For women without a personal history of cancer who have a *BRCA1/2* pathogenic variant, prophylactic (or preventative) surgery reduces the risk of developing cancer. However, risk-reducing surgery does not completely eliminate the risk of developing cancer, as residual risks remain after mastectomy and bilateral salpingo-oophorectomy. While prophylactic surgery is effective in cancer risk reduction, women should be counseled preoperatively about the potential morbidity of such procedures, and the possibility that surgery may affect libido, sexual functioning, and body image. Oophorectomy in premenopausal women can be associated with increased risks for bone and heart disease, and raises concerns about how to optimally manage surgical menopause and hormone therapy. These procedures are discussed further below.

Mastectomy — We agree with the National Comprehensive Cancer Network and recommend that *BRCA1/2* carriers be offered risk-reducing bilateral mastectomy [83]. However, the decision about whether or not to undergo such surgery is based on personal preference, given that effective screening is available. (See 'Breast cancer screening' below.)

In both retrospective and prospective observational studies, risk-reducing or prophylactic bilateral mastectomy decreases the incidence of breast cancer by 90 percent or more in patients at risk of hereditary breast cancer, with most studies focusing on *BRCA1/2* mutation carriers [84-92]. As an example, in one large, prospective, multi-institutional international study that included over 2400 women with a known *BRCA1/2* mutation, no patients developed breast cancer following mastectomy (0 of 247 women), whereas 98 of 1372 women (7 percent) who did not undergo mastectomy did [90].

Patients who opt to proceed with mastectomy are most often undergoing skin-sparing mastectomy with or without preservation of the nipple-areolar complex followed by immediate breast reconstruction. Nipple-areolar-sparing mastectomy in particular provides superior cosmetic results, with low recurrence risks [93,94]. As an example, in a multi-institution review of 346 *BRCA1/2* carriers undergoing either bilateral mastectomy or contralateral mastectomy with nipple-areolar sparing there were no cases of breast cancer, whereas, based on models, 22 would have been expected [93]. Although the follow-up was relatively brief (median, 34 months), in experienced hands, this procedure is considered to be an acceptable option for risk reduction. (See "Mastectomy", section on 'Skin-sparing mastectomy' and "Mastectomy", section on 'Nipple-areolar-sparing mastectomy'.)

Bilateral salpingo-oophorectomy — For *BRCA1/2* carriers, rrBSO is recommended for women who have completed childbearing, and should be performed by age 35 to 40 or individualized based on age of onset of ovarian cancer in the family [83,95-98]. In *BRCA2* carriers, one can consider delaying this procedure until age 40 to 45. Whenever possible, patients should be referred to a gynecologic oncologist for a discussion about this surgery, and specific protocols have been recommended for pathologic review and follow-up of abnormal findings [83]. Salpingectomy and delayed oophorectomy, as a means of preserving fertility during childbearing years, has also been evaluated and is discussed elsewhere. (See "Risk-reducing salpingo-oophorectomy in patients at high risk of epithelial ovarian and fallopian tube cancer", section on 'BSO versus salpingectomy alone'.)

- **Improvements in ovarian cancer risks and mortality** – rrBSO not only decreases the risk of ovarian cancer in *BRCA1/2* mutation carriers, but also decreases mortality [90,96,97]. In a 2014 meta-analysis of three prospective studies of rrBSO in *BRCA1/2* carriers, the procedure was associated with an 80-percent reduction in ovarian cancer (risk ratio [RR] 0.19, 95% CI 0.13-0.27) and a 68-percent reduction in all-cause mortality (RR 0.32, 95% CI 0.27-0.38) [99].

- **Continued risk of peritoneal carcinoma after rrBSO** – Peritoneal carcinoma should be considered a phenotypic variant of ovarian cancer. Women who undergo rrBSO remain at risk for developing this cancer [100-103], which is much less common than ovarian cancer but associated with high mortality, similar to that of stage III epithelial ovarian cancer [104,105]. A review of five studies including 846 patients with *BRCA1/2* mutations concluded the risk of peritoneal cancer after rrBSO was 1.7 percent (range, 0.5 to 10.7 percent) [106]. Subsequently, a large prospective study including 1045 patients estimated a 4.3 percent cumulative incidence of peritoneal carcinoma in *BRCA1/2* mutation carriers at 20 years after rrBSO [107]. The risk appears to be highest in *BRCA1* carriers, although an association with *BRCA*2 cannot be excluded; peritoneal carcinomas have been reported in a few women with *BRCA*2 mutations [107-109]. Furthermore, risk appears to be higher among patients with serous tubal intraepithelial

carcinoma (STIC) found at the time rrBSO (hazard ratio [HR] 33.9), translating to a 10-year risk of 28 percent, versus 0.9 percent for those without STIC at the time of surgery [103]. Malignancy found at the time of surgery is discussed in more detail elsewhere. (See "Risk-reducing salpingo-oophorectomy in patients at high risk of epithelial ovarian and fallopian tube cancer", section on 'Occult malignancy on pathology'.)

- **Effect on breast cancer risk –** Although previous data suggest that rrBSO may be beneficial for reduction of breast cancer risk, other data have called this into question, particularly for *BRCA1* carriers [110]:

  - In the 2010 prospective study described above [90], rrBSO was also found to decrease breast cancer risk in *BRCA1* (HR 0.63, 95% CI 0.41-0.96) and *BRCA2* carriers (HR 0.36, 95% CI 0.16-0.82).

  - However, in an analysis of a nationwide cohort of over 800 *BRCA1/2* carriers with no prior personal history of cancer, the HR for breast cancer following rrBSO was 1.09 (95% CI 0.67-1.77) [97]. This analysis aimed to minimize biases due to selection, lead time, and short follow-up. The authors noted that rrBSO, when performed prior to menopause, may have a slight protective effect on breast cancer risk.

  - Finally, a study of 3722 *BRCA1/2* carriers unaffected by cancer with 5.6 years' follow-up found that rrBSO had a nonsignificant trend to a reduced risk of breast cancer in *BRCA2* carriers (HR 0.65, 95% CI 0.37-1.16), but not *BRCA1* carriers (HR 0.96, 95% CI 10.73-1.26). In analyses evaluating effect of rrBSO when stratified by age, reduction in breast cancer risk in *BRCA2* mutation carriers diagnosed prior to age 50 years was statistically significant (age-adjusted HR 0.18, 95% CI 0.05-0.63), but was not in *BRCA1* carriers (age-adjusted HR 0.79, 95% CI 0.55-1.13) [111].

Thus, we concur with the recommendation for *BRCA1/2* carriers to undergo rrBSO with the primary aim to decrease the risk of and mortality attributable to ovarian and fallopian tube cancer. Based on available data, we feel that rrBSO also reduces the risk of breast cancer in *BRCA2* carriers prior to age 50, but not in *BRCA1* carriers. (See "Risk-reducing salpingo-oophorectomy in patients at high risk of epithelial ovarian and fallopian tube cancer".)

Women who undergo rrBSO will likely experience side effects of surgically induced menopause. Discussion of hormone therapy (HT) for management of menopausal symptoms is found below. These women are also at an increased risk of developing osteoporosis. They should be counseled about osteoporosis prevention and screening. (See 'Hormone therapy' below and "Screening for osteoporosis in postmenopausal women and men" and "Overview of the management of osteoporosis in postmenopausal women", section on 'Lifestyle measures'.)

Role for other prophylactic surgery? — The only proven risk-reducing procedure for ovarian cancer in *BRCA1/2* mutation carriers is rrBSO. We do not routinely recommend hysterectomy at the time of rrBSO for prevention purposes. Hysterectomy may be indicated for other reasons or to allow the use of unopposed estrogen replacement therapy. Of note, there are no national guidelines that recommend routine hysterectomy in *BRCA1/2* mutation carriers. While studies have reported a possible small, excess risk of uterine cancers in mutation carriers [56,58,59,112], the absolute risk is low, and it is not clear that the benefits associated with hysterectomy are sufficiently large enough to warrant the risks associated with surgery. While hysterectomy is not indicated to reduce cancer risk, some carriers may, however, choose to undergo this surgery at the time of rrBSO in order to enable them to take unopposed estrogen HT without increasing their risk of endometrial cancer. It is therefore critical to have at least an initial discussion about these options preoperatively. (See 'Hormone therapy' below.)

There is controversy about whether it is appropriate to perform a salpingectomy alone for *BRCA1/2* mutation carriers who wish to defer oophorectomy [113,114], based upon a possible fallopian tube origin for some ovarian cancers [115,116]. The Society of Gynecologic Oncology (SGO) Clinical Practice Statement states that salpingectomy may be appropriate and feasible as a strategy for ovarian risk reduction, but further study is needed to determine safety of this practice [113]. However, the statement and a lengthier explication make clear that this procedure does **not** eliminate the risk of ovarian cancer, and it does **not** reduce the risk of breast cancer [113,117]. Guidelines from the National Comprehensive Cancer Network thus indicate that salpingectomy alone is not the standard of care [83].

Ongoing randomized controlled trials or prospective clinical trials are evaluating this question but until there are sufficient data from these studies, we do not offer salpingectomy without an oophorectomy for these women. (See "Opportunistic salpingectomy for ovarian, fallopian tube, and peritoneal carcinoma risk reduction".)

Hormone therapy

Clinical approach — Prior to using HT to manage menopausal symptoms in *BRCA1/2* carriers who have undergone rrBSO, a shared decision-making process must include counseling women about nonhormonal options and the lack of population-specific data regarding HT.

While the data are somewhat limited, we feel that estrogen-alone HT is a reasonable option for younger mutation carriers [118], particularly those who have undergone risk-reducing mastectomy and hysterectomy. For carriers not undergoing risk-reducing mastectomy, we counsel regarding a theoretically increased breast cancer risk, although data are limited. Nonhormonal options are also an option for menopausal symptoms and osteoporosis

prevention and treatment in BRCA carriers who have undergone rrBSO. (See "Menopausal hot flashes", section on 'Nonhormonal pharmacotherapy'.)

Women who plan to take systemic HT after rrBSO should be counseled about the possible risks and benefits of HT and possible ways to mitigate these risks. These include:

- Limiting the duration of HT – Some clinicians begin HT after surgery and then make a plan with the patient to taper it within several years. Another approach is to stop HT at 51 years old, the average age of natural menopause.

- Concurrent hysterectomy – To enable use of unopposed estrogen for management of menopausal symptoms without incurring a risk of endometrial cancer, some women choose to undergo concomitant hysterectomy at the time of rrBSO. However, hysterectomy is not otherwise routinely indicated, as discussed above. (See 'Role for other prophylactic surgery?' above.)

  The rationale for possible hysterectomy in this setting is as follows. Estrogen therapy alone appears to incur a lower risk of breast cancer than estrogen-progestin therapy. However, unopposed estrogen therapy in a woman with a uterus leads to endometrial cancer. A potential alternative is an ultra-low-dose transdermal estrogen formulation, with which progestin opposition is required only periodically (eg, every six to 12 months). (See "Preparations for menopausal hormone therapy", section on 'Transdermal estrogen'.)

- Prophylactic mastectomy. (See 'Mastectomy' above.)

Systemic hormone therapy — Our approach to HT in patients who have undergone rrBSO is discussed above. (See 'Clinical approach' above.)

There are no high-quality data in this setting, but overall, studies suggest that the risk of breast cancer is not increased in younger *BRCA* carriers (≤45 years) taking HT after rrBSO; among carriers older than 45 years, studies are conflicting, but there may be an increased risk of breast cancer, potentially related to time of exposure to HT around the natural age of menopause [90,119-121]. Examples of available data are as follows:

- In a prospective cohort study of 872 *BRCA1* mutation carriers who had undergone oophorectomy, HT was not associated with an increased risk of breast cancer at a median follow-up of 7.6 years (HR 0.97, 95% CI 0.62-1.52) [119]. In carriers taking any type of HT, there was no increase in risk of subsequent breast cancer compared with controls. However, in those taking estrogen plus progesterone HT, the 10-year actuarial risk of breast cancer was 22 percent, as compared with 12 percent in those taking estrogen alone. There were no statistically significant differences based on age.

- In a retrospective cohort study of 306 *BRCA1/2* mutation carriers who had undergone rrBSO, 36 patients were diagnosed with breast cancer at a median follow-up of 7.3 years, 13.5 percent in the HT group and 10.3 percent in the non-HT group (OR 1.4, 95% CI 0.7-2.7) [122]. In women who were ≤45 years at the time of rrBSO, HT did not affect breast cancer rates; however, those older than 45 years who took HT had higher rates of breast cancer than those who did not take HT (21 versus 8 percent; OR 3.4, 95% CI 1.2-9.8).

There is a substantial body of evidence among non-*BRCA1/2* carriers regarding the association of exogenous HT with breast cancer, predominantly hormone receptor-positive breast cancer. Representative data are as follows:

- The most influential data come from the Women's Health Initiative trial, which showed that the use of combined estrogen-progestin HT resulted in a significantly increased risk of breast cancer in postmenopausal women over the age of 50. By contrast, there was no increase in breast cancer risk in women who received unopposed estrogen. The relationship between HT and breast cancer is discussed in detail separately. (See "Menopausal hormone therapy and the risk of breast cancer".)

- In breast cancer survivors, data from randomized trials show a significant increase in rates of breast cancer recurrence with the use of HT; this risk appears to be present for both estrogen-progestin and estrogen-alone therapy, although data regarding specific regimens are limited [123]. (See "Menopausal hormone therapy and the risk of breast cancer", section on 'Personal history of breast cancer'.)

However, the generalizability of these data to premenopausal women who undergo rrBSO is unclear. These women differ from the postmenopausal population studied in the Women's Health Initiative trial: they are likely to be younger than age 51 and have had surgical rather than natural menopause. Additionally, although *BRCA* carriers are at a high risk of breast cancer, they cannot be equated with women who have been diagnosed with breast cancer.

Vaginal estrogen therapy — For carriers with symptomatic vaginal atrophy, nonhormonal options may be used as first-line therapy. However, we have a low threshold to use vaginal estrogen to treat persistent symptoms. (See "Genitourinary syndrome of menopause (vulvovaginal atrophy): Treatment".)

Vaginal estrogen therapy is the most effective treatment for vaginal atrophy. It alleviates symptoms of dyspareunia and vaginal dryness, and may also result in decreased incidence of urinary tract infections and overactive bladder symptoms. Low-dose vaginal estrogen therapy for treatment of local symptoms typically does not raise the serum estrogen concentration above the average level following natural menopause. There are no data regarding the risk of breast cancer in high-risk women treated with vaginal estrogen therapy.

Cancer surveillance — For female *BRCA1/2* carriers who do not wish to pursue (or would rather delay) surgical risk reduction, breast cancer surveillance should be offered, and ovarian cancer screening may be performed [83]. While breast and ovarian (including fallopian tube and peritoneal) cancers present the greatest risk, carriers have elevated risks for other cancers, including prostate cancer and pancreatic cancer. (See "Overview of hereditary breast and ovarian cancer syndromes".)

Women with *BRCA1/2* pathogenic variants should be educated regarding signs and symptoms of breast and ovarian cancer as appropriate. (See "Clinical manifestations, differential diagnosis, and clinical evaluation of a palpable breast mass" and "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Clinical features and diagnosis" and "Breast cancer in men" and "Breast cancer in men", section on 'Presentation'.)

Breast cancer screening — The following screening strategy is recommended by expert groups for women with *BRCA1/2* pathogenic variants who have not undergone risk-reducing surgery, and should be individualized as needed [83,95,124]:

- Beginning at age 18, self-breast exams performed periodically may facilitate awareness of changes, and clinical breast examination should be performed every 6 to 12 months beginning at age 25.
- Magnetic resonance imaging (MRI) for breast cancer screening is recommended annually beginning at age 25, or earlier depending on the earliest age of breast cancer in the family [83,125].
- Mammography with consideration of tomosynthesis should begin at age 30 or be individualized if the earliest age of onset in the family is under age 25. Breast MRIs and mammography may be staggered by 6 months.

  However, the sensitivity of mammography for detecting breast cancer in mutation carriers appears to be lower than in other high-risk women, which may be due to [83,95,126-128]:

  - Higher breast density [128].
  - Differences in morphologic features (eg, less spiculation due to lack of tumor-surrounding fibrosis) [127].
  - The frequent development of interval malignancies [129].

The addition of breast MRI to the breast cancer surveillance strategy in high-risk women increases breast cancer detection rates, increases the number of patients diagnosed at an earlier stage of disease, is cost effective (image 1) [79,81,130-132], and is supported in multiple guidelines [83,124,133]. However, the mortality impact of including breast MRI in the surveillance strategy is not clear. Representative data are as follows:

- In a systematic review of 11 nonrandomized studies in which high-risk women were screened by both MRI and mammography, MRI was more sensitive but less specific than mammography, but the combination of the two modalities was both more sensitive and specific compared with mammography alone [134]. For example, the sensitivity and specificity of detecting a Breast Imaging Reporting and Data System (BI-RAD) ≥4 lesion were 32 and 99 percent, respectively, with mammography; 75 and 96 percent, respectively, with MRI; and 84 and 99 percent, respectively, with combined-modality therapy.

- In a prospective study in which women with a high risk for breast cancer were screened with annual mammography and MRI, and were followed for a median of five years if they developed breast cancer, the overall survival at six years in *BRCA1/2* carriers with invasive cancer was 93 percent (95% CI 79.0-97.6) [130]. While these data are promising, the lack of a control group makes it hard to conclude that MRI was associated with a survival benefit.

- In a prospective cohort study of 1275 *BRCA1/2* carriers followed for a mean of 3.2 years, the addition of MRI to mammography did not increase the number of women diagnosed with breast cancer, but those screened with MRI were more likely to be diagnosed with ductal carcinoma in situ (DCIS) or stage I disease (13.8 versus 7.2 percent, respectively) as opposed to stage II to IV disease (1.9 versus 6.6 percent, respectively) [131]

While the risk of radiation-associated breast cancer from breast imaging for the average-risk patient is believed to be small or nonexistent, women at high genetic risk may be more susceptible to radiation-induced carcinogenesis because of the role of *BRCA1/2* proteins in DNA repair. In a retrospective study of 1993 carriers of *BRCA1/2* mutations, any exposure of diagnostic radiation before age 30 was associated with an increased risk of breast cancer (HR 1.90, 95% CI 1.20-3.00), with a dose-response pattern. By contrast, in a report based upon a questionnaire sent to known *BRCA1/2* mutation carriers, exposure to mammographic screening (mean age at first screening mammogram, 35 years of age) was not associated with an increased risk of breast cancer when adjusted for parity, oral contraceptive use, family history, and ethnicity. Further research is needed, and current recommendations by most groups support screening these women with a combination of mammography and MRI scanning rather than breast MRI exclusively [135-138].

Data from large studies evaluating the role of breast ultrasound in addition to other imaging modalities have not demonstrated any additional benefit of this procedure [139-141]. Thus, we do not routinely recommend it to mutation carriers who are already undergoing MRI and mammogram.

Ovarian cancer screening — For carriers who are of the age range of recommended rrBSO and opt not to pursue it, we offer ovarian cancer screening. This consists of concurrent transvaginal ultrasound (preferably day 1 to 10 of menstrual cycle) and cancer antigen (CA) 125 (best performed after day 5 of menstrual cycle) every six months beginning at age 30 or 5 to 10 years before the earliest age of first diagnosis of ovarian cancer in the family according to previous guidelines from the National Comprehensive Cancer Network [142]. However, we acknowledge that 2023 guidelines do not discuss this strategy and there is a lack of high-quality data to inform these recommendations; as such, some patients may reasonably prefer not to undergo screening [143].

Screening for other cancers — There is no consensus regarding screening for melanoma or pancreatic cancer; however, recommendations may be based on an individual's family history. Possible recommendations in carriers include full-body skin exams and pancreatic cancer screening, for those with affected relatives [83]. However, there was no consensus about what age to initiate screening, how often to repeat it, and how to follow up after abnormal findings. We generally recommend that *BRCA2* carriers obtain full-body skin exams as a precaution, and follow the International Cancer of the Pancreas Screening Consortium guidelines for screening for pancreatic cancer, as detailed elsewhere. (See "Familial risk factors for pancreatic cancer and screening of high-risk patients", section on 'Pancreatic cancer screening'.)

With respect to colon cancer screening, guidelines for management in *BRCA1/2* carriers do not differ from those in the general population. However, if an individual has a family history of colon cancer or a prior history of adenomas or other conditions that may increase risk, more aggressive screening may be recommended [83].

Chemoprevention

Tamoxifen — For female *BRCA2* carriers who opt against mastectomies, we offer tamoxifen or aromatase inhibitors (AIs) for risk reduction for women. However, based on the patient's age and general health, the option of risk-reducing mastectomy should be rediscussed periodically with patients, as medical chemoprevention is less effective than surgery. (See "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention", section on 'BRCA carriers'.)

Only limited data are available regarding the preventive benefit of tamoxifen in *BRCA1/2* mutation carriers. Evidence for the benefit of tamoxifen in women who have never had a diagnosis of breast cancer comes from a subset analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention trial (P-1 trial). Tamoxifen reduced breast cancer risk by 62 percent in *BRCA2* carriers (relative risk [RR] 0.38, 95% CI 0.06-1.56), but not in *BRCA1* carriers (RR 1.67, 95% CI 0.32-10.07) [144]. However, this analysis is limited by the small number of mutation carriers (of the 288 women in the study who

developed breast cancer, only 8 had *BRCA1* pathogenic variants and 11 had *BRCA2* pathogenic variants) [145]. There are no data addressing the preventive benefit of raloxifene or an AI in patients with *BRCA1/2* mutations. However, in large chemoprevention studies of postmenopausal women at increased risk for breast cancer, both raloxifene and AIs have demonstrated reductions in the risk of breast cancer [146-148].

A differential effect of tamoxifen in *BRCA2* as compared with *BRCA1* mutation carriers may be attributed to estrogen receptor (ER) status of *BRCA1*- and *BRCA2*-associated tumors. Tamoxifen might be expected to have an impact only against ER-positive tumors, and *BRCA2*-associated tumors have a greater likelihood than *BRCA1*-associated tumors of being ER positive.

Oral contraceptives — We suggest that all carriers undergo rrBSO at an age before which they are at the highest risk for ovarian cancer, and therefore oral contraceptives as chemoprevention agents are not indicated. For patients who have taken oral contraceptives (or who have opted against rrBSO), we discuss that evidence supports a reduced risk of ovarian cancer in carriers who take oral contraceptive pills, although a theoretic risk of increased breast cancer exists. However, this has not been clearly supported in the literature.

A meta-analysis of 18 comparative, retrospective studies of oral contraceptive use in *BRCA1/2* mutation carriers included 1503 cases of ovarian cancer and 2855 cases of breast cancer [149]. Ever-use of oral contraceptives in *BRCA1/2* mutation carriers was associated with a reduced risk of ovarian cancer (RR 0.50, 95% CI 0.33-0.75); this effect was found to a similar degree in both *BRCA1* and *BRCA2* mutation carriers. The protective effect increased with longer duration of use. The largest study in the meta-analysis, a case-control study that included 798 women with ovarian cancer, found a 5 percent decrease in risk of ovarian cancer per year of oral contraceptive use [150]. In addition, oral contraceptive use appears to be associated with a decreased risk of fallopian tube cancer in the general population [151].

There has been concern that oral contraceptives may increase the risk of breast cancer in mutation carriers. In the meta-analysis described above, there was no evidence of a significantly increased breast cancer risk in oral contraceptive users overall, for users of current formulations of oral contraceptives, or in the first 10 years after cessation of use [149]. (See 'Chemoprevention' above.)

One limitation of these studies is that all the data are for use of oral contraceptives. Other formulations of estrogen-progestin contraceptives (patch, vaginal ring) have not been studied in this clinical context; thus, it is unknown whether they provide similar ovarian cancer prevention.

Chemoprevention of ovarian cancer with agents other than estrogen-progestin contraceptives (eg, vitamin D) is under investigation. Protective factors against ovarian

cancer in the general population are discussed in detail separately. (See "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Incidence and risk factors", section on 'Protective factors'.)

Fertility — Evidence is mixed regarding whether *BRCA* carriers have decreased fertility. While several studies have suggested a lower serum anti-Müllerian hormone (AMH) in *BRCA* carriers relative to controls [152-154], others have not confirmed this finding [153,155]. In the largest available analysis (250 *BRCA* carriers and 578 controls), it was suggested that female *BRCA1* carriers had an approximately 33 percent lower AMH level relative to controls, although levels in *BRCA2* carriers were not diminished [156]. This finding may represent decreased ovarian reserve, and therefore fertility counseling may be appropriate for *BRCA1* carriers, if decisions regarding chemotherapy or delayed childbearing are being considered. Discussion of the approach to infertility is discussed elsewhere. (See "Overview of infertility".)

MANAGEMENT OF MALE BRCA1/2 CARRIERS WITHOUT CANCER

For men, screening for breast and prostate cancers is generally recommended.

Cancer surveillance — There are no proven risk-reducing surgical options for male mutation carriers. Therefore, the following screening strategy is recommended for men (with *BRCA1/2* mutations) (see "Breast cancer in men"):

- Monthly breast self-examination starting at age 35.
- Clinical breast examination every 12 months starting at age 35.
- Mammography – Guidelines now recommend consideration of annual mammogram, particularly for *BRCA2* carriers, beginning at age 50 or 10 years before the earliest known male breast cancer in the family [83].
- Prostate cancer screening starting at age 40 for *BRCA2* carriers and consideration of prostate screening for *BRCA1* carriers at age 40 [83]. Other guidelines also suggest that age at diagnosis of any affected family members should be factored into screening discussions [157]. (See "Screening for prostate cancer".)
    - A potential benefit of prostate-specific antigen screening is that *BRCA1/2* status may be a factor in deciding whether men with early-stage/localized prostate cancer choose surgery versus active surveillance [157]. Given the potentially aggressive nature of *BRCA1/2*-associated prostate cancers, the former option may be preferred. (See "Localized prostate cancer: Risk stratification and choice of initial treatment".)
- The approach to screening for other cancers is identical to that adopted for female *BRCA1/2* carriers. (See 'Screening for other cancers' above.)

Our approach to cancer surveillance is generally the same for male *BRCA1* and *BRCA2* carriers (with one possible exception being prostate cancer). Although results from a cohort study of 6900 male *BRCA1/2* carriers suggested differences in the cancer spectrum between male *BRCA2* versus *BRCA1* carriers (eg higher risks of breast, prostate, and pancreatic cancer, but lower risk of colorectal cancer) [158], further data are needed to confirm these differences.

Role for chemoprevention? — Although tamoxifen is used to treat some men with hormone receptor-positive breast cancer, it is not recommended for use as chemoprevention in *BRCA1/2* carriers, whose overall risk is low. (See "Breast cancer in men".)

Given the high risk of prostate cancer in male *BRCA1/2* carriers, especially in *BRCA2* carriers, the question has been raised about whether they may be good candidates for chemoprevention with agents such as 5-alpha-reductase inhibitors. However, there are no data regarding the effectiveness of chemoprevention in male carriers. Information about prostate cancer chemoprevention is discussed separately. (See "Chemoprevention strategies in prostate cancer".)

REPRODUCTIVE COUNSELING

Pathogenic variants in many breast cancer genes, including *BRCA*, are inherited in an autosomal-dominant pattern, meaning that there is a 50 percent chance that children of *BRCA1/2* carriers will have inherited the cancer-predisposition variant. Reproductive counseling of *BRCA1/2* carriers includes education about prenatal diagnosis and assisted reproduction [142]. One option is preimplantation genetic diagnosis, which is used to analyze embryos (obtained by in vitro fertilization) genetically before their transfer into the uterus [159]. (See "Preimplantation genetic testing".)

In addition, *BRCA2* carriers who plan to have children with a partner who is also at increased risk of carrying a *BRCA2* pathogenic variant (eg, owing to personal/family cancer history or to the increased background frequency in individuals of Ashkenazi Jewish descent) are at risk of having offspring who may inherit a rare, recessive syndrome that is characterized by the co-occurrence of brain tumors, Fanconi anemia, and breast cancer [160]. This syndrome occurs in individuals who have two (biallelic) mutations in *BRCA2.* Biallelic mutations in *BRCA1* and other genes may also predispose to Fanconi anemia and other severe disorders; thus, reproductive risks should be discussed with these carriers as well [83,161,162].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hereditary breast

and ovarian cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Genetic testing for breast, ovarian, prostate, and pancreatic cancer (The Basics)")
- Beyond the Basics topics (see "Patient education: Genetic testing for hereditary breast, ovarian, prostate, and pancreatic cancer (Beyond the Basics)" and "Patient education: Medications for the prevention of breast cancer (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Introduction** – Women with inherited pathogenic variants in breast cancer type 1 and 2 susceptibility genes (*BRCA1* and *BRCA2*; referred in this topic as *BRCA1/2*) have markedly elevated risks of breast and ovarian cancer. Male carriers have increased risk for breast and prostate cancer. (See 'Introduction' above.)
- **Breast cancer risk reduction** – For women with a *BRCA1/2* pathogenic variant, we offer risk-reducing mastectomy. (See 'Mastectomy' above.)
  - For women with a *BRCA1/2* pathogenic variant who do not opt for bilateral mastectomy, we offer surveillance with annual mammography and magnetic resonance imaging (MRI). We initiate MRI at age 25 and mammography at age 30. (See 'Cancer surveillance' above.)
  - For female *BRCA2* carriers who do not opt for risk-reducing mastectomy, we suggest endocrine therapy for chemoprevention (**Grade 2C**). Although tamoxifen is the only

agent that has been studied specifically in *BRCA1/2* carriers, we extrapolate from studies demonstrating a protective effect of aromatase inhibitors and raloxifene in other high-risk postmenopausal women, and offer these agents to postmenopausal women who prefer these options based on side-effect profile. (See 'Chemoprevention' above and "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention".)

- **Epithelial ovarian cancer risk reduction** – For women with a *BRCA1/2* pathogenic variant, we recommend performing risk-reducing bilateral salpingo-oophorectomy (rrBSO) between age 35 and 40 for *BRCA1* carriers and between 40 and 45 for *BRCA2* carriers, when childbearing is complete, rather than screening (**Grade 1B**). Of note, an early age at diagnosis of ovarian cancer in the family may prompt consideration of such surgery at a younger age. The age for rrBSO may be younger based on age of onset within the family. (See 'Bilateral salpingo-oophorectomy' above.)

  - For carriers who have not undergone rrBSO, we discuss ovarian cancer screening with concurrent transvaginal ultrasound and cancer antigen (CA) 125. The ultrasound is preferably performed on days 1 to 10 of menstrual cycle, while CA 125 is best assessed after day 5 of menstrual cycle. These assessments may be performed every 6 months beginning at age 30 to 35, or 5 to 10 years before the earliest age of first diagnosis of ovarian cancer in the family. However, we acknowledge a lack of high-quality data to inform these recommendations, and patients may reasonably opt to avoid these screening procedures. (See "Screening for ovarian cancer", section on 'Lack of benefit of screening strategies'.)

- **Screening for other cancers** – There is no consensus regarding screening for melanoma or pancreatic cancer; however, recommendations may be based on an individual's family history. Increasingly, pancreatic cancer screening is considered in carriers with first- or second-degree relatives with pancreatic cancer. Additionally, full-body skin exams can be offered, particularly for *BRCA2* carriers. (See "Familial risk factors for pancreatic cancer and screening of high-risk patients", section on 'Pancreatic cancer screening'.)

- **Males with *BRCA1/2* pathogenic variants** – For men with *BRCA1/2* pathogenic variants, cancer surveillance options are limited. We encourage clinical and self-breast examination and also suggest mammography, particularly for *BRCA2* carriers. We initiate mammography at age 50 or 10 years prior to the earliest known breast cancer in the family. However, given limited data, some males may opt not to pursue mammography.

  We also perform prostate cancer screening, beginning at age 40 to 45. (See 'Cancer surveillance' above.)

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Topic 758 Version 70.0

GRAPHICS

Estimated risks for cancer with *BRCA1* and *BRCA2* pathogenic variants

Cancer type	Lifetime risk to age 70 in carriers*	Lifetime risk to age 70 in general population¶	Comments
Breast (female)	*BRCA1*: 57 to 72% *BRCA2*: 45 to 69%	9%	In most studies, lifetime risk in *BRCA1* carriers is higher than that observed in *BRCA2* carriers. The incidence of breast cancer diagnosed younger than 50 years of age is higher in *BRCA1* carriers compared with *BRCA2* carriers, but both groups have an increased risk of premenopausal breast cancer.
Contralateral (opposite) breast (female)	Up to 63% at 25 years postdiagnosis but highly dependent on age at diagnosis of first breast cancer	0.4% annual risk and 10% at 25 years postdiagnosis[1]	Risk is affected by other factors such as tamoxifen use and oophorectomy. Mutation carriers who have had lumpectomy have increased ipsilateral risks over long follow-up periods.
Ovarian	*BRCA1*: 39 to 59% *BRCA2*: 11 to 20%	1%	The incidence of ovarian cancer diagnosed younger than 50 years of age is higher in *BRCA1* carriers and overall rare in all carriers younger than 40 years old. Risk of fallopian tube cancer is also substantially elevated.
Prostate	*BRCA1*: Approximately 15 to 20% *BRCA2*: Approximately 13 to 30%	6% White Americans 10% Black Americans	Risk appears to be higher in *BRCA2* carriers and in males younger than 65 years old.
Breast (male)	*BRCA1*: 0.2 to 1% *BRCA2*: 2 to 7%	0.1%	Risk before age 50 is very low.
Pancreatic	*BRCA1*: 1 to 3% *BRCA2*: 2 to 5%	0.6%	

Colon	Not well defined	2%	Studies have not been consistent about whether risk is elevated. If elevated, risk is likely to be small.
Melanoma	Not well defined	Approximately 2% White Americans 0.1% Black Americans	Increased risk for ocular melanoma in *BRCA2* carriers.
Other sites	Not well defined	Varied	These sites may include cancer of the stomach, gall bladder, and biliary tree in *BRCA2* carriers, as well as uterine serous carcinoma in *BRCA1* and *BRCA2* carriers.

These risks are estimates based upon review of the literature that focuses on individuals identified based on a positive family history. Risk may differ (ie, may be lower) in individuals with a negative family history, although data are extremely limited. Specific studies have reported risks that are lower or higher than the ranges or estimates quoted; however, the estimates reported here are representative of findings from high-quality studies in *BRCA1* and *BRCA2* families. Risks will also vary based on an individual's current age and other risk factors. (Refer to UpToDate topic on cancer risks and management of *BRCA1/2* carriers without cancer.)

BRCA: breast cancer susceptibility genes; SEER: Surveillance, Epidemiology, and End Results.

* Risk to individuals over age 70 is higher, but data are generally unavailable.

¶ Lifetime risk at birth for all races unless otherwise specified.

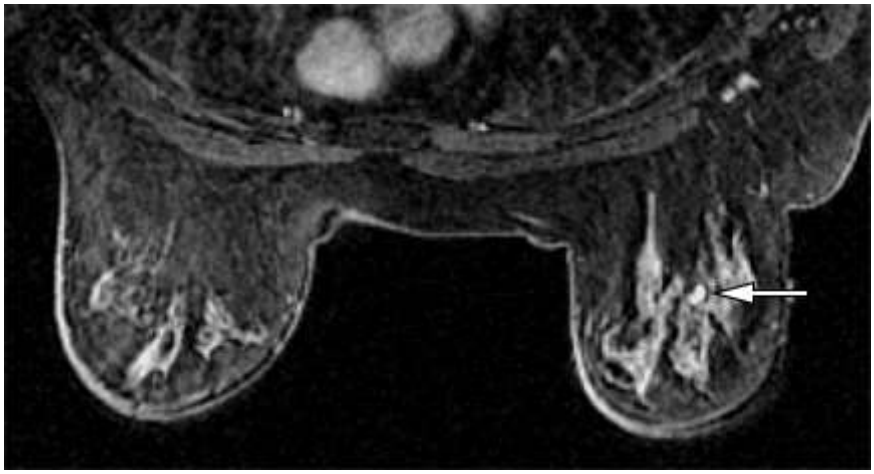
Data from: DevCan Version 6.7.9, April 2021, National Cancer Institute. Available at https://surveillance.cancer.gov/devcan/ (Accessed on April 29, 2022).

Reference:

1. *Giannakeas V, Lim DW, Narod SA, et al. The risk of contralateral breast cancer: a SEER-based analysis. Br J Cancer 2021; 125:601.*

Graphic 99937 Version 9.0

Breast MRI screening of BRCA carrier



Breast MRI is useful for screening women with genetic mutations that confer a very high risk for breast cancer. The figure depicts a breast MRI that was performed on a BRCA-1 gene carrier, revealing a focal circumscribed mass in left breast not visible on mammography (arrow). MRI-guided core biopsy confirmed an invasive ductal carcinoma.

MRI: magnetic resonance imaging; BRCA: breast cancer susceptibility gene

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Graphic 82565 Version 5.0

Contributor Disclosures

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