Primary Care Concerns In Breast Cancer Patients

Mary Anne Fenton, MD, FACP

Breast cancer is the most frequent solid tumor in women in **the United States** (**US**) and the second leading cause of cancer-related deaths. The **Surveillance, Epidemiology and End Results** (**SEER**) program of the National Cancer Institute projects 192,370 women will have been diagnosed with breast cancer in the year 2009.[1] Breast cancer incidence in the US declined by 6.7% in 2003,[2] a trend attributed to a decrease in use of **hormone replacement therapy** (**HRT**) after the Women's Health Initiative randomized controlled trial noted an excess of thromboembolic events and breast cancer secondary to HRT.[3]

Breast cancer mortality in the US has declined since 1990; this decline is thought to be due to early detection by mammography and effective adjuvant therapy.[4] Adjuvant chemotherapy reduces the annual risk of death by 38% for women younger than 50 and 20% for women age 50 to 69 years. Adjuvant endocrine therapy decreases the annual rate of mortality by 31% regardless of age for hormone receptor positive tumors.[5] Risks and benefits, patient's age and comorbid illnesses should be factored in recommendations regarding adjuvant therapy.

This review discusses prevention strategies and follow-up care of breast cancer survivors.

Identification of patients at high risk of developing breast cancer

Breast cancer risk factors include genetic and modifiable risk factors, and 75% of patients have no risk factors. Factors that may increase the baseline risk by up to 2-4-fold are listed in Table 1. Patients noted to be at increased risk may consider the option of chemoprevention with a **selective estrogen receptor modulator** (**SERM**), such as tamoxifen.

Several tumor suppressor genes are associated with an increase in breast cancer, including *BRCA1* and *BRCA2* gene mutations. Family history may identify patients at an increased risk due to *BRCA* with the option for increased surveillance or prevention. Family history should include a careful review of paternal and maternal family history of 3-4 generations, and age of onset of malignancies in the family. Patients with family history risk factors described in Table 2, with multiple family members with breast cancer and or ovarian cancer at early age of onset should be considered for referral for genetic counseling. The increased risk of breast cancer associated with *BRCA* mutations is estimated at 57% for *BRCA1* and 49% for *BRCA2* mutation carriers and ovarian cancer risk of 40% for *BRCA1* and 18% for *BRCA2* mutation carriers.[6]

Genetic counseling includes review of family history by a certified geneticist, calculation of risk of having a gene mutation associated with an increase in cancer, and discussion of the pros, cons, cost and insurance coverage for genetic testing (approximately $3000.00). Genetic testing is not universally covered, but is usually based on a patient's risk for the gene mutatio. The genetic counselor will review with the insurer if the test will be covered. Results of testing include the presence of a deleterious mutation, absence of a mutation, or the presence of a gene mutation of unknown significance.

Table 1. Risk Factors For Breast Cancer

- Female gender
- Age
- Family history
- Atypia and hyperplasia
- Prior history of breast cancer
- Exogenous estrogen therapy
- Early menarche
- Late menopause
- Nulliparity

Breast Cancer Chemoprevention

Chemoprevention trials show risk reduction benefits of 48% for invasive and/or noninvasive breast cancer with SERMs. Potential side effects associated to SERMs include an increase in thromboembolic events, cataracts and endometrial cancer. Practitioners may consider chemoprevention with a SERM such as tamoxifen for premenopausal patients and raloxifen for postmenopausal patients with a five-year projected breast cancer risk of >1.66%, (NCI breast Cancer Risk assessment tool available at http://www.cancer.gov/bcrisktool), or a history of lobular carcinoma *in situ* or atypical ductal hyperplasia. Side effects include hot flashes and increase in thromboembolic events and, for tamoxifen only, increase in endometrial cancer. The risk/benefit of chemoprevention favors

Table 2. Consider For Genetic Counseling

Non-Eastern European Jewish Women

- 3 or more first or second degree relatives at any age with breast cancer
- Breast and ovarian cancer in first and second degree relatives
- 2 first degree relatives with breast cancer, one diagnosed at or below the age of 50
- First degree relative with bilateral breast cancer
- Two or more first or second degree relatives with ovarian cancer
- History of male breast cancer
- First or second degree relative with breast and ovarian cancer

Eastern European Jewish women

- Any first degree relative with breast cancer or ovarian cancer
- 2 second degree relatives on the same side of the family with breast or ovarian cancer

Table 3. Adjuvant Endocrine Therapy Side Effects

Tamoxifen (pre and postmenopausal)
- Leg cramps
- Hot flashes
- Vaginal discharge
- Vaginal bleeding
- Uterine hyperplasia
- Bladder problems
- Endometrial cancer and sarcoma (rare)
- Cataracts
- Thromboembolic events

Aromatase inhibitors (postmenopausal)
- Hot flash
- Vaginal dryness
- Loss of bone density

women who are at low risk for thromboembolic events, women post hysterectomy and women with a higher breast cancer risk such as lobular neoplasia or atypical hyperplasia.

Adjuvant Treatment of Invasive Breast Cancer

Breast cancer prognostic features of size, lymph node involvement, grade, hormone receptor status, patient age, and menopause status are useful to stratify the risk of systemic recurrence. Predictive factors for response to therapy include hormone receptor status, and epidermal growth factor Her-2-neu overexpression. Genetic stratification assays such as the Oncotype DX, a 21-gene recurrence score DNA array that predicts response to chemotherapy for node-negative, estrogen receptor-positive patients, have undergone prospective validation and are commercially available.[7] For Her-2-neu-positive patients, adjuvant chemotherapy and trastuzumab, a humanized monoclonal antibody directed against Her-2-neu significantly reduces the risk of systemic recurrence, with an increase in cardiac toxicity.[8]

Adjuvant therapy for estrogen receptor-positive breast cancer includes tamoxifen and, for postmenopausal women, aromatase inhibitors. Tamoxifen is associated with endometrial proliferation, hyperplasia, polyps, endometrial cancer and rare incidence of uterine sarcoma, which has a poor prognosis. The risk of endometrial cancer with tamoxifen is increased 2-3 fold. Women on tamoxifen should be monitored closely for signs and symptoms of endometrial hyperplasia or cancer, such as abnormal vaginal spotting or bleeding. The **American College of Obstetricians and Gynecologists** (**ACOG**) recommends evaluation of all potential symptoms of endometrial effects of tamoxifen in post-menopausal women.[9] Endometrial effects of tamoxifen are less likely in a pre-menopausal woman who continues to menstruate. Routine screening with transvaginal ultrasound and/or endometrial biopsy are not recommended due to the low incidence of endometrial cancer and the high rate of "false-positive" ultrasound findings of thickened endometrial stripes in the absence of significant pathology with endometrial sampling[10].

Adjuvant therapy for estrogen receptor-positive post-menopausal women includes an aromatase inhibitor for 5 years or the sequence of tamoxifen followed by an aromatase inhibitor. Common side effects of adjuvant hormonal therapy are listed in Table 3. Aromatase inhibitors prevent the conversion of androgens to estrogens by the enzyme aromatase, but do not suppress ovarian estrogen production in a premenopausal woman.

Tamoxifen is a prodrug metabolized to endoxifen by the cytochrome P450 (CYP), enzyme 2D6. Polymorphisms or drug inhibitors of CYP2D6 appear to result in low levels of endoxifen, which may impact clinical benefit from tamoxifen.[11] Assays for CYP2D6 are available, but the reliability of the commercial assays and clinical significance of patients with mutant CYP2D6 enzymes are unclear. Medications including the selective serotonin reuptake inhibitors and serotonin and norepinephrine uptake inhibitors are often prescribed to breast cancer survivors to attenuate hot flashes and depression; these drugs may also impair CYP2D6 conversion of tamoxifen to endoxifen. Patients on tamoxifen should avoid paroxetine and fluoxetine. The serotonin and norephinephrine uptake inhibitor venlafaxine is a weak inhibitor of CYP2D6 and has little effect on tamoxifen metabolism.[12]

Primary Care follow-up after a diagnosis of Breast Cancer

There are several goals for breast cancer patient follow-up. Among them are early identification and treatment of potentially curable disease, including local breast recurrences or second primary breast cancer, adjuvant medication therapy compliance, management of treatment-related side effects, rehabilitation, and coordination of care with primary care physicians.

A routine follow-up visit by a physician trained in cancer surveillance is recommended every 3 to 4 months for the first 3 years, every 6 to 12 months for the 4th and 5th year, and then annually.[13] Additional surveillance methods can be seen in Table 4. There is no documented clinical benefit to routine CT scans, MRI, ultrasound, bone scans, positron emission tomography scanning, or blood tests other than monitoring toxicity of adjuvant therapy (common side effects of therapy are listed in Table 5) and evaluating new symptoms.

Routine patient follow-up visit includes history and review of symptoms to screen for symptoms of metastatic disease specifically presence of new or different headaches, cough, dyspnea, nausea, abdominal or bone pain, and a review of systems screening for therapy-related complications including hot flashes, vaginal discharge or dryness, dyspareunia, and depression. Mammograms should be performed 6 months after completion of radiation and then annually.

The time after a diagnosis of malignancy provides a teachable moment to address issues of overall health including

Table 4. Follow Up of Breast Cancer Survivors

- Evaluation by oncologist every 3-4 months for 3 years, every 6 months for years 3-5, then annually
- Breast self exam
- Mammogram
- Pelvic exam annually (tamoxifen)
- Screen for other cancers
- Bone density (aromatase inhibitors)
- Review cardiovascular risk factors

Table 5. Complications of therapy

Osteoporosis

Risks
- Chemotherapy
- Premature menopause
- Aromatase inhibitors

Evaluation
- Bone density

Intervention
- Exercise
- Calcium1200-1500 mg/d and vitamin D 1000 IU/d
- Bisphosphonate
- No raloxifen after diagnosis of ER positive breast cancer

Ovarian Failure and Sexual dysfunction

Risks
- Chemotherapy
- Ovarian suppression

Symptoms
- Hot flashes

Intervention
- Venlafaxine
- Gabapentin

Symptoms
- Vaginal dryness

Intervention
- Vaginal moisturizers and lubricants
- Avoid topical estrogens in patients on aromatase inhibitors

obesity, osteoporosis, second malignancies, cardiovascular disease, tobacco use, diabetes and functional decline. Oncologists and primary care physicians should encourage routine health care, cancer screening, modification in cardiovascular risk factors especially control of hypertension, smoking cessation, and glucose control. Patients should be queried annually for new family history of malignancies, specifically breast, ovarian, uterine and colon cancer, and refer to genetic counseling when appropriate (Table 2). Routine screening colonoscopies should be encouraged for women after age 50 or with a family history of colon cancer.

Cardiac disease, including **congestive heart failure** (**CHF**), is a cause of major morbidity and mortality for the older US population. Cardiac toxicity rates are higher for patients exposed to adjuvant anthracyclines chemotherapy or trastuzumab monoclonal antibody therapy for Her-2-neu gene amplification. CHF post anthracycline may be due to a "multiple hits" from chemotherapy, radiation therapy, and underlying cardiac risk factors such as hypercholesterolemia, hypertension, smoking, and diabetes. Early and aggressive treatment of hypertension with beta blockers and ACE inhibitors and other cardiac risk factors may attenuate progression to clinical CHF.

Patients prescribed adjuvant endocrine therapy have a high rate of noncompliance, including up to 50% for adjuvant tamoxifen,[14] and 25% for aromatase inhibitors.[15] The reasons can include forgetfulness, medication cost, side effects, and patient's lack of understanding of disease or benefits of therapy.[16] Practitioners are encouraged to review medication compliance, reinforce benefits of adjuvant endocrine therapy and address side effects.

A major issue for post-menopausal women on aromatase inhibitors is joint pain, which is present in up to 47% of patients[17] and is attributed to estrogen deprivation. Strategies such as switching to an alternative aromatase inhibitors and use of nonsteroidal anti-inflammatory medication may improve symptoms and compliance. The cost of oral adjuvant therapy can be addressed by the Partnership for Prescription Assistance (www.pparx.org), and other patient advocacy groups.

Sexual dysfunction and vasomotor dysfunction are common side effects of **chemotherapy-induced menopause** (**CIM**) and adjuvant endocrine therapy. These side effects include hot flashes, vaginal dryness, dyspareunia, genitourinary atrophy and decreased sexual drive. Vaginal moisturizers and lubricants can attenuate vaginal dryness and dyspareunia. Patients develop hot flashes due to CIM or adjuvant tamoxifen and aromatase inhibitors. Hot flashes may be reduced in rate and intensity with the serotonin norepinephrine uptake inhibitor antidepressant venlafaxine, the antihypertensive á-adrenergic agonist clonidine, or the anti-seizure ã-aminobutyric acid analog gabapentin.[18]

Breast cancer patients should avoid HRT and the SERM raloxifen. Adjuvant anastrozole, compared to tamoxifen results in significant loss of bone density, although patients with normal bone density prior to anastrozole did not develop osteoporosis.[19] Strategies for maintaining bone health start with a baseline bone density, adequate intake of calcium (1200mg/day) and vitamin D (800-1000 international units/day), women with low bone mineral density should have a serum 25/hydroxy vitamin D level checked and oral bisphosphonates for osteoporosis.[20] [21]

For estrogen receptor-positive patients, over half of recurrences occur after 5 years. Trials of longer duration adjuvant endocrine therapy are ongoing.

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Mary Anne Fenton, MD, FACP, is Assistant Clinical Professor, The Warren Alpert Medical School of Brown University.

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Correspondence

Mary Anne Fenton, MD, FACP
593 Eddy Street, George 3
Providence, RI, USA 02903
Phone : (401) 444-5391
Email: mfenton@lifespan.org