Chapter 5
Fertility Communication and High-Risk Patients

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Introduction

Due to improved genetic screening and cancer risk assessment among families, many women are now aware that they have an increased risk of developing breast or ovarian cancer at a young age. This cohort of young women, termed "previvors," faces unique concerns related to childbearing and cancer risk reduction. They must make decisions regarding prophylactic therapy and how, or whether, to balance preventive treatment with childbearing and breastfeeding. Often, interventions that effectively reduce cancer risk must be undertaken during the reproductive years, and may pose a permanent or temporary threat to fertility. The emergence of oncofertility has empowered these patients—who may have a high-risk family history of breast or ovarian cancer or carry deleterious genetic mutations—to take a proactive approach to both cancer prevention and fertility preservation. Fertility preservation may benefit high-risk patients who (1) are at increased risk of developing premenopausal breast or ovarian cancer and (2) may require a risk-reducing intervention prior to menopause that poses a threat to future fertility. In this chapter, we present the topics discussed during a high-risk consultation followed by case examples that illustrate effective communication about fertility preservation to patients at high risk for developing breast or ovarian cancer.

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T.K. Woodruff et al. (eds.), *Oncofertility Communication: Sharing Information and Building Relationships across Disciplines*, DOI 10.1007/978-1-4614-8235-2_5,

Who Are High-Risk Patients?

Women with a genetic predisposition to breast or ovarian cancer develop malignancies at a higher rate and younger age than the general population, indicating that preventive therapy could be undertaken before menopause. Because prophylactic interventions may temporarily or permanently compromise young patients' ability to have children, women at high risk for breast or ovarian cancer are in a unique position to benefit from fertility preservation options.

Approximately 10 % of breast cancer and 15 % of ovarian cancer patients have a heritable form of the disease, most commonly attributed to a mutation in the BRCA1 or BRCA2 gene. Women with germline BRCA1 or BRCA2 mutations tend to develop breast and ovarian cancer at a higher rate and earlier age than the baseline population. Female carriers of BRCA1 and BRCA2 mutations have a 45–65 % lifetime risk of developing breast cancer and an 11–39 % lifetime risk of developing ovarian cancer (Table 5.1) [1–3]. Although BRCA1 and BRCA2 mutations are most commonly implicated in hereditary breast cancer, other autosomal dominant cancer syndromes are also associated with an increased risk of breast cancer, including Li–Fraumeni syndrome (linked to TP53 mutations) and Cowden syndrome (related to PTEN mutations). In addition, ovarian cancer is associated with Lynch syndrome, cell nevus syndrome, and multiple endocrine neoplasia type 1 (MEN1) [4].

Women without a known genetic mutation but who have a strong family history of breast or ovarian cancer are also at increased risk for cancer. A review of 38 studies showed that the pooled estimate of relative risk of breast cancer in women with an affected first-degree relative was 2.1, and risk increased with each additional first-degree relative diagnosed with cancer [5]. Similarly, in a meta-analysis of 15 studies, the relative risk of ovarian cancer among women with at least one first-degree relative with disease was 3.1 [6].

Patients with a history of atypical ductal or lobular hyperplasia (ADH, ALH) or lobular carcinoma in situ (LCIS) represent another group at increased risk for breast cancer. Proliferative lesions with atypia (those with excessive growth of abnormal cells in the ducts or lobules of the breast tissue) confer a breast cancer risk four to five times that of an average-risk woman [7–9].

Table 5.1 Breast and ovarian cancer risk in BRCA mutation carriers

	Breast CA risk by age 70 (%)	Ovarian CA risk by age 70 (%)	References
General population	12	1.4	[1]
BRCA1	55–65	39	[2, 3]
BRCA2	45–47	11–17	[2, 3]

CA cancer

Prophylactic Interventions for High-Risk Patients

Prophylactic interventions are available to reduce the risk of developing breast and ovarian cancer; however, these approaches, which are often undertaken prior to menopause, have the potential to compromise a young patient's fertility. Guidelines for BRCA1/2 mutation carriers suggest that women consider prophylactic bilateral salpingo-oophorectomy (BSO) and prophylactic mastectomy after age 35 or as soon as they are finished having children; however, women with a strong family history of very early-onset cancer may also wish to pursue surgical interventions at a younger age. In the absence of prophylactic mastectomy, annual mammography and MRI screening are recommended; usually they are staggered every 6 months. Additionally, antiestrogen treatment with tamoxifen is recommended for breast cancer chemoprevention.

The therapeutic benefits of tamoxifen for high-risk patients are considerable; treatment can reduce the risk of developing invasive cancer by nearly 50 % [10]. However, tamoxifen is a teratogen, and pregnancy should be avoided during the recommended duration of therapy, which could extend up to 10 years [11]. At the dose used to treat breast cancer patients, tamoxifen generally does not cause cessation of ovulation. However, tamoxifen use may be associated with irregular or missed menses in some women, particularly when it is prescribed following cytotoxic chemotherapy. A significantly increased risk of amenorrhea at 1 year posttreatment was found among patients older than age 40 who were taking tamoxifen [12]. Additionally, there is a reported 15 % decrease in the odds of continuing menstrual cycles after the first 1–2 years of tamoxifen therapy, though some studies have also found this effect to be reversible and temporary [13–16]. As fertility begins to decline substantially after the age of 35, the considerable length of recommended tamoxifen therapy may be a critical deterrent for young, high-risk women.

Preventive interventions for women at high risk for ovarian cancer are particularly critical, as there are currently no effective screening algorithms for detecting early-stage ovarian cancer. Although clinical outcomes are good for early-stage ovarian cancer, 80 % of ovarian cancers are identified only after metastasis to the pelvic organs, abdomen, or beyond, at which point cure rates are low [17]. Prophylactic BSO dramatically reduces the risk of both breast and ovarian cancer in BRCA mutation carriers (by 50 % and 96 %, respectively) [18], but permanently eliminates the possibility of having biologic children if the patient's oocytes or embryos have not been preserved prior to oophorectomy. Oral contraceptives and tubal ligation have also been shown to reduce ovarian cancer risk [19], but these are not as effective as BSO. Unlike oophorectomy, however, they do allow for the possibility of a future pregnancy, as patients who have had tubal ligation may become pregnant through assisted reproductive technologies.

The decision to pursue prophylactic surgery is complex; often it is influenced by concerns about fertility, as well as worries about appearance, menopausal side effects, and sexuality. Despite these concerns, a survey of BRCA mutation carriers who have undergone prophylactic BSO found that approximately 97 % of patients

would pursue the surgery again and would recommend the surgery to other BRCA mutation carriers. Survey respondents also stated, however, that they would have benefitted from additional information about the impact of BSO on sexuality and cardiovascular health prior to undergoing the surgery [20]. Fertility is one of many concerns that physicians must address with high-risk patients considering BSO as an approach to cancer risk reduction.

Pregnancy and Cancer Risk

One topic that is highly relevant to the dialogue about fertility and cancer risk is the possible impact a pregnancy would have on cancer risk. Most large studies of BRCA1 and BRCA2 mutation carriers have shown that parity and number of live births positively correlate with a reduced breast cancer risk [21]. Additionally, fertility treatment has not been associated with an increased risk of breast cancer in BRCA mutation carriers. A case–control study of 1,380 pairs of BRCA1 and BRCA2 mutation carriers did not find an increased risk of breast cancer in women who had undergone fertility treatment compared to controls [22].

Communicating with High-Risk Patients

During the initial consultation with a high-risk patient of childbearing age, the objectives to be met include cancer risk assessment and discussion of strategies for cancer risk management. The approach to cancer risk reduction should take into account the patient's level of comprehension and concern about the risk of developing cancer, as well as the patient's childbearing goals. Typically, patients are referred for cancer risk assessment because of a strong family history of cancer or the identification of a deleterious genetic mutation. The patient's family cancer history is often discussed at the beginning of the encounter. A detailed family history includes affected relatives, types of cancer, cases of bilateral cancer, age at diagnosis, treatment procedures, and treatment outcomes. Any familial history of genetic testing is reviewed, and patients with a strong family history of cancer who have not yet had genetic testing are referred to a genetic counselor. The patient's personal medical history is also reviewed in detail. This includes prior illnesses and hospitalizations, medications, a review of prior breast imaging or biopsies, and an evaluation of hormone use including oral contraceptives and fertility treatments [23].

Focusing the discussion on how the patient's past medical history, family history, and mutation status affect the patient's personal risk of developing cancer helps to facilitate both patient and physician understanding of the patient's risk of developing cancer. This discussion also helps ensure that the patient is sufficiently informed and can actively participate in decision-making about preventive therapy. Risk assessment tools such as the Gail model, a breast cancer risk assessment tool, are often used to

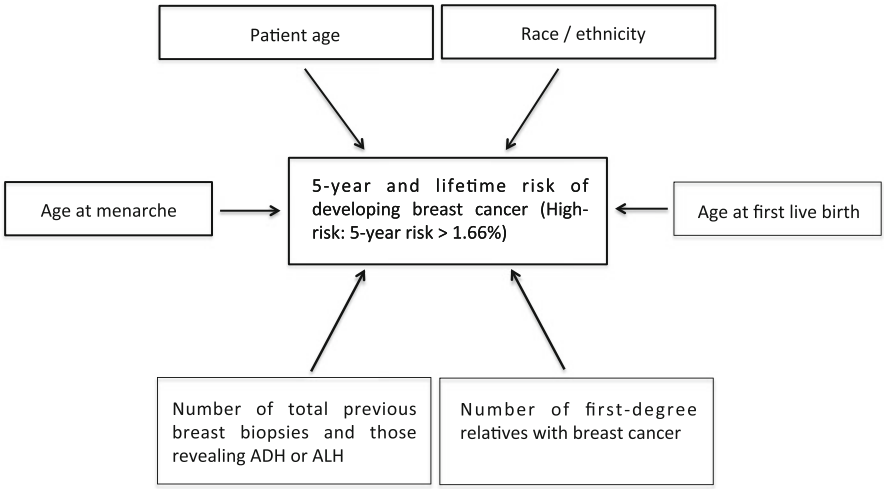

Fig. 5.1 Estimating 5-year and lifetime breast cancer risk using the Gail model. The Gail model is a risk assessment tool that estimates a patient's 5-year and lifetime risks of developing breast cancer. The model takes into account patient age, age of menarche, age at first birth or nulliparity, family history of breast cancer in a primary relative (mother, sister, daughter), race/ethnicity, number of prior breast biopsies, and number of prior biopsies yielding atypical hyperplasia [24]

help patients understand their risk relative to that of the general population. The Gail model estimates a woman's 5-year and lifetime risk of developing breast cancer (Fig. 5.1). The model accounts for patient age, age of menarche, age at first birth or nulliparity, family history of breast cancer in a primary relative (mother, sister, daughter), race/ethnicity, number of prior breast biopsies, and number of prior biopsies yielding atypical hyperplasia [24].

During the review of the patient's medical history, the patient's childbearing and lactation history are discussed, and it is at this time that the topic of fertility preservation may be introduced [23]. Having witnessed their relatives experience the impact of cancer treatment at a young age, many patients with a strong family history of cancer will prioritize their fertility concerns. To aid in the discussion of fertility preservation, often a basic question—such as, "Were you thinking about having a child?" or "Were you planning to have any more children?"—can help initiate the conversation [23]. Patients at high risk for breast or ovarian cancer face unique concerns related to fertility and cancer risk management, and it is critical that providers attempt to elicit and understand these concerns.

At this point, the consultation typically focuses on strategies for cancer prevention that take into account the patient's individual risk, her childbearing goals, and the patient's level of concern about her risk of developing cancer. When the strategies under consideration for cancer prevention pose a fertility threat, a discussion of available options for fertility preservation can be included in the high-risk consultation (Fig. 5.2). One of the advantages of discussing fertility preservation with high-risk patients (as opposed to patients who have already been diagnosed

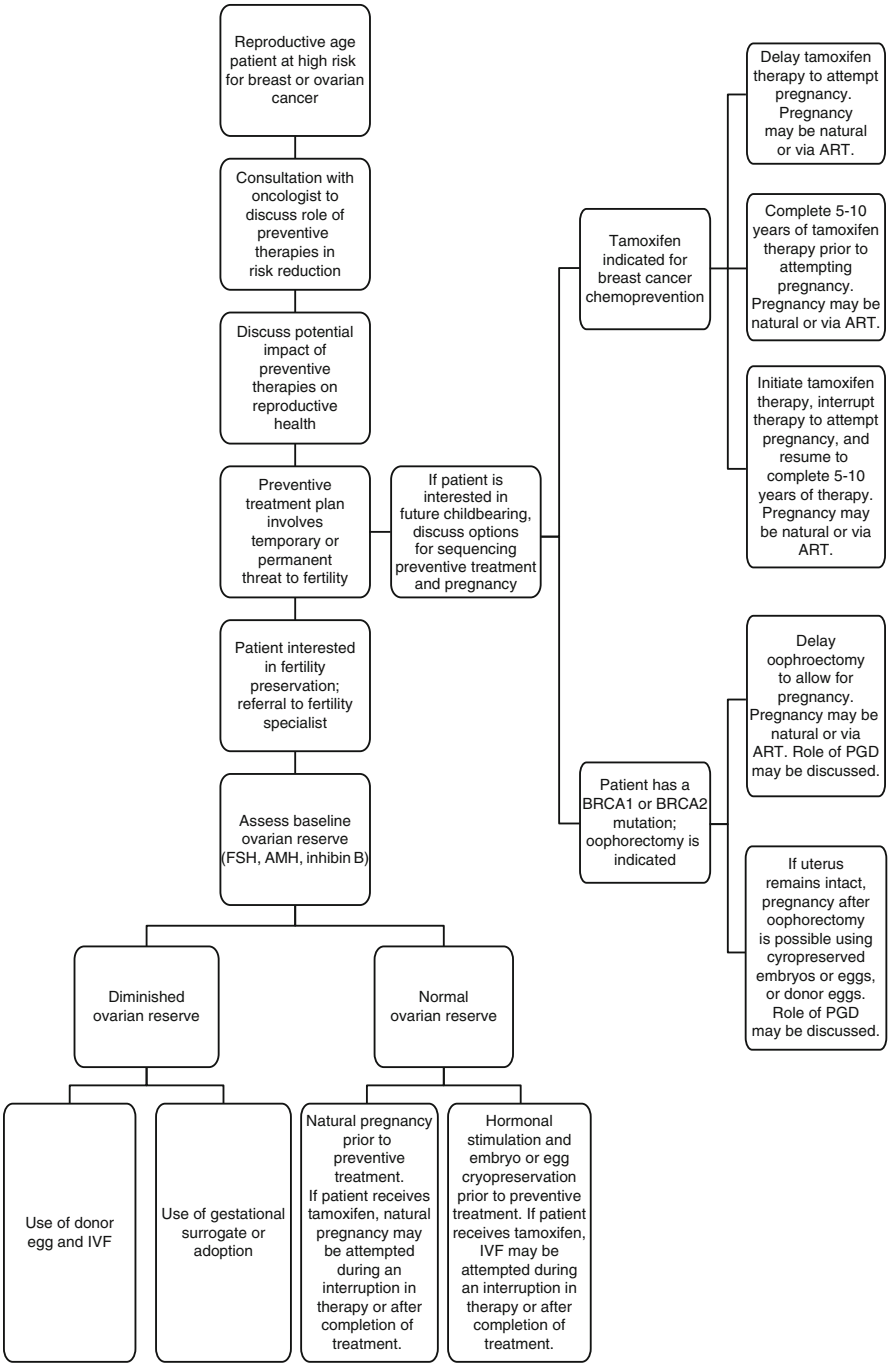

Fig. 5.2 Treatment guidelines for fertility preservation in young women at high risk for breast or ovarian cancer. A discussion about fertility as it pertains to preventive cancer treatment is an integral part of care for young patients at increased risk of breast and ovarian cancer. Referral to a

with cancer) is that there is ample time for the patient to consider her options without the time pressure imposed by the need for immediate cancer treatment. Ideally, the patient is referred for independent fertility preservation counseling with a fertility preservation specialist following the high-risk oncologic consultation. A second consultation with a fertility specialist ensures that the high-risk patient receives information about fertility preservation in a balanced and unbiased manner.

The following case examples explore the challenges that young patients face regarding the prioritization of preventive cancer therapy and reproductive goals. Case 1 describes a high-risk breast cancer patient who declined fertility preservation and suggests an alternative strategy for supporting fertility goals while managing cancer risk. Case 2 illustrates an approach to integrating fertility preservation into the preventive treatment plan for a BRCA1 mutation carrier.

Case #1: A High-Risk Breast Cancer Patient Who Declined Fertility Preservation

A 37-year-old woman presented for cancer risk assessment and preventive treatment. She had a personal history of atypical ductal hyperplasia and a family history of breast cancer, diagnosed in her mother at age 41. The patient's ADH had been diagnosed 2 years earlier by needle core biopsy and managed surgically by excision of the lesion. She had been receiving annual screening mammograms since the time of her ADH diagnosis but no other preventive therapy, and she expressed concern about her risk of developing breast cancer. The patient's 5-year Gail model risk score was calculated to be 2.5 %, compared to 0.4 % for an average-risk person. Patients with a 5-year predicted risk of breast cancer greater than 1.66 % are considered to be at high risk for breast cancer and are candidates for prophylactic tamoxifen therapy [10]. A 5-year course of tamoxifen was recommended for chemoprevention, along with annual screening mammography and a breast exam every 6 months. The patient

fertility specialist ensures that the patient receives accurate, unbiased information about fertility preservation. The fertility specialist can obtain information about the patient's premenopausal status by inquiring about menstrual history and measuring follicle stimulating hormone (FSH) on an early day in the menstrual cycle. Strategies for fertility preservation are determined based on the patient's ovarian function, preference, and decisions about preventive treatment. Patients receiving tamoxifen for breast cancer chemoprevention may attempt pregnancy naturally or via assisted reproductive technologies (ART) prior to initiating 5–10 years of therapy, during an interruption in a 5- to 10-year course of therapy, or after the completion of 5–10 years of treatment. BRCA mutation carriers may attempt pregnancy naturally or via ART prior to oophorectomy. It is possible for patients who retain an intact uterus to become pregnant after oophorectomy using ART. Preimplantation genetic diagnosis may be offered to BRCA mutation carriers who wish to reduce the risk of transmitting the mutation to offspring. AMH denotes antimullerian hormone, ART denotes assisted reproductive technologies, PGD denotes preimplantation genetic diagnosis, and IVF denotes in vitro fertilization. This figure was adapted from Fig. 2, Jeruss JS, Woodruff TK. Preservation of fertility in patients with cancer. The New England journal of medicine. 2009;360(9):902–11. Epub 2009/02/28

expressed concern about the possibility of experiencing menopausal side effects from tamoxifen but was reassured that menopausal symptoms are usually well tolerated. The patient agreed to initiate tamoxifen.

Because pregnancy is contraindicated during tamoxifen therapy and the patient would be at least 42 years of age at the conclusion of therapy, the issue of fertility preservation was discussed with the patient at the end of her initial consultation. The patient, who had a 5-year-old child, declined an oncofertility consultation and stated that she was not planning on having additional children. Nine months after initiating therapy, the patient returned to the clinic for a breast exam and expressed a desire to stop tamoxifen as she was now planning to have another child. She was again offered a fertility preservation consultation, but declined and stated that she wished to stop treatment to pursue a natural pregnancy and then resume tamoxifen therapy postpartum. The patient's individual high-risk status and the effect of stopping tamoxifen prematurely on this risk were reviewed. The patient was then advised to wait 8 weeks after stopping tamoxifen before attempting pregnancy; based on the half-life of tamoxifen, a 2-month "washout" period is recommended prior to becoming pregnant [25]. Eight months after stopping tamoxifen, the patient became pregnant. She resumed tamoxifen 6 months postpartum after she was finished breastfeeding and completed 4 additional years of therapy.

This case highlights the challenges that young high-risk patients face regarding how to balance preventive cancer treatment, childbearing, and breastfeeding. When a patient's childbearing plans change during her course of treatment, appropriate counseling should be provided and, within the context of the patient's treatment plan, effort should be made to support the patient's reproductive goals. Although treatment with at least a 5-year course of tamoxifen is recommended for chemoprevention, indirect evidence from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) suggests that antiestrogen therapy with tamoxifen can be delayed to allow for pregnancy [16, 26, 27]. Another study of patients who delayed initiation of tamoxifen therapy for 2 years and then completed a 5-year course showed a significantly improved disease-free survival rate (35 % reduction in recurrence risk) compared with the control group who did not take tamoxifen [28, 29]. Results from the Wisconsin Tamoxifen Study, where tamoxifen treatment was delayed 7–8 years, also showed a benefit for patients in the treatment versus control group [28, 30]. Together, these data support the potential for a tailored delay in tamoxifen therapy to allow for pregnancy, with the expectation that the patient is counseled to ultimately complete 5–10 years of therapy.

Case #2: A High-Risk Patient with a BRCA1 Mutation Who Desired Fertility Preservation

A 35-year-old woman with a family history of breast and ovarian cancer presented for cancer risk assessment and preventive treatment. Her sister was diagnosed with ovarian cancer at the age of 39, her mother was diagnosed with breast cancer at the age of 42, and her maternal grandmother died from ovarian cancer at the age of 51.

The patient was referred for genetic counseling and found to have a deleterious mutation in the BRCA1 gene. Preventive approaches discussed with her included breast cancer screening every 6 months with staggered MRI and mammograms, ovarian cancer screening with serum CA-125 and twice annual transvaginal ultrasound, BSO, and prophylactic mastectomy. The patient was interested in prophylactic mastectomy and considering risk-reducing BSO, but was concerned about the associated loss of fertility. She strongly desired a child, but did not currently have a partner and was unsure about the time in her life when she would be ready to conceive.

After consultation with a gynecological oncologist regarding BSO, the patient met with an oncofertility patient navigator and a reproductive endocrinologist. The reproductive endocrinologist discussed the patient's options for fertility preservation, including embryo cryopreservation with donor sperm and oocyte cryopreservation. Although oocyte cryopreservation has previously been offered on an experimental basis, recent guidelines from the American Society for Reproductive Medicine (ASRM) indicate that the procedure should no longer be considered experimental. Based on an examination of nearly 1,000 studies, the ASRM reports that pregnancy rates for in vitro fertilization and intracytoplasmic sperm injection (IVF/ICSI) are similar with cryopreserved versus fresh oocytes. Additionally, available data show no increase in chromosomal abnormalities or birth defects among children born from cryopreserved oocytes compared with those born from IVF/ICSI with fresh oocytes or the general population [31]. Ovarian tissue cryopreservation for BRCA1 mutation carriers would be considered experimental, however, with the majority of the resected ovarian tissue sent for pathologic analysis. A fraction of the ovarian tissue could be preserved for potential oocyte extraction with the hope of implementing currently developing technologies for in vitro oocyte growth and maturation, but none of the tissue would be intended for future reimplantation given the persistent risk of malignant transformation.

The patient also expressed concern about passing the BRCA mutation down to her future children and was advised that preimplantation genetic diagnosis (PGD) could be performed on her embryos to minimize the risk. She opted for oocyte cryopreservation and completed successful ovarian stimulation and oocyte harvest. Shortly after completing fertility preservation, the patient underwent risk-reducing BSO and prophylactic mastectomy. Six months after surgery, the patient stated that she was very satisfied with her decision to pursue risk-reducing BSO and felt more at ease about her risk of developing breast and ovarian cancer. The patient expressed that preserving her fertility had allowed her to pursue surgery without significant regret and served as a great source of comfort to her as she experienced the effects of surgical menopause. Three years later, the patient is married and she and her husband are considering having a child using the patient's banked oocytes.

Fertility concerns are a major factor for high-risk patients when making decisions about cancer risk management. The options for fertility preservation have the potential to influence patients' selection of risk-reducing strategies and when to pursue risk reduction. Thus, it is critical for patients to be educated about their options for fertility preservation early on in the process of cancer risk management. Oocyte and embryo cryopreservation are options for high-risk women who do not have a partner or who plan to undergo risk-reducing BSO prior to completing their families. For

BRCA mutation carriers concerned about passing the mutation on to their children, PGD offers a means to minimize this risk. Several studies have shown that high-risk patients often do not receive adequate information from their physicians about fertility preservation and PGD, and many are not aware of PGD as an option [32–34]. This information gap for high-risk women highlights the need for more effective education about fertility preservation and PGD and the importance of the referral to an oncofertility specialist for this patient population.

Conclusions

Patients at high risk for breast and ovarian cancer face complex decisions about how to prioritize preventive treatment, childbearing, and breastfeeding. Fertility preservation offers the possibility for high-risk patients—many of whom wish to initiate prophylactic therapy at a young age—to maintain the ability to have biologic children. It is critical that physicians who care for high-risk patients take time to approach the issues unique to this patient population with sensitivity and empathy. Interventions for cancer risk reduction should take into account patients' reproductive goals. Educating patients about fertility preservation early on in the discussion about prevention strategies allows patients the opportunity to receive appropriate counseling, consider the available options, and then incorporate fertility preservation into their risk reduction plans if desired.

It is an ongoing challenge for physicians to ensure that the high-risk patient has an accurate understanding of her cancer risk compared with the general population, and is sufficiently informed to actively participate in decision-making about preventive treatment and fertility preservation. Additionally, the physician should ensure that plans for fertility preservation complement the approach to cancer risk reduction and do not cause significant delays in the initiation of risk-reducing therapy. Given that high-risk patients are healthy and working to take a preemptive role in the preservation of good health, it follows that these patients would also be motivated to protect their fertility if given the option. Fertility preservation services are currently available to all high-risk patients under the age of 45 and to those who convey interest.

Acknowledgements This work was supported by the Oncofertility Consortium NIH 5UL1DE019587 and the Specialized Cooperative Centers Program in Reproduction and Infertility Research NIH U54HD076188.

References

1. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003;72:1117–30.
2. National Cancer Institute. PDQ genetics of breast and ovarian cancer. Bethesda, MD: National Cancer Institute; 2012.

3. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007; 25:1329–33.
4. Lindor NM, McMaster ML, Lindor CJ, Greene MH. Concise handbook of familial cancer susceptibility syndromes—second edition. J Natl Cancer Inst Monogr. 2008;1–93.
5. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA. Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer. 1997;71:800–9.
6. Stratton JF, Pharoah P, Smith SK, Easton D, Ponder BA. A systematic review and meta-analysis of family history and risk of ovarian cancer. Br J Obstet Gynaecol. 1998;105:493–9.
7. Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. N Engl J Med. 2005;353:229–37.
8. Ashbeck EL, Rosenberg RD, Stauber PM, Key CR. Benign breast biopsy diagnosis and subsequent risk of breast cancer. Cancer Epidemiol Biomarkers Prev. 2007;16:467–72.
9. American Cancer Society. Breast cancer facts & figures 2011–2012. Atlanta, GA: American Cancer Society; 2011.
10. Dunn BK, Ford LG. Breast cancer prevention: results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) breast cancer prevention trial (NSABP P-1: BCPT). Eur J Cancer. 2000;36 Suppl 4:S49–50.
11. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. 2013;381(9869):805–16.
12. Abusief ME, Missmer SA, Ginsburg ES, Weeks JC, Partridge AH. The effects of paclitaxel, dose density, and trastuzumab on treatment-related amenorrhea in premenopausal women with breast cancer. Cancer. 2010;116:791–8.
13. Port ER, Montgomery LL, Heerdt AS, Borgen PI. Patient reluctance toward tamoxifen use for breast cancer primary prevention. Ann Surg Oncol. 2001;8:580–5.
14. Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. CA Cancer J Clin. 2009;59:56–66.
15. McCowan C, Shearer J, Donnan PT, et al. Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. Br J Cancer. 2008;99:1763–8.
16. Hulvat MC, Jeruss JS. Fertility preservation options for young women with breast cancer. Curr Opin Obstet Gynecol. 2011;23:174–82.
17. Bast Jr RC, Hennessy B, Mills GB. The biology of ovarian cancer: new opportunities for translation. Nat Rev Cancer. 2009;9:415–28.
18. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med. 2002;346:1616–22.
19. Narod SA, Risch H, Moslehi R, et al. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. N Engl J Med. 1998;339:424–8.
20. Campfield Bonadies D, Moyer A, Matloff ET. What I wish I'd known before surgery: BRCA carriers' perspectives after bilateral salipingo-oophorectomy. Fam Cancer. 2011;10:79–85.
21. Cullinane CA, Lubinski J, Neuhausen SL, et al. Effect of pregnancy as a risk factor for breast cancer in BRCA1/BRCA2 mutation carriers. Int J Cancer. 2005;117:988–91.
22. Kotsopoulos J, Librach CL, Lubinski J, et al. Infertility, treatment of infertility, and the risk of breast cancer among women with BRCA1 and BRCA2 mutations: a case-control study. Cancer Causes Control. 2008;19:1111–9.
23. Jeruss JS. Discussing fertility preservation with breast cancer patients. Cancer Treat Res. 2010;156:461–6.
24. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989;81:1879–86.
25. Braems G, Denys H, De Wever O, Cocquyt V, Van den Broecke R. Use of tamoxifen before and during pregnancy. Oncologist. 2011;16:1547–51.
26. Hershman DL, Kushi LH, Shao T, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol. 2010;28:4120–8.

27. Grunfeld EA, Hunter MS, Sikka P, Mittal S. Adherence beliefs among breast cancer patients taking tamoxifen. Patient Educ Couns. 2005;59:97–102.
28. Gradishar WJ, Hellmund R. A rationale for the reinitiation of adjuvant tamoxifen therapy in women receiving fewer than 5 years of therapy. Clin Breast Cancer. 2002;2:282–6.
29. Delozier T, Switsers O, Genot JY, et al. Delayed adjuvant tamoxifen: ten-year results of a collaborative randomized controlled trial in early breast cancer (TAM-02 trial). Ann Oncol. 2000;11:515–9.
30. Love RR, Olsen MR, Havighurst TC. Delayed adjuvant tamoxifen in postmenopausal women with axillary node-negative breast cancer: mortality over 10 years. J Natl Cancer Inst. 1999;91:1167–8.
31. Practice Committees of American Society for Reproductive Medicine; Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. Fertil Steril. 2012;99(1):37–43.
32. Quinn GP, Vadaparampil ST, Tollin S, et al. BRCA carriers' thoughts on risk management in relation to preimplantation genetic diagnosis and childbearing: when too many choices are just as difficult as none. Fertil Steril. 2010;94:2473–5.
33. Quinn G, Vadaparampil S, Wilson C, et al. Attitudes of high-risk women toward preimplantation genetic diagnosis. Fertil Steril. 2009;91:2361–8.
34. Vadaparampil ST, Quinn GP, Knapp C, Malo TL, Friedman S. Factors associated with preimplantation genetic diagnosis acceptance among women concerned about hereditary breast and ovarian cancer. Genet Med. 2009;11:757–65.