Review Article

Primary Care

Assessing the Risk of Breast Cancer

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EACH year in the United States, breast cancer is diagnosed in more than 170,000 women.[1] Despite this substantial burden of disease, however, assessment of breast-cancer risk has received very little attention outside the oncology clinic.[2,3] In primary care, the main result of the recognition of individual variation in breast-cancer risk is the use of age to determine recommendations regarding mammography (older age is a strong risk factor for breast cancer).[4]

Recent developments in the ability to predict and alter breast-cancer risk warrant a new look at the role of assessment of this risk in primary care. Physicians must become adept at evaluating breast-cancer risk and counseling women about its effect on medical decisions. To provide both the rationale and the tools for evaluating breast-cancer risk, this article examines the effects of breast-cancer risk on medical decisions and explains current methods of assessing risk.

Why Evaluate Breast-Cancer Risk?

Several important medical decisions may be affected by a woman's underlying risk of breast cancer. These decisions include whether to use postmenopausal hormone-replacement therapy, at what age to begin mammographic screening, whether to use tamoxifen to prevent breast cancer, and whether to perform prophylactic mastectomy to prevent breast cancer.

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Decisions about Postmenopausal Hormone-Replacement Therapy

Observational studies suggest that postmenopausal hormone-replacement therapy halves the risk of coronary heart disease and osteoporosis but increases the risk of breast cancer by 30 to 40 percent.[5-7] Because the reductions in the risk of coronary heart disease and osteoporosis are greater than the increase in the risk of breast cancer, and because the average woman's risk of dying from coronary heart disease is much greater than her risk of dying from breast cancer, most experts argue that the benefits of hormone-replacement therapy outweigh the risks in most women.[8,9]

However, the balance between the risks and the benefits of hormone-replacement therapy may shift for women who have a substantially increased risk of breast cancer. Although the relative risk associated with hormone-replacement therapy does not appear to be higher in women with a family history of breast cancer, decision analysis suggests that the absolute benefit of hormone-replacement therapy (measured as the net increase in life expectancy) falls as the risk of breast cancer increases.[9-12] In one such model, hormone-replacement therapy no longer increased life expectancy for women with a lifetime breast-cancer risk above 30 percent and an average risk of cardiac events. Although the number of postmenopausal women with such a high risk of breast cancer is small, assessment of breast-cancer risk provides valuable information for use in making decisions about hormone-replacement therapy.[13-15] Furthermore, assessment of breast-cancer risk may reassure the larger number of women with a risk below this threshold that the benefits of hormone-replacement therapy outweigh its risks.

The number of women who use individual assessments of breast-cancer risk to make decisions about postmenopausal therapy may increase as alternatives to hormone-replacement therapy become available. Raloxifene, a selective estrogen-receptor modulator, provides less protection against coronary heart disease and osteoporosis than hormone-replacement therapy, but it may reduce the risk of breast cancer.[16-18] Because of these trade-offs in risk reduction, it is likely that breast-cancer risk will be an important factor in determinations of the expected relative benefits of raloxifene and hormone-replacement therapy. As a woman's risk of breast cancer increases, the relative benefit of raloxifene as compared with hormone-replacement therapy will increase. A recent decision analysis suggests that if the goal is to increase life expectancy, raloxifene is the preferred alternative for postmenopaus-

al women who are at substantially increased risk of breast cancer.[10]

Decisions about the Use of Mammography for Women 40 to 49 Years of Age

The routine use of screening mammography in women 50 years old or older reduces mortality from breast cancer by approximately one third.[19] This reduction comes without substantial risks and at an acceptable economic cost.[20,21] However, the use of screening mammography is more controversial in women under the age of 50, for several reasons. First, because breast density is generally higher in younger women, screening mammography is less likely to detect early breast cancer at a curable stage. Thus, the reduction in mortality from breast cancer is lower.[22] Second, also because of their higher breast density, screening mammography in younger women results in more false positive tests, with the associated anxiety and unnecessary biopsies.[23] Third, because women under the age of 50 are less likely to have breast cancer, fewer women in this age group will benefit from screening.[1] Fourth, the lower incidence of breast cancer among these women increases the cost of mammography per year of life saved to more than $100,000.[24] Expert panels have concluded that, on a population basis, the benefits of screening mammography in women between 40 and 49 years of age still outweigh the risks. The goal of maximizing the benefit of mammography while minimizing its risks remains uncontested.[25,26]

Although the assessment of breast-cancer risk cannot improve the efficacy of mammography, targeting mammography to women at higher risk of breast cancer can improve the balance of risks and benefits.[27-29] Among women at higher risk, mammography results in a greater absolute decrease in the risk of death from breast cancer and is more cost effective. A higher prevalence of disease results in a lower proportion of false positive tests. In one analysis of women 40 to 49 years of age, an abnormal mammogram was more than three times as likely to be associated with cancer in a woman with a family history of cancer as in a woman without a family history of cancer.[23]

Several authors have published risk-based recommendations for mammographic screening.[28,29] A recent article focusing on women 40 to 49 years of age described procedures to determine whether a woman's risk equaled that of a 50-year-old woman without risk factors for breast cancer.[29] Because the benefit of mammography is widely accepted to exceed the risks for all 50-year-old women, these procedures can be used to determine whether a younger woman's risk of breast cancer meets this criterion.

Decisions about the Use of Tamoxifen for the Prevention of Breast Cancer

Tamoxifen, a selective estrogen-receptor modulator, is the first drug shown to reduce the incidence of breast cancer in healthy women. The Breast Cancer Prevention Trial randomly assigned more than 13,000 women with a five-year risk of breast cancer of 1.7 percent or more to tamoxifen or placebo.[30] After a mean follow-up period of four years, tamoxifen had reduced the incidence of breast cancer by 49 percent as compared with the incidence with placebo. Although two European randomized, controlled trials of tamoxifen did not show a benefit, these trials were statistically underpowered, had high rates of noncompliance, and included women who continued to take hormone-replacement therapy.[31,32] Tamoxifen is currently the only drug approved by the Food and Drug Administration for reducing the risk of breast cancer. Because published trials of raloxifene were not designed to assess its efficacy in preventing breast cancer, raloxifene has not been approved for reducing the risk of breast cancer.[33] Clinical trials are now comparing the efficacy of raloxifene with that of tamoxifen in reducing the risk of breast cancer.

Assessment of breast-cancer risk is important in making decisions about tamoxifen, for several reasons. First, because the Breast Cancer Prevention Trial enrolled only women with a five-year breast-cancer risk of 1.7 percent or more, it is unclear whether the benefit of tamoxifen applies to women at lower risk. Clinical experts in breast-cancer prevention recommend that tamoxifen be used only by women whose risk of breast cancer is at or above this threshold.[33]

Second, although they are rare, tamoxifen has side effects, including venous thromboembolism, endometrial cancer, and cataracts. In women taking tamoxifen, deep venous thromboses occurred 1.6 times as often and pulmonary emboli 3 times as often as in control women. The increased risk of endometrial cancer was also substantial (relative risk, 2.5); however, the increased risk was restricted to early-stage cancers in postmenopausal women. Cataract surgery was required almost twice as often among women taking tamoxifen. Thus, for women to choose or for physicians to advocate the preventive use of tamoxifen, the benefits must outweigh these risks. Although no formal risk–benefit analysis is currently available, the higher a woman's risk of breast cancer, the more likely it is that the reduction in the incidence of breast cancer will outweigh these other risks.

Third, as the risk of breast cancer increases, the absolute benefit of tamoxifen increases. For women at relatively low risk of breast cancer, the absolute benefit may be relatively small. For women at very high risk of breast cancer, the absolute benefit is correspondingly great.

Decisions about Prophylactic Mastectomy

A recent retrospective cohort analysis of 639 women at high risk for breast cancer found that prophylactic mastectomy reduced the risk by more than 90 percent.[34] Although this risk reduction is impressive,

the trade-offs involved in prophylactic mastectomy are substantial. Prophylactic mastectomy involves extensive and potentially disfiguring surgery with unknown effects on the long-term quality of life.[35] Furthermore, the reduction in breast-cancer risk achieved by prophylactic mastectomy depends on a woman's underlying risk of breast cancer. A decision analysis involving women who were carriers of *BRCA1* or *BRCA2* mutations found that the benefit of prophylactic mastectomy differed substantially according to the breast-cancer risk conferred by the mutations.[36] For women with an estimated lifetime risk of 40 percent (approximately four times the population risk), prophylactic mastectomy would add almost three years of life, whereas for women with an estimated lifetime risk of 85 percent, prophylactic mastectomy would add more than five years.

HOW TO EVALUATE BREAST-CANCER RISK

Average Risk

Understanding the average risk of breast cancer provides a necessary context for individual risk assessments. The average lifetime risk of breast cancer in the U.S. female population at birth is 12 percent, or approximately one in eight.[37] The longer a woman lives without cancer, the lower is her risk of breast cancer over the remainder of her lifetime. Thus, a 50-year-old woman who has not had breast cancer has an 11 percent chance of having breast cancer in her lifetime, and a 70-year-old woman who has not had breast cancer has a 7 percent chance of having breast cancer in her lifetime.

Epidemiologic Risk Factors

Many studies have evaluated risk factors for breast cancer.[13-15,38-46] Several factors have been consistently associated with an increased risk (Table 1). However, because many of these risk factors may interact, evaluating the risk conferred by combinations of risk factors is challenging. Other risk factors have been less consistently associated with breast cancer (such as diet, use of oral contraceptives, lactation, and abortion) or are rare in the general population (such as radiation exposure), and are not included in currently used prediction models.[41-46]

Risk-Prediction Models

Four models are currently available to predict the risk of breast cancer, of which two are used most often. The most commonly used model was developed by Gail et al. from the Breast Cancer Detection Demonstration Project, a large mammographic-screening program conducted in the 1970s.[39] This model incorporates the number of first-degree relatives with breast cancer (0, 1, or ≥2), age at menarche (<12, 12 to 13, or ≥14 years), age at first live birth (<20, 20 to 24, 25 to 29 or nulliparous, or ≥30 years), and the number of breast biopsies (0, 1, or ≥2). It predicts the cumulative risk of breast cancer according to decade up to the age of 90 years. To determine eligibility for trial entry, the Breast Cancer Prevention Trial used a revised Gail model that also incorporates race, presence of atypical hyperplasia on breast biopsy, and 1987 population rates of breast cancer and death from other causes.

To calculate breast-cancer risk with the Gail model, a woman's risk factors are translated into an overall risk score by multiplying her relative risks from several categories (age at menarche, number of breast biopsies, family history, and age at first live birth) (Table 2). This risk score is then multiplied by an adjusted population risk of breast cancer to determine the individual risk of breast cancer. Because the effects of risk factors interact and vary with age, the risk of breast cancer is most easily calculated with a software program that is available from the National Cancer Institute at http://cancernet.nci.nih.gov/h_detect.html. The results of calculations of five-year and lifetime risks of breast cancer with the Gail model for women with various risk factors are presented in Table 3.

The other commonly used prediction model was developed by Claus et al. on the basis of data from the Cancer and Steroid Hormone Study, a large, population-based, case–control study of breast cancer.[47] This model is based on assumptions of the prevalence of high-penetrance genes for susceptibility to breast cancer. As compared with the Gail model, the Claus model incorporates more extensive information about

TABLE 1. ESTABLISHED RISK FACTORS FOR BREAST CANCER.

RISK FACTOR	RELATIVE RISK	STUDY
Age (≥50 vs. <50 yr)	6.5	Ries et al.[1]
Family history of breast cancer		
First-degree relative	1.4–13.6	Rockhill et al.[13] Madigan et al.[14] Bruzzi et al.[15] Slattery and Kerber[38] Gail et al.[39]
Second-degree relative	1.5–1.8	Slattery and Kerber[38]
Age at menarche (<12 vs. ≥14 yr)	1.2–1.5	Rockhill et al.[13] Bruzzi et al.[15] Gail et al.[39]
Age at menopause (≥55 vs. <55 yr)	1.5–2.0	Madigan et al.[14] Bruzzi et al.[15]
Age at first live birth (>30 vs. <20 yr)	1.3–2.2	Rockhill et al.[13] Madigan et al.[14] Bruzzi et al.[15] Gail et al.[39]
Benign breast disease		
Breast biopsy (any histologic finding)	1.5–1.8	Rockhill et al.[13] Bruzzi et al.[15] Gail et al.[39]
Atypical hyperplasia	4.0–4.4	Dupont and Page[40]
Hormone-replacement therapy	1.0–1.5	Folsom et al.[6] Colditz et al.[7]

TABLE 2. RELATIVE RISK OF BREAST CANCER ACCORDING TO THE GAIL MODEL.*

RISK FACTOR	RELATIVE RISK
Category A	
Age at menarche	
⩾14 yr	1.00
12–13 yr	1.10
<12 yr	1.21
Category B	
No. of breast biopsies and woman's age	
0	
Any age	1.00
1	
<50 yr	1.70
⩾50 yr	1.27
⩾2	
<50 yr	2.88
⩾50 yr	1.62
Category C	
No. of 1st-degree relatives with breast cancer and woman's age at 1st live birth	
0	
<20 yr	1.00
20–24 yr	1.24
25–29 yr or nulliparous	1.55
⩾30 yr	1.93
1	
<20 yr	2.61
20–24 yr	2.68
25–29 yr or nulliparous	2.76
⩾30 yr	2.83
⩾2	
<20 yr	6.80
20–24 yr	5.78
25–29 yr or nulliparous	4.91
⩾30 yr	4.17

*Composite risk scores for women under 50 years of age and for those 50 or more years old are derived by multiplying the appropriate relative risks from categories A, B, and C. These risk scores are then translated into five-year and lifetime risks by using adjusted population rates of breast cancer.

family history, but it excludes risk factors other than family history. On the basis of knowledge of first- and second-degree relatives with breast cancer and their age at diagnosis, the Claus model provides individual estimates of breast-cancer risk according to decade from 29 to 79 years of age. Claus-model predictions for women with one first-degree relative with breast cancer, one second-degree relative with breast cancer, and two first-degree relatives with breast cancer are shown in Table 4. Predictions for other combinations of relatives with breast cancer (two second-degree relatives, mother and maternal aunt, and mother and paternal aunt) are also available.[47]

Two other risk-prediction models were developed for genetic counseling of women with a strong family history of breast cancer.[48,49] These models apply only to women who have either a mother or a sister with breast cancer and are less commonly used than the Gail and Claus models.

Although relatively few studies have attempted to validate risk-prediction models for breast cancer, the Gail model has received the most attention, with validation studies in four populations.[50-53] In general, the Gail model appears to be accurate for women undergoing routine mammographic screening but probably overestimates the risk among young women who are not undergoing regular mammography. An analysis of the Breast Cancer Prevention Trial data found that the ratio of observed to predicted cancers among the study participants was 1.03 (95 percent confidence interval, 0.88 to 1.21).[51] The one study that compared the Gail and Claus models found only moderate agreement between the two methods in a high-risk population of women (intraclass correlation coefficients, 0.43 to 0.55).[54] Thus, for women to whom the Claus model is applicable (those with at least one first- or second-degree relative with breast

TABLE 3. CLINICAL EXAMPLES OF RISK PREDICTIONS ACCORDING TO THE GAIL MODEL.

CURRENT AGE (YR)	RACE	NO. OF FIRST-DEGREE RELATIVES WITH BREAST CANCER	NO. OF BREAST BIOPSIES	AGE AT MENARCHE	AGE AT FIRST LIVE BIRTH	5-YEAR BREAST-CANCER RISK	BREAST-CANCER RISK TO THE AGE OF 90
				years		percent	
40	Black	0	0	14	19	0.3	3.7
40	White	0	0	14	19	0.4	6.7
40	White	1	0	14	19	0.9	16.4
40	White	1	1	14	19	1.5	19.9
40	White	1	1	12	19	1.6	21.6
40	White	1	1	12	30	1.8	23.2
40	White	2	2	12	30	3.4	25.2
50	White	1	1	12	30	2.3	20.1
60	Black	1	1	12	30	2.0	9.4
60	White	1	1	12	30	3.4	16.6

TABLE 4. CUMULATIVE RISK OF BREAST CANCER ACCORDING TO THE CLAUS MODEL.

NO. OF RELATIVES WITH BREAST CANCER AND THEIR AGE AT DIAGNOSIS	CUMULATIVE BREAST-CANCER RISK ACCORDING TO AGE				
	39 YR	49 YR	59 YR	69 YR	79 YR
			percent		
One 1st-degree relative					
20–29 yr	2.5	6.2	11.6	17.1	21.1
30–39 yr	1.7	4.4	8.6	13.0	16.5
40–49 yr	1.2	3.2	6.4	10.1	13.2
50–59 yr	0.8	2.3	4.9	8.2	11.0
60–69 yr	0.6	1.8	4.0	7.0	9.6
70–79 yr	0.5	1.5	3.5	6.2	8.8
One 2nd-degree relative					
20–29 yr	1.4	3.5	7.0	11.0	14.2
30–39 yr	1.0	2.7	5.6	9.0	12.0
40–49 yr	0.7	2.1	4.5	7.6	10.4
50–59 yr	0.6	1.7	3.8	6.7	9.4
60–69 yr	0.5	1.7	3.8	6.7	9.4
70–79 yr	0.4	1.3	3.2	5.8	8.3
Two 1st-degree relatives					
Younger age at diagnosis 20–29 yr					
Older age at diagnosis					
20–29 yr	6.9	16.6	29.5	41.2	48.4
30–39 yr	6.6	15.7	27.9	39.1	46.0
40–49 yr	6.1	14.6	26.1	36.6	43.4
50–59 yr	5.5	13.3	23.8	33.5	39.7
60–69 yr	4.8	11.7	21.0	29.7	35.4
70–79 yr	4.1	9.9	17.9	25.6	30.8
Younger age at diagnosis 30–39 yr					
Older age at diagnosis					
30–39 yr	6.2	14.8	26.5	37.1	43.7
40–49 yr	5.6	13.4	23.9	33.7	39.9
50–59 yr	4.8	11.6	20.9	29.6	35.3
60–69 yr	4.0	9.6	17.5	25.1	30.2
70–79 yr	3.2	7.7	14.3	20.7	25.2
Younger age at diagnosis 40–49 yr					
Older age at diagnosis					
40–49 yr	4.8	11.7	21.0	29.8	35.4
50–59 yr	3.9	9.6	17.4	24.9	30.0
60–69 yr	3.0	7.5	13.9	20.2	24.6
70–79 yr	2.3	5.8	10.8	16.1	20.0
Younger age at diagnosis 50–59 yr					
Older age at diagnosis					
50–59 yr	3.0	7.5	13.8	20.0	24.5
60–69 yr	2.2	5.6	10.5	15.7	19.5
70–79 yr	1.6	4.2	8.1	12.4	15.8
Younger age at diagnosis 60–69 yr					
Older age at diagnosis					
60–69 yr	1.6	4.1	8.0	12.2	15.6
70–79 yr	1.2	3.0	6.1	9.8	12.8
Younger age at diagnosis 70–79 yr					
Older age at diagnosis					
70–79 yr	0.8	2.3	4.9	8.1	10.9

cancer), the predictions of the Gail and Claus models may differ.

Genetic-Susceptibility Testing

Two major breast-cancer-susceptibility genes have been identified, *BRCA1* and *BRCA2*.[55,56] Women with mutations in either of these genes have a lifetime risk of breast cancer of 60 to 85 percent and a lifetime risk of ovarian cancer of 15 to 40 percent.[57,58] Several studies have identified familial characteristics that increase the likelihood of carrying a *BRCA1* or *BRCA2* mutation.[59,60] These include early-onset breast cancer, breast and ovarian cancer, and Ashkenazi Jewish ancestry.

Testing for mutations in *BRCA1* and *BRCA2* is an important tool for predicting breast-cancer risk in two sets of circumstances.[61] First, in families with known mutations in *BRCA1* or *BRCA2*, genetic testing can separate women who carry the familial mutation (with the associated 60 to 85 percent lifetime risk of breast cancer) from those who do not. Women who test negative are at the same risk as women without a family

history of breast cancer. Second, in families that have risk factors for carrying a *BRCA* mutation but do not have a known mutation, genetic testing can identify a substantial number of women with *BRCA* mutations. These women also have a lifetime breast-cancer risk of 60 to 85 percent. However, women from these families who test negative for *BRCA* mutations remain at increased risk because of their family history of breast cancer. Although their risk falls by an amount equal to the probability that *BRCA* mutations would have explained their particular familial pattern, this decrement is often relatively small, except in the Ashkenazi population, where *BRCA* mutations may explain a substantial proportion of hereditary breast cancer. Models are not currently available to adjust predictions of breast-cancer risk for a negative *BRCA* test.

Although the probability of carrying a *BRCA1* or *BRCA2* mutation varies substantially according to the actual combination of risk factors in a given family, the presence of certain major risk factors or combinations of risk factors has been proposed as a reasonable criterion for consideration of testing for *BRCA* mutations (Table 5). As a first step in this process, the patient is given genetic counseling before testing to provide her with information about the probability that she carries a mutation in *BRCA1* or *BRCA2* and the benefits, risks, and limitations of testing. This is complex information that a woman needs to make an informed decision about *BRCA* testing.[61]

For women from families without risk factors for a *BRCA* mutation, genetic testing is unlikely to provide useful information about breast-cancer risk. Because *BRCA* mutations are rare in the non-Ashkenazi general population, with an estimated prevalence of approximately 1 in 1000, they account for less than 5 percent of the overall population burden of breast cancer.[62] Thus, women from low-risk families rarely test positive, and a negative test will not provide important new information about their risk of breast cancer.

Selecting a Prediction Method

Several factors influence the selection of a risk-prediction method for an individual woman. Different methods may be appropriate in different settings. Although qualitative assessment of breast-cancer risk factors may be sufficient for a woman 40 to 49 years old to make a decision about mammography, determining eligibility for tamoxifen prophylaxis requires a numerical probability estimate from a prediction model, and deciding whether to undergo prophylactic mastectomy often involves genetic-susceptibility testing. Although many women have difficulty manipulating probabilities in numerical exercises, genetic counseling and programs for the assessment of cancer risk have traditionally used probabilistic information in counseling.[63,64] In most settings, a numerical estimate of a woman's risk is useful information that can also be presented qualitatively.

TABLE 5. FAMILY-HISTORY RISK FACTORS FOR CARRYING A *BRCA1* OR *BRCA2* MUTATION.

Known *BRCA1* or *BRCA2* mutation
Breast and ovarian cancer
Two or more family members under 50 years of age with breast cancer
Male breast cancer
One or more family members under 50 with breast cancer plus Ashkenazi ancestry
Ovarian cancer plus Ashkenazi ancestry

For a woman with risk factors for carrying a *BRCA1* or *BRCA2* mutation, the first step is to determine whether she is interested in pursuing genetic testing. If she is, she should be referred, if possible, to a center that provides specialized genetic counseling for *BRCA* testing. A list of specialized centers can be found at http://cancernet.nci.nih.gov/genesrch.shtml or can be obtained by telephoning the Cancer Information Service at 1-800-422-6237 (1-800-4-CANCER). If referral is not possible or desired, appropriate individual counseling about the potential benefits, risks, and limitations of testing should be provided by the health care professional who ordered the test.[61] For women who choose to undergo testing and are found to carry a *BRCA* mutation, current evidence suggests that the lifetime risk of breast cancer is between 60 and 85 percent, and further assessment of breast-cancer risk with other prediction models is not meaningful.

For women with risk factors for carrying a *BRCA1* or *BRCA2* mutation who test negative for *BRCA* mutations or who choose not to undergo testing, and for women with one or more first- or second-degree relatives with breast cancer, the Claus model offers the most comprehensive assessment of family history. It can be supplemented by the Gail model, as modified by the Breast Cancer Prevention Trial, for purposes of making decisions about tamoxifen use. For women without first- or second-degree relatives with breast cancer, the Claus model is not applicable.

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REFERENCES

1. Ries LAG, Kosary CL, Hankey BF, Miller BA, Clegg L, Edwards BK, eds. SEER cancer statistics review, 1973-1996: tables and graphs. Bethesda, Md.: National Cancer Institute, 1999.
2. Offit K, Brown K. Quantitating familial cancer risk: a resource for clinical oncologists. J Clin Oncol 1994;12:1724-36.
3. Vogel VG. Assessing women's potential risk of developing breast cancer. Oncology (Huntingt) 1996;10:1451-8, 1461-3.
4. Preventive Services Task Force. Screening for breast cancer: guide to clinical preventive services. 2nd ed. Alexandria, Va.: International Medical Publishing, 1996:73-87.

5. Grodstein F, Stampfer MJ, Colditz GA, et al. Postmenopausal hormone therapy and mortality. N Engl J Med 1997;336:1769-75.
6. Folsom AR, Mink PJ, Sellers TA, Hong CP, Zheng W, Potter JD. Hormonal replacement therapy and morbidity and mortality in a prospective study of postmenopausal women. Am J Public Health 1995;85:1128-32.
7. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med 1995;332:1589-93.
8. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med 1992; 117:1016-37.
9. Col NF, Eckman MH, Karas RH, et al. Patient-specific decisions about hormone replacement therapy in postmenopausal women. JAMA 1997; 277:1140-7.
10. Col NF, Pauker SG, Goldberg RJ, et al. Individualizing therapy to prevent long-term consequences of estrogen deficiency in postmenopausal women. Arch Intern Med 1999;159:1458-66.
11. Colditz GA, Rosner BA, Speizer FE. Risk factors for breast cancer according to family history of breast cancer. J Natl Cancer Inst 1996;88:365-71.
12. Sellers TA, Mink PJ, Cerhan JR, et al. The role of hormone replacement therapy in the risk for breast cancer and total mortality in women with a family history of breast cancer. Ann Intern Med 1997;127:973-80.
13. Rockhill B, Weinberg CR, Newman B. Population attributable fraction estimation for established breast cancer risk factors: considering the issues of high prevalence and unmodifiability. Am J Epidemiol 1998;147: 826-33.
14. Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN. Proportion of breast cancer cases in the United States explained by well-established risk factors. J Natl Cancer Inst 1995;87:1681-5.
15. Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. Am J Epidemiol 1985;122:904-14.
16. Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med 1997;337:1641-7.
17. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. JAMA 1999;281:2189-97.
18. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. JAMA 1999;282:637-45.
19. Kerlikowske K, Grady D, Rubin SM, Sandrock C, Ernster VL. Efficacy of screening mammography: a meta-analysis. JAMA 1995;273:149-54.
20. Mettler FA, Upton AC, Kelsey CA, Ashby RN, Rosenberg RD, Linver MN. Benefits versus risks from mammography: a critical reassessment. Cancer 1996;77:903-9.
21. Lindfors KK, Rosenquist CJ. The cost-effectiveness of mammographic screening strategies. JAMA 1995;274:881-4. [Erratum, JAMA 1996;275: 112.]
22. Hendrick RE, Smith RA, Rutledge JH III, Smart CR. Benefit of screening mammography in women aged 40–49: a new meta-analysis of randomized controlled trials. In: Journal of the National Cancer Institute monographs no. 22. Bethesda, Md.: National Cancer Institute, 1997:87-92.
23. Kerlikowske K, Grady D, Barclay J, Sickles EA, Eaton A, Ernster V. Positive predictive value of screening mammography by age and family history of breast cancer. JAMA 1993;270:2444-50.
24. Salzmann P, Kerlikowske K, Phillips K. Cost-effectiveness of extending screening mammography guidelines to include women 40 to 49 years of age. Ann Intern Med 1997;127:955-65. [Erratum, Ann Intern Med 1998; 128:878.]
25. Mammography recommendations for women ages 40-49. Bethesda, Md.: National Cancer Advisory Board, 1997:1-5.
26. Rowe PM. ACS orders mammography for younger women. Lancet 1997;349:928.
27. Eddy DM. Screening for breast cancer. Ann Intern Med 1989;111: 389-99.
28. Taplin SH, Thompson RS, Schnitzer F, Anderman C, Immanuel V. Revisions in the risk-based Breast Cancer Screening Program at Group Health Cooperative. Cancer 1990;66:812-18. [Erratum, Cancer 1991;67: 2400.]
29. Gail M, Rimer B. Risk-based recommendations for mammographic screening for women in their forties. J Clin Oncol 1998;16:3105-14. [Erratum, J Clin Oncol 1999;17:740.]
30. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371-88.
31. Powles T, Eeles R, Ashley S, et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. Lancet 1998;352:98-101.
32. Veronesi U, Maisonneuve P, Costa A, et al. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. Lancet 1998;352:93-7.
33. Chlebowski RT, Collyar DE, Somerfield MR, Pfister DG. American Society of Clinical Oncology technology assessment on breast cancer risk reduction strategies: tamoxifen and raloxifene. J Clin Oncol 1999;17:1939-55.
34. Hartmann LC, Schaid DJ, Woods JE, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med 1999;340:77-84.
35. Stefanek ME. Bilateral prophylactic mastectomy: issues and concerns. In: Journal of the National Cancer Institute monographs no. 17. Bethesda, Md.: National Cancer Institute, 1995:37-42. (NIH publication no. 94-03837.)
36. Schrag D, Kuntz KM, Garber JE, Weeks JC. Decision analysis — effects of prophylactic mastectomy and oophorectomy on life expectancy among women with *BRCA1* or *BRCA2* mutations. N Engl J Med 1997; 336:1465-71. [Erratum, N Engl J Med 1997;337:434.]
37. Feuer EJ, Wun LM, Boring CC, Flanders WD, Timmel MJ, Tong T. The lifetime risk of developing breast cancer. J Natl Cancer Inst 1993;85: 892-7.
38. Slattery ML, Kerber RA. A comprehensive evaluation of family history and breast cancer risk: the Utah Population Database. JAMA 1993;270: 1563-8.
39. 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.
40. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med 1985;312:146-51.
41. Smith-Warner SA, Spiegelman D, Yaun SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA 1998;279: 535-40.
42. Hunter DJ, Spiegelman D, Adami H-O, et al. Cohort studies of fat intake and the risk of breast cancer — a pooled analysis. N Engl J Med 1996; 334:356-61.
43. Freudenheim JL, Marshall JR, Vena JE, et al. Lactation history and breast cancer risk. Am J Epidemiol 1997;146:932-8.
44. Rosenberg L, Palmer JR, Rao RS, et al. Case-control study of oral contraceptive use and risk of breast cancer. Am J Epidemiol 1996;143:25-37.
45. Michels KB, Willett WC. Does induced or spontaneous abortion affect the risk of breast cancer? Epidemiology 1996;7:521-8.
46. Hildreth NG, Shore RE, Dvoretsky PM. The risk of breast cancer after irradiation of the thymus in infancy. N Engl J Med 1989;321:1281-4.
47. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer: implications for risk prediction. Cancer 1994; 73:643-51.
48. Anderson DE, Badzioch MD. Risk of familial breast cancer. Cancer 1985;56:383-7.
49. Ottman R, Pike MC, King MC, Henderson BE. Practical guide for estimating risk for familial breast cancer. Lancet 1983;2:556-8.
50. Costantino JP, Gail MH, Pee D, et al. Validation studies for models projecting the risk of invasive and total breast cancer incidence. J Natl Cancer Inst 1999;91:1541-8.
51. Gail MH, Benichou J. Assessing the risk of breast cancer in individuals. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer prevention. Philadelphia: J.B. Lippincott, 1992:1-15.
52. Bondy ML, Lustbader ED, Halabi S, Ross E, Vogel VG. Validation of a breast cancer risk assessment model in women with a positive family history. J Natl Cancer Inst 1994;86:620-5.
53. Spiegelman D, Colditz GA, Hunter D, Hertzmark E. Validation of the Gail et al. model for predicting individual breast cancer risk. J Natl Cancer Inst 1994;86:600-7.
54. McGuigan KA, Ganz PA, Breant C. Agreement between breast cancer risk estimation methods. J Natl Cancer Inst 1996;88:1315-7.
55. Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994; 266:66-71.
56. Wooster R, Bignell G, Lancaster J, et al. Identification of the breast cancer susceptibility gene BRCA2. Nature 1995;378:789-92. [Erratum, Nature 1996;379:749.]
57. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of *BRCA1* and *BRCA2* among Ashkenazi Jews. N Engl J Med 1997;336:1401-8.
58. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet 1998;62:676-89.
59. Couch FJ, DeShano ML, Blackwood MA, et al. *BRCA1* mutations in women attending clinics that evaluate the risk of breast cancer. N Engl J Med 1997;336:1409-15.

60. Shattuck-Eidens D, Oliphant A, McClure M, et al. BRCA1 sequence analysis in women at high risk for susceptibility mutations: risk factor analysis and implications for genetic testing. JAMA 1997;278:1242-50.
61. Hoskins KF, Stopfer JE, Calzone KA, et al. Assessment and counseling for women with a family history of breast cancer: a guide for clinicians. JAMA 1995;273:577-85.
62. Ford D, Easton DF, Peto J. Estimate of the gene frequency of BRCA1 and its contribution to breast and ovarian cancer incidence. Am J Hum Genet 1995;57:1457-62.
63. Schwartz LM, Woloshin S, Black WC, Welch HG. The role of numeracy in understanding the benefit of screening mammography. Ann Intern Med 1997;127:966-72.
64. Rosser EM, Hurst JA, Chapman CJ. Cancer families: what risks are they given and do the risks affect management? J Med Genet 1996;33:977-80.