

Oncology Advanced Practitioners and Breast Cancer Prevention

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Abstract

One in eight American women will be diagnosed with breast cancer. Advanced practitioners in oncology can offer risk assessments, counseling, genetic testing, and make both behavioral and pharmacologic recommendations for breast cancer risk reduction. The role of oncology advanced practitioners in conjunction with genetic counselors is key in what is now considered the standard of care. This article will summarize the current state of breast cancer prevention and the role of oncology advanced practitioners.

One in eight American women will be diagnosed with breast cancer. It is estimated that 276,480 women and 2,620 men in the United States will be diagnosed with invasive breast cancer and 48,530 people will be diagnosed with non-invasive (in situ) breast cancer (American Cancer Society, 2020). An estimated 42,690 Americans will die from breast cancer in 2020 (American Cancer Society, 2020). It is also estimated that 30% of all cancers diagnosed in women will be breast cancer.

Between 2002 and 2003, invasive breast cancer rates began decreasing, likely due to the decreased use of hormone replacement therapy following the 2002 publication of the Women's Health Initiative that found a higher risk of breast cancer in hormone replacement therapy us-

ers (American Cancer Society, 2017; Coombs, Cronin, Taylor, Freedman, & Boyages, 2010; Ravdin et al., 2007). This decline in incidence occurred primarily in Caucasian women, in women who were 50 years of age and older, and for estrogen receptor (ER)-positive disease (American Cancer Society, 2017). In the following year, the incidence rate of breast cancer was stable, but the trends varied by race and age.

PERCEIVED NEED

Patients and health-care providers alike are interested in breast cancer prevention. Other disciplines besides oncology often seek resources for up-to-date recommendations from oncology professionals. Table 1 lists the most common referral sources to a high-risk cancer clinic. The most common reason for referral is the

Table 1. Most Common Referral Sources for High-Risk Cancer Clinics

- Patients
- Surgeons
- Tumor boards
- Oncology team
- Genetic counselors
- Health departments
- Rural health clinics
- Obstetrics and Gynecology
- Family practice/Internal medicine
- Breast centers/Mammography centers

patient's own perceived risk of breast cancer or the provider's assessment of a patient's family history of breast cancer. Another common reason for referral is for discussion of risk related to menopausal hormone therapy. The oncology advanced practitioner (AP) can be a key provider to provide this education.

ROLES OF ONCOLOGY APs IN BREAST CANCER PREVENTION

The Role of the Oncology Nurse Practitioner or Physician Assistant

Oncology APs in a high-risk cancer clinic will first perform a comprehensive risk assessment after a thorough history. There are known risk factors for cancer, some of which are modifiable and some that are not. Known nonmodifiable risk factors include age, sex, race, earlier age at menarche, age at first live birth (or nulliparity), later menopause, family history of breast cancer, breast density, bone mineral density, inherited genetic mutations, and proliferative breast disease (Chen, 2019). Modifiable risk factors might include lifestyle and environmental factors such as obesity, alcohol consumption, smoking, night-shift work, exposure to therapeutic ionizing radiation, and use of exogenous

hormones (Chen, 2019). There are also protective factors that can reduce the breast cancer risk such as breastfeeding, oophorectomy before age 45, and regular physical activity (Chen, 2019).

There are several breast cancer risk prediction models that may be used. The most common models are the Breast Cancer Risk Assessment Tool, Claus model, and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA). Table 2 lists multiple risk assessment models that may be used. Models may be used to assess the risk of developing a breast cancer, the risk of carrying a genetic mutation for breast cancer, or both (Cintolo-Gonzalez et al., 2017). There are strengths and limitations to each model, and the selection of model(s) must be appropriate for the individual.

Once breast cancer risk has been determined and presented to the patient, recommendations for screening can be made. The National Comprehensive Cancer Network (NCCN) Guidelines (2020a) give screening recommendations for different groups at higher risk, such as those who have a lifetime risk of more than 20% or patients who have received thoracic radiation therapy between the ages of 10 and 30. Other categories include those with a Gail model risk of more than 1.7% or women with a history of lobular carcinoma in situ (LCIS) or those with atypical hyperplasia. Screening and follow-up recommendations include clinical breast exam, self-breast exam, annual mammography with or without tomosynthesis, annual breast MRI, and consideration of risk reduction strategies. This is the opportune time to teach women how to perform a breast self-exam. A three-generation family history will determine if referral to genetics is appropriate.

Table 2. Common Breast Cancer Risk Assessment Models

Model	Link
Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)	https://www.nature.com/articles/s41436-018-0406-9#change-history
BRCAPRO	https://projects.iq.harvard.edu/bayesmendel/models
Breast Cancer Risk Assessment Tool (Gail model)	https://bcrisktool.cancer.gov
Breast Cancer Surveillance Consortium Risk Calculator	http://tools.bcsc-scc.org/BC5yearRisk
iPrevent	https://www.petermac.org/iprevent
Tyrer-Cuzick Model (IBIS)	http://www.ems-trials.org/riskevaluator

Part of comprehensive cancer preventative care includes assessment of family history of cancer care. Hereditary cancer genetic testing and breast cancer prevention have gone hand in hand since the conception of genetic testing for hereditary cancer in the early 1990s. This began with the discovery of and ability to test for pathogenic variants in the *BRCA1* and *BRCA2* genes. *BRCA1* and *BRCA2* are highly penetrant genes that cause a woman's risk for breast cancer to increase to 45% to 65% by age 70 if she carries a pathogenic variant in either gene (Centers for Disease Control and Prevention, 2014; Chen & Parmigiani, 2007; National Cancer Institute, 2015). Individuals with pathogenic variants in these genes also have increased risk for other cancers including ovarian cancer, pancreatic cancer, and melanoma. The identification of a hereditary predisposition to certain cancer types enables increased cancer surveillance to detect cancer at more treatable stages or allow for prophylactic surgical options or medications and lifestyle changes to reduce overall risk for these cancer types.

The Role of the Genetic Counselor

As knowledge expands, genetic testing is now an integral part of prevention as well as cancer care. Recently, more genes have been discovered that are associated with hereditary cancer, and treatment options are emerging based on the genetic composition of tumors. Recent technologic advances have enabled simultaneous testing for mutations in multiple genes (panel genetic testing) via next-generation sequencing, with results available in a few weeks. Genetic testing for cancer is now substantially more complex, with at least 80 hereditary cancer genes now available for clinical genetic testing and numerous laboratories performing genetic testing. Table 3 is a list of genes available for clinical testing and associated with increased risk for breast cancer. The rapid growth of genetics in the oncology field leads to challenges. With more extensive and widespread genetic testing, there is increased detection of genes with moderate penetrance without established clinical guidelines and of variants of uncertain significance (VUS) or genetic variants unknown to be either disease-causing or benign (Lumish et al., 2017). 5% to 10% of all breast cancers are heredi-

tary and due to mutations in monogenic, highly penetrant genes, and 30% occur in women with a family history of breast cancer and may be due to genes and genetic variants of moderate risk (Lynch, Silva, Snyder, & Lynch, 2008). The clinical implications of moderately penetrant or moderate risk genes are still being determined. This presents difficulty in the application of this knowledge regarding cancer prevention.

With the continual growth of information and the ever-evolving understanding of genetics and its correlation to cancer predisposition, the public, general health-care professionals, and even oncology specialists cannot expect to remain fully informed on this complex topic, much less provide the complicated care required for patients and their families in the setting of genetic testing. A health-care provider dedicated to the specialty of cancer genetics is necessary (Swiderski, 2011).

Genetic counselors are uniquely trained to navigate the complexities of hereditary cancer genetic testing for patients. The purpose of cancer genetic counseling is to educate clients about their chance of developing cancer, help them derive personal meaning from cancer genetic information, and empower them to make educated, informed decisions about genetic testing, cancer screening, and cancer prevention (Trepanier et al., 2004). Studies show that genetic counseling can alleviate cancer-specific distress (Mikkelsen, Sunde, Johansen, & Johnsen, 2009), lower levels of worry (Bjorvatn et al., 2007), create higher accuracy in perceived cancer risks (Moyer, 2014), and provide more appropriate genetic testing which, in turn, saves health-care dollars (Haidle et al., 2017). Genetic testing for hereditary causes for cancer is an integral part of comprehensive cancer care and prevention. Genetic counselors are well equipped to guide patients and their families through this difficult time. Genetic counselors also serve as a vital resource for health-care providers.

The Role of the Oncology Pharmacist

The NCCN Guidelines (2020b) offer risk reduction strategies for women with a life expectancy of more than 10 years. These might include a risk-reducing agent, prophylactic surgery, and lifestyle modifications. The oncology pharmacist is part of the multidisciplinary team in breast cancer prevention.

Table 3. Genes Associated With Increased Risk of Breast Cancer (Not All Inclusive)

Gene (in alphabetical order)	Lifetime risk of breast cancer ^a	Other cancers at increased risk	Name of associated syndrome
<i>ATM</i>	17%-52%	Ovarian cancer, pancreatic cancer, prostate cancer	
<i>BARD1</i>	20%-25%	None known at this time	
<i>BRCA1/2</i>	Up to 87%	Ovarian cancer	Hereditary breast and ovarian cancer syndrome
<i>BRIP1</i>		Ovarian cancer	
<i>CDH1</i>	39%-60%	Stomach cancer	Hereditary diffuse gastric cancer syndrome
<i>CHEK2</i>	20%-37%	Colorectal cancer, prostate cancer	
<i>MRE11A</i>	b	Ovarian cancer	
<i>MSH6</i>		Colorectal, endometrial, ovarian, gastric, small intestine, liver, gallbladder, upper urinary tract, and brain cancers	Lynch syndrome
<i>NBN</i>	20%-30%	Brain tumors, prostate cancer	Nijmegen breakage syndrome
<i>NF1</i>	40%-50%	Brain and spinal tumors, neurofibroma, optic glioma	
<i>PALB2</i>	33%-58%	Ovarian cancer	
<i>PMS1/2</i>	b	Colorectal, endometrial, ovarian, gastric, small intestine, liver, gallbladder, upper urinary tract, and brain cancers	Lynch syndrome
<i>PTEN</i>	77%-85%	Colon cancer, endometrial cancer, kidney cancer, skin cancer, thyroid cancer	PTEN hamartoma tumor syndrome; Cowden syndrome
<i>RAD51D</i>	26%	Ovarian cancer	
<i>STK11</i>	32%-54%	Colorectal cancer, endometrial cancer, lung cancer, ovarian cancer, pancreatic cancer, stomach cancer	Peutz-Jegher syndrome
<i>TP53</i>	50% or more	Adrenocortical carcinoma, bone and soft tissue cancers (sarcomas), brain tumors, colon cancer, leukemia	Li-Fraumeni syndrome

Note. Retrieved from Online Mendelian Inheritance In Man (2020); Susan G. Komen. (2020).

^aThe age up to which lifetime risk was estimated varied among studies.

^bRisk estimate not available, but breast cancer was noted in higher rates than in that of the general population without this genetic mutation.

The oncology pharmacist plays an important role in the care of women at high risk for breast cancer. Several factors influence the choice of appropriate pharmacologic interventions for risk reduction in high-risk patients. These issues may include patient-specific factors affecting medication choices, the patient's ability to adhere to a drug regimen, potential side effects, as well as drug interactions that may decrease the intended effects of therapy or increase toxicity.

Currently, only one class of drugs, selective estrogen receptor modifiers (SERMs), which includes tamoxifen and raloxifene, are FDA approved for

risk reduction of breast cancer in premenopausal (tamoxifen) and postmenopausal (raloxifene and tamoxifen) high-risk patients. Several trials proved benefit in both pre- and postmenopausal women. Overall, this class provides 31% to 67% reduction in ER-positive breast cancer incidence (Visvanathan et al., 2013). Newer treatment options in the postmenopausal population are aromatase inhibitors (AIs), exemestane, anastrozole, and letrozole. However, these medications are not FDA approved for the prevention of breast cancer but only for the treatment of hormone receptor-positive breast cancer patients; therefore, this use is considered

off-label therapy (Visvanathan et al., 2013). Nevertheless, recent trials (Goss et al., 2011; Jenkins et al., 2008) explored the use of these medications in the postmenopausal patient population and found a reduction in ER-positive breast cancer from 58% to 73%. Selective estrogen receptor modifiers act by antagonizing the estrogen receptor in the breast tissue while agonizing receptors in both endometrial and bone tissues. This antagonism in the breast tissue leads to a reduction in breast cancer. Aromatase inhibitors act by blocking the effects of aromatase, an enzyme responsible for the production of estrogen from the precursor androgen. This reduces circulating estrogen throughout the body and decreases the risk of breast cancer.

Adherence can be an issue with any oral treatment, but especially when a preventive medication is prescribed. Education is a key component of any oral medication prescription. Oncology APs can start a discussion with the patient informing them of possible side effects and appropriate handling of the chosen regimen (Hicks, Cope, Novak, & Scherer, 2017). Selective estrogen receptor modifiers and AIs both reduce the risk of breast cancer, but the mechanisms cause different spectrums of adverse effects. Common side effects for SERMs include hot flashes, depression, and mood swings, while AIs are generally associated with hot flashes, depression, mood swings, decreases in bone density, and joint pain. Major side effects that may preclude the use of certain medications include risk for endometrial cancer and increased risk of venous thromboembolisms (deep vein thrombosis and pulmonary embolism) with SERMs and increased bone degradation causing an increase in fractures with AIs. Special consideration should be given to patients at higher risk for complications from these side effects. Determination of the right therapy for a patient considers both comorbid conditions that may preclude use of a medication strategy and mitigation strategies for possible side effects. Counseling points should include measures for dealing with hot flashes (see Table 4). Joint pain with AIs will often subside after continued movement throughout the day. Table 5 describes methods of dealing with these arthralgias. It should be noted, however, that due to the lack of well-designed studies, most approaches for the treatment of AI-induced arthralgias are empiric.

Table 4. Strategies for Managing Hot Flashes in the Individual at High Risk for Breast Cancer

- Gabapentin
- Venlafaxine
- Other medications such as paroxetine, bupropion, citalopram, fluoxetine
- Alternative therapy such as acupuncture, hypnosis, relaxation therapy
- Clonidine
- Cognitive behavior techniques
- Physical relief items such as pillow toppers, back pads, fans, neck coolers
- Exercise
- Weight loss
- Vitamin E
- Yoga

Note. Due to the lack of well-designed studies, most approaches for the treatment of hot flashes are empiric. Information from Barton et al (2018); Carroll & Kelley (2009); Garcia et al. (2015); Johns et al. (2016); Kaplan & Mahon (2014); Lesi et al. (2016); Morrow, Mattair, & Hortobagyi (2011); Thurston et al. (2015).

Discussion about adherence is also needed. A study examining adherence to chemoprevention in high-risk patients estimated that only 60% of patients would finish 5 years of therapy in a high-risk breast clinic (Roetzheim et al., 2015). Ideally,

Table 5. Literature Review of the Management of Arthralgias Secondary to Aromatase Inhibitors

- Consider switching to another aromatase inhibitor
- Vitamin D as needed to maintain normal levels (30–74 ng/mL)
- High-dose NSAIDs or selective COX-2 inhibitors short-term therapy, then titration to minimum effective dosage
- Acupuncture
- Regular exercise
- Concurrent use of calcium and bisphosphonate as appropriate
- Duloxetine 30 mg daily × 7 days, then 60 mg thereafter
- Referral to rheumatology as appropriate
- Analgesics
- Anti-inflammatories
- Nonpharmacologic treatments: heat, hot showers, physical exercise (load-bearing), smoking cessation, weight loss
- Physical therapy or occupational therapy
- Glucosamine

Note. Due to the lack of well-designed studies, most approaches for the treatment of AI-induced arthralgias are empiric. NSAID = nonsteroidal anti-inflammatory drug. Information from Brant (2012); Briot et al. (2010); Chlebowski (2009); Crew et al. (2007); Henry et al. (2011); Henry, Giles, & Starnes (2008); Khan et al. (2008); Presant et al. (2007).

the patient is asked about adherence at every visit and documentation is made (Ramirez & Campen, 2017). Finally, APs must assess for possible drug-drug interactions with patients and ensure the medication list is updated. Patient education includes reminders to consult with a pharmacist before adding any new medications so that potential new interactions can be identified and appropriate steps can be taken to enhance the care of the patient pharmacologically. This is especially important with oral oncolytics, as any interaction may increase the toxicity or decrease the efficacy of the treatment (Hicks et al., 2017). For example, tamoxifen is a substrate of liver degradation (CYP2D6), and medications that induce or inhibit this enzyme, such as some selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors, can greatly decrease circulating concentrations of the oncolytic. Table 6 lists drugs that might interact with tamoxifen or raloxifene. Drugs that could potentially interact with an AI are noted in Table 7.

SURGICAL AND BEHAVIORAL RECOMMENDATIONS FOR THE HIGH-RISK PATIENT

Prophylactic surgery may be considered for those at the highest risk for breast cancer. This could include prophylactic bilateral mastectomy or prophylactic oophorectomy. Prophylactic mastectomy is generally only considered in women with a genetic mutation that confers a high risk of breast cancer, compelling family history, or potentially those with a history of thoracic radiation before 30 years of age (NCCN, 2020b). Data have supported the protective effects of prophylactic bilateral oophorectomy; however, there is now some

conflicting data that may refute this in women with *BRCA1* or *BRCA2* mutation (NCCN, 2020b; Heemskerk-Gerritsen et al., 2015).

Lifestyle modifications may also reduce the risk of breast cancer. Data from the Women's Health Initiative Dietary Modification Trial, a randomized clinical trial examining the effects of a low-fat diet on breast cancer incidence and outcome, showed that the adoption of a low-fat diet (increased portions of vegetables, fruits, and grains) significantly reduces the risk of death from breast cancer in postmenopausal women. The study group of 48,835 postmenopausal women aged 50 to 79 years with no previous history of breast cancer had 8% fewer breast cancers (although rates were not statistically significant; Chlebowski et al., 2019). Other lifestyle modification discussions could include smoking cessation and decrease in alcohol use. Daily exercise for 30 minutes a day, 5 days a week is encouraged. Walking, a weight-bearing exercise, is known to aid in the prevention of osteoporosis as well as decrease breast cancer risk (Augustin et al., 2017; Curry & Hogstel, 2001; Kraschnewski & Schmitz, 2017).

Participation in a clinical trial may be appropriate, especially for those with a genetic mutation. Data about available preventative trials may be accessed at <https://clinicaltrials.gov/ct2/results?term=prevention&cond=breast+cancer>. Those with certain genetic mutations may also be entered into a registry so that more may be learned about the natural history of certain mutations. Knowledge gained will contribute to finding more effective ways to manage the risk for developing cancer.

CONCLUSION

The management of the person at high risk for breast cancer is multidisciplinary. Oncology advanced practitioners, such as nurse practitioners,

Table 6. Selective Estrogen Reuptake Modulator Drug Interactions

Tamoxifen		Raloxifene
Amiodarone	Fluoxetine	No major interactions
Bupropion	Paroxetine	
Carbamazepine	Phenytoin	
Diltiazem	Rifampin	
Duloxetine	St. John's wort	
Sertraline		

Table 7. Aromatase Inhibitor Drug Interactions

Exemestane	Anastrozole	Letrozole
St. John's wort	Estrogen derivatives	No major interactions
Phenytoin		
Rifampin		
Carbamazepine		

physician assistants, and pharmacists, along with genetic counselors, each provide particular skills and up-to-date knowledge to address breast cancer risk reduction. ●

Disclosure

The authors have no conflict of interest to disclose.

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