Assessing Breast Cancer Risk in Women

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Understanding modifiable and nonmodifiable factors that increase or decrease breast cancer risk allows family physicians to counsel women appropriately. Nonmodifiable factors associated with increased breast cancer risk include advanced age, female sex, family history of breast cancer, increased breast density, genetic predisposition, menarche before age 12 years, and natural menopause after age 45 years. Hormonal factors associated with breast cancer include advanced age at first pregnancy, exposure to diethylstilbestrol, and hormone therapy. Environmental factors include therapeutic radiation. Obesity is also associated with increased rates of breast cancer. Factors associated with decreased cancer rates include pregnancy at an early age, late menarche, early menopause, high parity, and use of some medications, such as selective estrogen receptor modulators and, possibly, nonsteroidal anti-inflammatory agents and aspirin. No convincing evidence supports the use of dietary interventions for the prevention of breast cancer, with the exception of limiting alcohol intake. (*Am Fam Physician*. 2008;78(12):1361-1366. Copyright © 2008 American Academy of Family Physicians.)

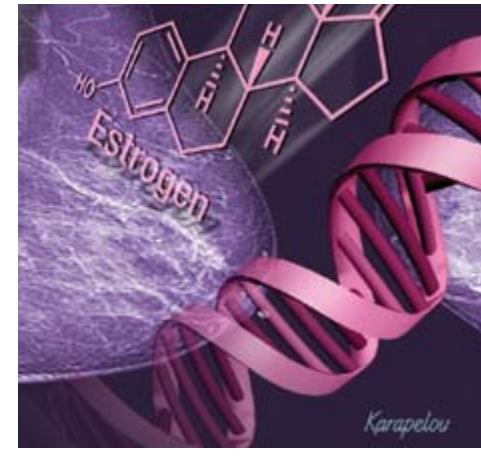

ILLUSTRATION BY JOHN W. KARAPELOU

The lifetime cumulative incidence rate of breast cancer ranges from one in seven to one in nine. This implies that if all women lived to age 85 years, approximately 12.5 percent would develop breast cancer. However, this risk is not distributed evenly among all women. Although statistical models can help physicians predict risk for some patients,[1,2] risk assessment can be inconsistent for the same patient between different models.[3,4] Of the risk factors most strongly associated with breast cancer, the two most notable are nonmodifiable: age and female sex. The incidence of breast cancer is significantly greater in postmenopausal women, and age is often the only known risk factor.

Understanding modifiable and nonmodifiable factors that increase or decrease breast cancer risk allows family physicians to counsel women appropriately *(Table 1)*.[5-46] It also allows women the opportunity to participate more actively in their health care. Although there is no definitive evidence on the effectiveness of risk factor modification for the prevention of breast cancer, patients can consider making behavioral changes that may reduce their risk of breast cancer (e.g., increasing exercise, decreasing alcohol consumption). Breast cancer screening with mammography is recommended in current guidelines,[47] but some women may wish to discuss their individual risk before deciding whether to undergo screening. Additional information to assist physicians and patients in discussing breast cancer screening has been published.[48]

Factors That Increase Risk

NONMODIFIABLE RISK FACTORS

Reproductive and Hormonal Factors. Increased lifetime estrogen exposure is associated with increased rates of breast cancer. One theory about the hormonal influence on breast cancer risk is that breast development and maturation occur against a backdrop of cyclical and periodic hormonal influences on the breast that arise from endogenous or exogenous sources. Early menarche (i.e., before age 12 years) is associated with higher lifetime risk, but the greatest effect of

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
The decision to screen for breast cancer with mammography should be individualized based on risk factors and patient preferences.	C	47, 48
The USPSTF recommends that women whose family history is associated with an increased risk for deleterious *BRCA1* and *BRCA2* mutations be referred for genetic counseling and evaluation for *BRCA* testing.	B	2
The USPSTF recommends against routine referral for genetic counseling and routine *BRCA* testing in women whose family history is not associated with an increased risk for deleterious *BRCA1* and *BRCA2* mutations.	B	2
Postmenopausal women should not take hormone therapy unless the benefits outweigh the apparent increased risk for breast cancer.	C	25, 26
The USPSTF recommends that physicians discuss chemoprevention with women who are at high risk for breast cancer and at low risk for adverse effects from chemoprevention.	B	55

USPSTF = U.S. Preventive Services Task Force.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

early menarche may be in increased rates of breast cancer in premenopausal women; natural menopause (i.e., after age 45 years) is more strongly associated.[10] The current median age of menopause is 51.4 years.[49]

Studies evaluating exogenous hormone administration have shown that although the absolute risk is low, the relative risk (RR) of breast cancer is increased in women who took diethylstilbestrol while pregnant (RR, 1.35; 95% confidence interval [CI], 1.05 to 1.74).[50] However, their exposed daughters do not have an increased risk of breast cancer.[51] The risk, if any, associated with infertility treatments has yet to be clarified.

Breast Density. Increased breast density is an independent nonmodifiable risk factor for breast cancer. Women who have a breast density of at least 75 percent on mammography have an odds ratio of breast cancer of 4.7 (95% CI, 3.0 to 7.4) compared with women who have breast density of 10 percent or less.[28]

Genetic Mutations and Family History. Known genetic mutations account for only 3 to 5 percent of all breast cancers.[20-22] Although 60 percent of inherited cancers result from *BRCA1* and *BRCA2* mutations, there are at least 20 other genes that are known to contribute to inherited breast cancers.[20-22] The cumulative lifetime risk of breast cancer attributable to genetic mutations is controversial, with estimates ranging from 25 to 85 percent. The *BRCA* genes are most prevalent in persons of Ashkenazi Jewish descent, but they have been found in multiple communities worldwide,[23] so it is important not to assume the absence of a genetic component in women of other racial and ethnic heritages. Paternal family history is important when considering referral for genetic counseling, because *BRCA* mutations are inherited in an autosomal-dominant pattern and may increase susceptibility to other cancers. The U.S. Preventive Services Task Force (USPSTF) has recommended that physicians offer genetic testing to several groups of women *(Table 2)*.[2]

Other Factors. Benign breast disease and previous biopsy is associated with increased risk of breast cancer if proliferative patterns are seen. Atypia and a history of breast cancer are strongly associated with breast cancer.[17] Therapeutic radiation, such as mantle radiation for Hodgkin's disease, significantly increases risk.[18]

POTENTIALLY MODIFIABLE RISK FACTORS

Hormone Therapy. During menopause and beyond, the risk associated with hormone therapy depends on the duration and formulation of therapy and, possibly, patient characteristics. Brief, intermittent use of estrogen alone does not increase risk. Recent long-term estrogen use (longer than five years) increases risk, and combined estrogen-progestin use increases risk greater than estrogen alone, especially in leaner women.[24] The decrease in breast cancer incidence rates in 2003 may be attributed to cessation of hormone therapy after the results of the Women's Health Initiative were released in 2002.[25] The associated risk appears to decrease significantly within two to three years after hormone therapy ends.

Pregnancy. Women who become pregnant early in life (before age 20 years) and who carry the pregnancy to term have a decreased lifetime risk of breast cancer compared with nulliparous women, but they may have an increased risk for about 15 years after the pregnancy.[9] Regardless of maternal age, increasing parity is associated with a decreased risk for breast cancer compared with nulliparity. Compared with nulliparous women, patients with more than five full-term pregnancies are about 50 percent less likely to develop breast cancer.[10]

Table 1. Risk Factors for Breast Cancer

Factor	*Comments*
Factors associated with decreased risk	
Bilateral oophorectomy before 50 years of age*	RR is reduced 50 percent compared with women who have never had the procedure[5,6]
Breastfeeding*	RR is reduced 4.3 percent for every 12 months of breastfeeding[7,8]
First full-term pregnancy before 20 years of age*	Risk is reduced in women who are younger at time of first delivery (e.g., in women who are approximately 60 years of age at the time of breast cancer diagnosis, the OR is 0.68 if they delivered their first child at age 20 years versus 0.79 if they first delivered at age 35 years)[9]
Menarche at or after 14 years of age	Risk is reduced 10 percent per two-year delay in menarche after 12 years of age[10]
Parity	Risk progressively decreases with increasing number of full-term pregnancies (e.g., OR of developing breast cancer after one full-term pregnancy is 1.0 versus 0.70 after five full-term pregnancies)[9,10]
Physical activity*	RR is reduced as much as 30 percent (dose-dependent) in premenopausal women[11,12]
	RR is reduced 11 to 22 percent in postmenopausal women, depending on exertional level and leanness[11,12]
Use of selective estrogen receptor modulators*	Risk is reduced; amount of reduction depends on initial risk stratification[13-15]
Factors associated with increased risk	
Age	Cumulative incidence is 1.8 percent at 50 years of age
	Cumulative incidence is 3.8 percent at 60 years of age
	Cumulative incidence is 6.3 percent at 70 years of age
Alcohol intake*	RR is increased 7.1 percent per drink consumed beyond one drink per day[16]
Biopsy findings	Proliferative with atypia: risk is increased 4.24-fold[17]
	Proliferative without atypia: risk is increased 1.88-fold[17]
BMI*	Risk increases with increasing BMI; risk is increased 1.59-fold in women with BMI greater than 31 kg per m^2; postmenopausal weight gain of more than 20 kg increases risk 1.99-fold[18,19]
Established *BRCA1* or *BRCA2* mutation	Risk is increased; exact level of risk is unknown[20-23]
Family history of breast cancer	Lifetime incidence of breast cancer is increased 5.5 percent in women with one affected first-degree relative and 13.3 percent in women with two[22]
History of ovarian cancer	Risk is increased
Hormonal exposure	Hormone therapy: combination therapy with estrogen plus progesterone for more than five years increases risk more than the use of estrogen alone. Risk decreases five years after discontinuing therapy[24,25]
	Oral contraceptives: risk may be slightly increased with any use (OR, 1.19; 95% CI, 1.09 to 1.29), especially in parous women who use oral contraceptives for at least four years before their first full-term pregnancy (OR 1.52, 95% CI, 1.26 to 1.82)[26,27]
Increased breast density	Risk is increased[28]
Ionizing radiation	Significant risk exists, especially in youngest treatment cohorts[18]
Menopause after 45 years of age	Risk is increased about 3 percent for each year menopause is delayed[10]
Factors with unknown or no apparent effect	
Benign breast lesion	No effect in women with nonproliferative patterns[17]
Diet	Coffee, tea, and other caffeine-containing drinks: no effect[29]
	Dietary phytoestrogens: no consistent effect[30]
	Fat: no consistent effect[31,32]
	Fruits and vegetables: no consistent effect[33-35]
Medication use	Antibiotics: no consistent effect, unlikely[36-40]
	Aspirin and nonsteroidal anti-inflammatory drugs: no consistent effect[41-45]
Miscarriage and induced abortion	No effect[46]
Smoking	No consistent effect[16]

BMI = body mass index; CI = confidence interval; OR = odds ratio; RR = relative risk.

**—Potentially modifiable risk factor.*

Information from references 5 through 46.

Table 2. Testing for *BRCA* Mutations: Recommendations From the USPSTF

Persons with a family history of breast or ovarian cancer in a relative with a known deleterious *BRCA* mutation should be tested.
Ashkenazi Jewish women should be tested if any first-degree relative (or two second-degree relatives on the same side of the family) have breast or ovarian cancer.
Non-Ashkenazi Jewish women should be tested if one of the following risk factors is present:
Two first-degree relatives with breast cancer, one of whom was diagnosed before 50 years of age
At least three first- or second-degree relatives with breast cancer, regardless of age at diagnosis
At least two first- or second-degree relatives with ovarian cancer, regardless of age at diagnosis
A combination of breast and ovarian cancers among first- and second-degree relatives
A first-degree relative with bilateral breast cancer
A first- or second-degree relative with both breast and ovarian cancers, regardless of age at diagnosis
A male relative with a history of breast cancer

NOTE: *First-degree relatives are those who are one meiosis away from a particular family member (i.e., parent, sibling, offspring). Second-degree relatives include grandparents, aunts, uncles, and cousins.*

USPSTF = U.S. Preventive Services Task Force.

Information from reference 2.

Breastfeeding is associated with reduced rates of breast cancer over a woman's lifetime; the duration of breastfeeding is key. Early studies suggested that risk was reduced in premenopausal women who have breastfed,[7] and extensive recent analysis shows a 4.3 percent RR reduction for every 12 months of breastfeeding.[8]

When counseling young women about breast cancer risk, it is reasonable to advise them of the benefits of breastfeeding in terms of breast cancer risk reduction, in addition to the multiple other benefits of breastfeeding.

MODIFIABLE RISK FACTORS

Dietary Factors. Many studies have assessed a wide range of dietary factors as they relate to breast cancer risk. One of the main challenges with these studies is the difficulty in accurately assessing diet in study subjects.

Alcohol consumption is associated with an increased risk of breast cancer. A pooled analysis of cohort studies showed that the RR of developing breast cancer is 1.09 in women who consume three fourths to one drink per day (95% CI, 1.04 to 1.13), and those who consume two to five drinks per day have an RR of 1.41 (95% CI, 1.18 to 1.69).[16] The use of supplemental folate may reduce the incidence of breast cancer in persons who drink alcohol.[52] Women should consider limiting alcohol intake to no more than one drink per day.

Behavioral and Lifestyle Factors. Breast cancer risk is lower in pre- and postmenopausal women who exercise regularly.[11] Studies of obese women show that breast cancer incidence is reduced before menopause and increased after menopause; postmenopausal weight gain itself is a significant risk factor.[53] One theory for this association is that obese women have increased production of endogenous estrogen in peripheral adipose tissue.[19]

Reproductive and Hormonal Factors. Elevated estradiol, testosterone, and sex hormone–binding globulin levels are not associated with increased breast cancer risk in postmenopausal women.[54] In women with a family history of breast cancer[5] and in women with *BRCA1* and, possibly, *BRCA2* mutations, bilateral oophorectomy is associated with reduced risk of breast cancer, especially if performed before age 40 years.[6] However, no guidelines recommend prophylactic oophorectomies in women with genetic mutations.

Nonhormonal Medications. Selective estrogen receptor modulators, particularly tamoxifen (Nolvadex, brand no longer available in the United States) and raloxifene (Evista), have been shown in randomized controlled trials to decrease breast cancer risk in higher-risk populations (i.e., women with significant family history, known *BRCA* mutations, and, possibly, mantle radiation exposure during childhood).[13-15] The USPSTF recommends discussion of prophylactic therapy for women with known increased risk for breast cancer.[55]

Factors With Unknown Effects on Risk

DIET

Recent interest has prompted study of a subgroup of soy and related foods (e.g., chickpeas, red clover, tea, rye grains, broccoli) as sources of phytoestrogens. Studies within the European Prospective Investigation into Cancer and Nutrition (EPIC) study have not shown that phytoestrogens and isoflavones are associated with a significant reduction in breast cancer risk.[30] An extensive pooled analysis of eight separate studies did not show any risk reduction associated with a wide variety of fruits and vegetables.[33] The EPIC study reached similar conclusions.[34] Although a diet containing fruits and vegetables benefits an overall healthy lifestyle, consumption does not affect breast cancer risk.

BEHAVIORAL AND LIFESTYLE FACTORS

The effects of cigarette smoking on breast cancer risk can be confounded by those of associated alcohol use.[16] The exact risks of smoking and of exposure to secondhand smoke are unclear.[56,57]

NONHORMONAL MEDICATIONS

Because aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis and, in turn, limit production of endogenous estrogen, it is possible that breast cancer risk can be reduced by regular use of these drugs. The effect of frequent (at least weekly) doses of aspirin and other NSAIDs on breast cancer risk is unclear.

Factors That Do Not Affect Risk

DIET

Dietary fat does not seem to increase the risk for breast cancer, regardless of the amount consumed, its source, or its fatty acid composition.[31] A randomized controlled primary prevention trial within the Women's Health Initiative did not show that postmenopausal women who consumed a low-fat diet had a decreased risk of breast cancer.[32] Numerous studies show that consumption of caffeine, coffee, and caffeinated tea does not increase the risk of breast cancer.[29]

REPRODUCTIVE AND HORMONAL FACTORS

Miscarriages and induced abortions have no effect on breast cancer risk beyond the benefit caused by parity.[46]

The evidence on the effect of hormonal contraception is mixed. A recent meta-analysis of case-control studies showed that risk is slightly increased with any use,[26] whereas other well-designed studies have shown no effect on a woman's risk of developing breast cancer.[27] Any risk associated with newer injectable, implantable, transdermal, and intravaginal contraceptives, which offer decreased dosage but achieve higher serum concentrations of the drug, has not been determined.

NONHORMONAL MEDICATIONS

Most case-control studies examining the possible role of antibiotics in breast cancer risk have found no association.[35-38]

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