Evaluating and Reducing Breast Cancer Risk

Independence Blue Cross

EVALUATING AND REDUCING BREAST CANCER RISK is an important part of keeping women healthy. Several developments in the last five years have provided new tools to help accomplish this goal.[1,2]

Individual Breast Cancer Risk Assessment

Individual breast cancer risk assessment **can be done by several different methods. Short-term and long-term breast cancer risk varies substantially among women, according to their risk factors for breast cancer. (Table 1)**

- The most widely used and validated method is the **Gail prediction model.**[3,4] (Table 4) The Gail model can be applied to any woman, regardless of her risk factors. In general, women without a first-degree relative with breast cancer, prior breast biopsy, or late age at first live birth will not have a significantly elevated risk and may not need full risk calculation. Software for the Gail model can be obtained from the National Cancer Institute (http://bcra.nci.nih.gov/brc).[5]

- The next most widely used method is based on the **Claus prediction tables**.[6] The Claus tables are applicable to women who have at least one first or second-degree relative with breast cancer.

- Use of **genetic testing for mutations in BRCA1 and BRCA2,** the two major breast cancer susceptibility genes identified to date, can also be considered for women who have risk factors for carrying a mutation. (Table 2) Because of the complexity involved in BRCA1/2 testing, women considering testing should receive specialized pre-test and post-test education from practitioners experienced in genetic testing.[7]

Breast Cancer Risk Reduction

Breast cancer risk reduction **can be accomplished through lifestyle modification, medical interventions, and/or prophylactic surgery.** In general, a woman's individual risk should guide which level of intervention is considered. (Table 3) In addition to individual breast cancer risk, the optimal strategy for risk reduction depends upon an individual's values, preferences and attitude towards risk.

Lifestyle Modification

1. Alcohol intake of 3 or more drinks a day has consistently been shown to increase the risk of breast cancer.[8] Women should be counseled to **drink alcohol only in moderation** (about one drink a day) if they choose to drink at all.

2. **Moderate, regular physical activity** has consistently been shown to reduce the risk of breast cancer.[9] Women should be counseled to get 30 minutes of moderate physical activity most days of the week. Activities that qualify as moderate physical activity include: walking briskly, climbing stairs, biking, most yard work, dancing, as well as sports and exercise programs.[10]

3. High intake of dietary fat or low intake of fruits and vegetables has been associated with increased breast cancer risk in some studies but not all.[11,12] Women should be counseled that a **low fat diet, high in fruits and vegetables,** is beneficial for their overall health and may reduce their risk of developing breast cancer. Because of conflicting animal data and the absence of experimental human studies, insufficient evidence is available to recommend for or against intake of plant estrogens (including soy isoflavones).[13]

Medical Interventions

1. **Chemoprophylaxis** with tamoxifen reduces the risk of developing breast cancer by 49% in women with a 5-year breast cancer risk >1.67%.[14] Potential adverse effects include venous thromboembolism, low-grade endometrial cancer and cataracts, as well as menopausal symptoms in premenopausal women. Tamoxifen should be considered for women with a five-year Gail model breast cancer risk over 1.67%.[15] (See insert for Gail model.)

2. Raloxifene, currently FDA-approved for the treatment and prevention of osteoporosis in post-menopausal women, has been shown to reduce the risk of breast cancer in postmenopausal women with osteoporosis.[16]

   Raloxifene may be considered for post-menopausal women to prevent or treat osteoporosis, especially if they are at moderate or high breast cancer risk and are not taking tamoxifen.[7]

3. Considerable observational evidence indicates that hormone replacement therapy increases the risk of breast cancer by 25-30% after 5 years.[17,18] Short-term hormone replacement therapy for symptomatic relief is unlikely to result in a substantial increase in the absolute risk of breast cancer, even for women at moderate or high risk. **Careful consideration should be given to use of long-term hormone replacement therapy in women at moderate or high breast cancer risk, who do not have significant menopausal symptoms or osteoporosis risk.**

Prophylactic Surgery

In general, surgical interventions are only considered for women at very high risk, e.g. women with a BRCA1/2 mutation or whose personal or family history places them at very high risk. Referral to a specialized cancer risk evaluation program should be considered as part of the decision to undergo prophylactic surgery.

1. Prophylactic mastectomy reduces the risk of breast cancer by 90%.[19,20] Side effects include operative morbidity and mortality as well as changes in sensation and appearance.

2. Premenopausal prophylactic oophorectomy may reduce the risk of breast cancer by up to 50%.[21,22] Side effects include operative morbidity and mortality, menopausal symptoms and accelerated development of osteoporosis and atherosclerotic disease.[23,24] It is not known how subsequent use of hormone replacement therapy modifies these effects.

Table 1. Risk factors for breast cancer in women without previous breast cancer

Strong*	BRCA 1/2 mutation
	Prior chest radiation therapy
	History of ductal carcinoma in situ
	History of atypical hyperplasia
Moderate*	Family history of breast cancer
	Age at childbirth ≥ 30
	History of breast biopsy
Weak*	Early age at menarche (< 12)
	Use of postmenopausal hormone replacement for ≥ 5 years

* Although estimates of the size of the effect differ somewhat between studies, strong risk factors generally increase risk by more than 2 fold (RR>2.0), moderate risk factors between 50% and 2 fold (RR 1.5 to 2.0), mild risk factors by less than 50% (RR 1.1-1.4)

Table 2. Risk factors for BRCA 1/2 mutation

Known BRCA 1/2 mutation in family member
Breast and/or ovarian cancer in multiple family members
Two or more family members diagnosed with breast cancer under 50 years of age
Ashkenazi ancestry plus one or more family members diagnosed with breast cancer under 50
Ashkenazi ancestry plus ovarian cancer in family member
Breast cancer in male family member

Table 3. Breast Cancer Risk Reduction Strategies

	Consider Lifestyle Modification	Consider Medical Intervention	Consider Surgical Intervention
Low Risk (5 year risk <1.67%, lifetime risk <15%)	√		
Moderate Risk (5 year risk 1.67%-3%, lifetime risk 15-30%)	√	√	
High Risk (5 year risk >3%, lifetime risk 30-60%)	√	√	
Very High Risk e.g. BRCA1/2 Mutation (lifetime risk 60-85%)	√	√	√

Using the Gail Model to Predict Individual Breast Cancer Risk

Using the Gail Model to Predict Individual Breast Cancer Risk involves three steps. In Step 1, a woman's risk factors are used to identify her relative risk in each of the three categories (A, B and C) in Table 4 and a composite relative risk is calculated by multiplying together the relative risks from each of these categories. In Step 2, the average risk of breast cancer for a woman without risk factors is calculated by summing the annual risks of breast cancer from the woman's current age until the time point of interest. (Table 5) Often, five-year risk is calculated but other time periods may also be of interest. In Step 3, an individualized risk is estimated by multiplying the risk for a woman without risk factors by the composite relative risk.

Table 4. Relative Risk (RR) of Breast Cancer According to the Gail Model*

Risk Factor	RR
Category A	
Age at menarche	
≥14	1.00
12-13	1.10
<12	1.21
Category B	
Number of biopsies:	
Current age <50	
0	1.00
1	1.70
≥2	2.88
Current age ≥50	
0	1.00
1	1.27
≥2	1.62
Category C	
Number of 1st-degree relatives with breast CA:	
If age at first live birth <20:	
0	1.00
1	2.61
≥2	6.80
If age at first live birth 20-24:	
0	1.24
1	2.68
≥2	5.78
If age at first live birth 25-29 or nulliparous:	
0	1.55
1	2.76
≥2	4.91
If age at first live birth ≥30:	
0	1.93
1	2.83
≥2	4.17

Table 5. Absolute Risk of Breast Cancer For White and Black Women Without Risk Factors**

Number of Breast Cancers Developed Per Year Per 100 Women		
Age Range	White Women***	Black Women***
35-39	0.04	0.03
40-44	0.07	0.06
45-49	0.11	0.07
50-54	0.13	0.08
55-59	0.16	0.09
60-64	0.19	0.12
65-69	0.23	0.12
70-74	0.24	0.13
75-79	0.26	0.15

* Step 1: To calculate a woman's relative risk of breast cancer, multiply the relative risks from categories A, B, and C together. For example, a 62-year-old woman who underwent menarche at age 14, has had one breast biopsy, has one first degree relative with breast cancer and her first live birth at 23 years of age has a relative risk of 1.00*1.27*2.68= 3.40. This composite relative risk is then used to adjust the population risk of breast cancer in the absence of risk factors for the woman's individual risk profile.

** Step 2: To calculate absolute risk, sum the number of cancers developed per year during the years following the woman's current age. For example, to estimate the future five-year risk for a 62-year-old woman, you would add the breast cancers from two years in the 60-64 category (0.19 + 0.19) and three years in the 65-69 category (0.23 +0.23 +0.23), for a total of 1.07, or an approximate 1% five-year risk.

*** Specific estimates have not yet been developed for Native American, Asian or Pacific Islander women.

Step 3: The final 5-year risk for this 62-year-old woman is the product of 3.4 from Step 1 and 1.07 from Step 2 or 3.4 * 1.07 = 3.25%.

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