Strengths and Limitations of Breast Cancer Risk Assessment

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Purpose/Objectives: To evaluate current definitions of breast cancer risk and breast cancer risk assessment models, including the Gail, Claus, and BRCAPRO models, and discuss potential markers to enhance and standardize individual risk assessment.

Data Sources: Published articles, conference proceedings, and textbooks.

Data Synthesis: Defining high risk for breast cancer development is explored, and options for high-risk women are discussed. The risk factors frequently used for risk evaluation, including age, age at menarche, age at first live birth, past history of breast biopsy, family history of breast cancer, and the presence of atypical hyperplasia, are reviewed.

Conclusions: Current models of breast cancer risk assessment are limited. Exploring the progression from healthy tissue to malignancy through techniques such as fine needle aspiration, ductal lavage, and nipple aspiration may lead to more precise individualized risk prediction.

Implications for Nursing: More accurate information regarding personal breast cancer risk is necessary. Oncology nurses may facilitate the use of appropriate tools that provide the most individualized risk assessment.

Key Points . . .

- ➤ Assessing individual breast cancer risk has not been articulated in the United States despite an abundance of research devoted to risk factors.
- ➤ Currently employed risk assessment tools include the Gail model, the Claus model, and BRCAPRO.
- ➤ Exploring biologic markers such as atypical hyperplasia using minimally invasive methods (e.g., fine needle aspiration, ductal lavage, nipple aspiration) may enhance risk prediction.

Goal for CE Enrollees:

To enhance nurses' knowledge about breast cancer risk factors, risk assessment models, and potential areas for refinement.

Objectives for CE Enrollees:

1. Summarize the impact of known risk factors on the development of breast cancer.
2. Discuss the strengths and limitations of currently used breast cancer risk assessment models.
3. Describe the potential role of pathologic information in more precisely determining breast cancer risk.

Fear of developing breast cancer is well founded among women in the United States. Breast cancer is the leading cause of death among women aged 35–50 years and the second-leading cause of death in women older than 50 years (Jemal et al., 2005). Approximately 40,000 women will die from this disease in the United States in 2005. Refining the science of breast cancer risk assessment has become more important with the availability of genetic testing for mutations associated with an increased risk of breast cancer development and the manufacture of medications to reduce breast cancer risk (Hollingsworth, Nall, & Dill, 2002).

A standardized algorithm for breast cancer risk assessment is not available at this time in the clinical setting. Women are categorized as either having possible genetic or hereditary risk or as having risk factors unrelated to a family history of breast cancer. Genetic testing is limited as a risk assessment tool because only a small percentage of women carry known genetic mutations that result in an increased risk of breast cancer development. Mathematical models calculate probabilities of developing breast cancer over specified periods of time; however, the factors included in the models contribute a relatively small degree of risk for the eventual development of breast cancer. Hollingsworth et al. (2002) suggested that

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tissue- or serum-based strategies should be the next step in refining risk assessment, given that 70% of women who develop breast cancer have no identifiable risk factors.

Addressing inadequacies in breast cancer risk assessment may help to illuminate warning signs to women and healthcare providers as to who is at greatest risk for breast cancer development. This article will discuss risk assessment currently undertaken using the Gail and Claus models. In addition, the BRCAPRO program for assessing the probability of having known breast cancer genetic mutations will be discussed. Significant risk factors used in the clinical setting to determine risk will be outlined, as well as prevention options available to women deemed high risk. Abnormal epithelial breast cell cytology will be discussed as a potentially important risk factor to enhance current prediction models.

The Concept of High Risk

Defining High Risk

When is a woman at high risk for developing breast cancer? The generally agreed-upon risk factors currently used in various combinations in risk assessment models include being older than 65 years, experiencing early menarche (before 12 years of age), being nulliparous or having a first child after age 30, having a history of breast biopsy, and having a family history of breast cancer (Singletary, 2003). Radiation exposure at a young age (i.e., < 12 years) or as a treatment for Hodgkin disease also is associated with a higher risk of breast cancer development; however, it is not used as a risk factor in current risk assessment models (Clemons, Loijens, & Goss, 2000). The presence of atypical hyperplasia in breast tissue or fluid samples as a risk marker has shown significance in several studies (Fabian et al., 2000; Wrensch et al., 2001). Various techniques to obtain this finding through histology and cytology have been discussed in greater detail in another article (Baltzell, Eder, & Wrensch, 2005). Other factors contributing smaller degrees of risk for breast cancer development include drinking more than two alcoholic beverages per day, having a high body mass index in women older than 55 years, using hormone replacement therapy, and experiencing menopause after 55 years of age. Singletary succinctly listed the risk factors for breast cancer development (see Table 1). As more of these risk factors are present, the chance of developing breast cancer increases. The presence of a mutated *BRCA1* or *BRCA2* gene is currently the generally agreed-upon definition of high risk for breast cancer development. Multiple first-degree relatives with breast cancer and no mutated *BRCA1* or *BRCA2* gene in a woman's family history may suggest high-risk status, perhaps related to unknown genetic mutations.

If high risk was defined as a woman who has risk factors carrying a relative risk of greater than 2 (relative risk is the ratio of breast cancer risk among women with identified risk factors to the risk of breast cancer among women without those identified risk factors), then risk factors such as age, past personal history of breast cancer, lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS), biopsy findings of hyperplasia with atypia, atypia with a positive family history of breast cancer, first-degree relative with premenopausal breast cancer, more than two first-degree relatives with breast cancer, and known *BRCA1* or *BRCA2* mutations would provide information correlated with high risk. However, the majority of women seen in the clinical setting will not have information about their cellular or genetic risk factors (i.e., LCIS, DCIS, hyperplasia with atypia, *BRCA1* and *BRCA2* mutations). Obtaining information about these cellular or genetic risk factors may lead to a more concise and accurate definition of "high risk."

Accurate risk assessment is becoming increasingly important as potential prevention options, particularly prophylactic surgery and chemoprevention (Singletary, 2003), become available; however, these options are accompanied by their own set of risks. A decision to proceed with prophylactic surgery or chemoprevention should be made with as precise an assessment as possible. Because each of the currently available assessment tools uses different variables to assess risk, a precise definition is elusive. According to Verp, Cummings, and Olopade (2001), most cancers develop as a result of a combination of genetic and environmental factors. Despite years of research dedicated to articulating the risk factors leading to breast cancer development, no model completely calculates a woman's risk with great accuracy, with the exception of genetic testing indicating the presence of a *BRCA1* or *BRCA2* mutation (Winer, Morrow, Osborne, & Harris, 2001). Even genetic testing models are limited, given that they are based on very few of the possible mutations that increase breast cancer risk and are only definitive in families in which these mutations have been demonstrated (Berry et al., 2002).

Hamolsky and Facione (1999) described the importance of assisting women in making realistic appraisals of their personal risks. They reported that breast cancer risk estimates are misleading for many women because each woman has her own unique circumstances. According to Kelly (2000), although most women have beliefs regarding the cause of breast cancer, not all of those beliefs fit with current scientific findings. Women consistently overestimate their risk of developing breast cancer, which can lead to screening avoidance and psychological morbidity (Armstrong, Eisen, & Weber, 2000; Black, Nease, & Tosteson, 1995). Not every woman who has all of the currently recognized risk factors will develop breast cancer; therefore, more accurate risk assessment tools must be developed. Given that prophylactic surgery or chemopreventive drugs are the currently available breast cancer prevention choices, a woman must feel confident that her risk assessment is as complete as possible.

Breast Cancer Prevention Options

In the clinical setting, a limited number of breast cancer prevention options are available for women determined to be at extremely high risk for developing breast cancer (i.e., *BRCA1* or *BRCA2* mutations, a strong family history of breast cancer in first-degree relatives). These options include prophylactic surgery, chemopreventive drugs, and lifestyle modifications. If an extensive family history of breast cancer is found, genetic counseling or testing, if appropriate, should be offered to ascertain whether a *BRCA1* or *BRCA2* mutation is present. Although high penetrance genes are thought to account for only 10%–20% of breast cancers, the risk of developing breast cancer in the presence of these genes is high (Hamolsky & Facione, 1999).

Prophylactic mastectomy is associated with a risk reduction of more than 90% in women with strong family histories of breast cancer (Hartmann et al., 1999). The risk reduction associated with this procedure was similar for women with a strong family history and a subset of women with positive

Table 1. Risk Factors for Breast Cancer

Risk Factor	Category at Risk	Comparison Category	Relative Risk
Alcohol intake	2 drinks per day	Nondrinker	1.2
Body Mass Index	80th percentile, age 55 or greater	20th percentile	1.2
Hormone replacement therapy with estrogen and progesterone	Current user for at least 5 years	Never used	1.3
Radiation exposure	Repeated fluoroscopy	No exposure	1.6
	Radiation therapy for Hodgkin's disease	No exposure	5.2
Early menarche	Younger than 12 years	Older than 15 years	1.3
Late menopause	Older than 55 years	Younger than 45 years	1.2–1.5
Age at first childbirth	Nulliparous or 1st child after 30	1st child before 20	1.7–1.9
Current age	65 or older	Less than 65	5.8
Past history of breast cancer	Invasive breast carcinoma	No history of invasive breast carcinoma	6.8
Other histologic findings	Lobular carcinoma in situ	No abnormality detected	16.4
	Ductal carcinoma in situ	No abnormality detected	17.3
Breast biopsy	Hyperplasia without atypia[a]	No hyperplasia	1.9
	Hyperplasia with atypia	No hyperplasia	5.3
	Hyperplasia with atypia and positive family history	No hyperplasia, negative family history	11.0
Cytology (fine-needle aspiration, nipple aspiration fluid)	Proliferation without atypia[a]	No abnormality detected	2.5
	Proliferation with atypia	No abnormality detected	4.9–5.0
	Proliferation with atypia and positive family history	No abnormality detected	18.1
Family history	1st-degree relative 50 years or older with postmenopausal breast cancer	No 1st- or 2nd-degree relative with breast cancer	1.8
	1st-degree relative with premenopausal breast cancer	No 1st- or 2nd-degree relative with breast cancer	3.3
	2nd-degree relative with breast cancer	No 1st- or 2nd-degree relative with breast cancer	1.5
	Two 1st-degree relatives with breast cancer	No 1st- or 2nd-degree relative with breast cancer	3.6
Germline mutation	Heterozygous for *BRCA1,* age < 40	Not heterozygous for *BRCA1,* age < 40	200.0[b]
	Heterozygous for *BRCA1,* age 60–69	Not heterozygous for *BRCA1,* age 60–69	15.0[b]

[a] There is controversy over whether pathologic hyperplasia detected in breast biopsy samples is directly equivalent to cytologic hyperplasia detected in samples obtained through FNA [fine needle aspiration] or nipple aspiration.

[b] Begg (2002) has suggested that these relative risks are subject to ascertainment bias and may overestimate the true risk associated with germline mutations in BRCA genes.

Note. From "Rating the Risk Factors for Breast Cancer" by S.E. Singletary, 2003, *Annals of Surgery, 237,* p. 475. Copyright 2003 by Lippincott Williams and Wilkins. Reprinted with permission.

BRCA1 and *BRCA2* mutations. Although genetic testing is not suggested routinely for screening, a detailed family history indicating many relatives with breast or ovarian cancers may warrant offering genetic counseling. If a woman is found to be positive for genetic alterations of genes *BRCA1* or *BRCA2,* prophylactic mastectomy may be recommended. Love, Newcomb, and Trentham-Dietz (2002) recognized the magnitude of suggesting such a prevention strategy by stating, "In the absence of clinically applicable comprehensive risk models for individual patients, indications for prophylactic mastectomy must be strong and specific" (p. 210).

The removal of a woman's ovaries, or prophylactic oophorectomy, has been effective in reducing breast cancer risk in women with a known *BRCA1* or *BRCA2* mutation. Removing the ovaries in premenopausal women diminishes the amount of estrogen circulating that can stimulate breast cancer cells. When this source of estrogen is eliminated in women with genetic mutations known to increase risk of breast cancer development, risk has been reduced by approximately 50% (Olopade & Artioli, 2004).

Chemoprevention is described as "the use of specific natural and synthetic chemical agents to reverse or suppress carcinogenesis and prevent the development of invasive cancer" (Hamolsky & Facione, 1999, p. 427). At present, the agents used for chemoprevention are a group known as selective estrogen receptor modulators (SERMs). Tamoxifen is the most widely prescribed SERM, and raloxifene currently is being evaluated for its effectiveness in preventing breast cancer development. SERMs act as estrogen agonists in some tissue (e.g., bone, endometrial) and as estrogen antagonists in other tissue (e.g., breast) (Brinton, Lacey, & Devesa, 2002). In the National Surgical Adjuvant Breast and Bowel Project (NSABP), a 49% lower risk of breast cancer was found in a tamoxifen-treated group versus a placebo-treated group (Fisher et al., 1998). Differences were apparent in groups within various studies; in a trial at the Royal Marsden Hospital, Eeles and Powles (2000) found that

SERMs were less effective in women with *BRCA1* and *BRCA2* mutations. Fisher et al. reported that the greatest risk reduction was in women with atypical hyperplasia. Risks associated with taking SERMs include stroke, deep vein thrombosis, and uterine cancer. Brinton et al. noted that although the overall results of SERM trials are informative, the analyses are less useful to individuals and their clinicians trying to make informed decisions regarding the appropriateness of this prevention strategy. That is, clinical guidelines are not yet clear about the recommendation of SERMs for breast cancer prevention.

Lifestyle changes have been examined in an effort to determine which may modify breast cancer risk. Dietary fat has been studied extensively as a risk factor for breast cancer development. According to Kushi and Giovannucci (2002), recommendations to reduce fat intake to prevent cancer risk are unwarranted. Drake (2001) reported that female joggers were less likely to develop breast cancer than those who did not jog. In another study, lifelong physical activity was potentially useful in reducing breast cancer risk (Bernstein, Henderson, Hanisch, Sullivan-Halley, & Ross, 1994). Physical activity in young women is associated with delayed menarche and anovulatory cycles, perhaps reducing overall lifetime exposure to estrogen. Although studies have not found a highly significant association between lifestyle variables and breast cancer prevention, a reduced-fat diet and increased exercise may be beneficial in regard to other diseases (e.g., cardiovascular disease). Love et al. (2002) created a table of possible primary prevention strategies categorized by age group (see Table 2). These interventions relate to the timing of breast tissue development and the role of hormonal changes leading to breast cancer susceptibility but do not necessarily include truly feasible or desirable modifications or programs for women. To recommend breast cancer prevention strategies, a comprehensive breast cancer risk assessment is necessary.

Table 2. Primary Prevention Interventions Most Important at Different Ages

Age	Primary Prevention Interventions
Preadolescence and adolescence	Limit chest and breast radiation Tobacco avoidance Regular exercise Avoid excessive calories and weight gain Increase fruits and vegetables: carotenoids and folic acid
Childbearing years	Early first full-term pregnancy Lactation, for long duration Avoid weight gain Regular exercise No or limited alcohol
In the 40s	Avoid weight gain Weight loss Regular exercise *The following interventions are most appropriate for women with extensive family history of breast cancer or known* BRCA1 *or* BRCA2 *mutations:* Prophylactic oophorectomy Prophylactic mastectomy SERM therapy
Menopausal years	Avoid weight gain Weight loss Regular exercise Limit estrogen replacement therapy *The following intervention is most appropriate for women with extensive family history of breast cancer or multiple identified breast cancer risk factors:* SERM therapy

SERM—selective estrogen receptor modulator

Note. From "Prevention of Breast Cancer" by R.R. Love, P.A. Newcomb, and A. Trentham-Dietz in *Cancer of the Breast* (5th ed., p. 218) by W.L. Donegan and J.S. Spratt (Eds.), 2002, Philadelphia: Saunders. Copyright 2002 by Elsevier. Reprinted with permission.

Risk Factors

Age, age at menarche, age at first live birth, family history of breast cancer, past history of breast biopsy, and the presence of atypical hyperplasia are risk factors that can be taken into account when assessing breast cancer risk. Table 3 summarizes the potential modifiability of these risk factors.

Age

Of all the commonly used risk factors to predict breast cancer, increasing age is believed to have the most significance (Winer et al., 2001). In more than 50% of women diagnosed with breast cancer, increasing age is the only identifiable risk factor (Madigan, Ziegler, Benichou, Byrne, & Hoover, 1995). Risk of breast cancer development increases steadily until age 70, at which point risk actually declines (Kelly, 2000). The commonly quoted 1 in 8 risk is derived from the addition of age-stratification risk numbers. Women aged 20–50 years have a 2% risk of breast cancer development (1 in 50), women aged 50–70 years have a 6% risk of breast cancer development (1 in 17), and women aged 70–80 years have a 3% risk (1 in 33) (Kelly). These are generalized risk numbers that cannot be used effectively for individual risk assessment. In nonhereditary breast cancers, the increased risk of breast cancer with advancing age may come more from "wear and tear" on genetic material, providing an opportunity for mutations to occur or from decreased immune surveillance. Recent statistics are listed in Table 4 and show the increased number of diagnoses as women age (Jemal et al., 2005).

Age at Menarche

Risk assessment often categorizes age at menarche as less than 12 years or more than 15 years, representing higher versus lower risk, respectively. If lifetime exposure to estrogen is associated with risk determination for breast cancer, then the number of actual cycles an individual has provides important estrogen exposure information. Age at menarche has received more attention in recent years because of observations of earlier onset of puberty in the United States (Lee, Guo, & Kulin, 2001). The combinations of higher fat and protein diets and effective disease control are believed to have had an impact on lowering the age of menarche (Henderson, Pike, Bernstein, & Ross, 1996). MacMahon et al. (1982) reported that establishment of ovulatory cycles and increased hormone levels found in women who experienced early menarche play a role in promoting breast cancer risk. Henderson et al. suggested that for women of equivalent age, those with more than 40 years of menstruation have twice the risk of those with fewer than 30 years of menstruation. Strategies for decreasing risk may

Table 3. Summary of Risk Factor Modification Feasibility

Risk Factors	Risk Modifiable?	Risk Modifiable at Age of Concern[a]	Advantages	Disadvantages
Age	No	No	Not applicable	Not applicable
Age at menarche	Possibly	No	Encouragement of increased exercise and lifelong healthy habits	Adolescence is the time of increased body image distortion and onset of eating disorders. The effect on other disease development is unknown.
Age at first live birth	Yes	No	Could confer a protective period postpregnancy at critical time for breast carcinogenesis	Economic instability associated with young maternal age may create other health issues that are more threatening than breast cancer development.
Past history of breast biopsy	Partially	No	Obtain information related to high-risk cellular abnormalities via less invasive methods (e.g., fine needle aspiration, nipple aspirate fluid, lavage).	Less invasive methods are not commonly practiced; accurate pathology reading is crucial for risk information.
Family history of breast cancer	No	No	Not applicable	Not applicable
Atypical hyperplasia	Unknown	Possibly[b]	Not applicable	Not applicable

[a] Age of concern is defined as the age at which risk for breast cancer development increases significantly. For purposes of this table, age 40 begins the "age of concern" based on the probability increase from 1 in 228 (age birth to 39) to 1 in 24 (age 40–59).

[b] Petrakis et al. (1996) found an increase in cytologic detection of epithelial hyperplasia in breast fluids after increased consumption of soy protein in a small study of women aged 30–58. This indicates the possibility of exogenous influences in altering the progression of atypical hyperplasia.

include looking at adolescence as an effective intervention age. Encouraging increased amounts of exercise and healthy eating habits may influence menarche onset by a small margin; however, each year of menarche delay may provide a significant decrease in later breast cancer risk. In addition to the benefit of fewer menstrual cycles resulting in decreased estrogen exposure in the breast tissue, exercise and healthy eating may contribute to decreased weight gain in adulthood. Adipose tissue is a major source of estrogen in postmenopausal women. Weight loss and low body mass index are associated with a decreased risk of breast cancer in postmenopausal women; however, this type of advice should be given cautiously. Recommending "thinness" to an adolescent girl may be associated with the development of eating disorders such as anorexia nervosa and bulimia (Martin & Ammerman, 2002). In addition, the burden of possible breast cancer development should not be added to adolescent worries, particularly if the timing of menarche can be altered only by radical shifts in lifestyle.

Age at First Live Birth

Chie et al. (2000) compared age at first pregnancy for breast cancer cases and controls and found a modest increased risk in breast cancer development (odds ratio = 1.07, confidence interval = 1.01–1.13) for each five-year increase in age at first full-term pregnancy. MacMahon et al. (1970) reported that women with their first full-term pregnancy before age 20 had a third of the breast cancer risk compared with women having their first full-term pregnancy after age 35. A short-term increased risk of breast cancer development may occur after pregnancy at any age; however, mammary cells become differentiated after this risk period, resulting in less susceptibility to carcinogenesis. This increased risk period is believed to last approximately 10 years (Bruzzi et al., 1988). An early pregnancy allows for mammary cell differentiation at an early age in a woman's reproductive life, perhaps conferring a protective effect during later high-risk years. Brinton et al. (2002) found the protective effect of early pregnancy only with full-term pregnancy. Singletary (2003) suggested that this is because of cell differentiation in preparation for lactation in the later stages of pregnancy. Brinton et al. also reported that nulliparous women and women who give birth around age 30 share a similar risk of breast cancer development. A full-term pregnancy after age 30 is associated with higher risk than nulliparity, possibly as a result of the increased risk period immediately after pregnancy. Brinton et al. speculated that already initiated cells may progress during the short-term high-risk period following later-age pregnancy. Because the protective effect of pregnancy is associated with maternal age of less than 20 years of age, it is unlikely to be a risk factor that is altered easily. However, the social trend toward later maternal age at pregnancy is continuing in North American societies (Lee et al., 2003), but changing reproductive choice, as suggested by Love et al. (2002), is unrealistic in any risk intervention strategy.

Table 4. Advancing Age and Corresponding Increase in Breast Cancer Rates

Age (Years)	% Diagnosed With Breast Cancer	Actual Number of Cases per Interval
0–39	0.4	1 in 228
40–59	4.0	1 in 24
60–79	7.0	1 in 14
Lifetime risk[a]	12.0	1 in 8

[a] With each age interval passed without a breast cancer diagnosis, risk for that category should be subtracted from subsequent age intervals (Kelly, 2000).

Note. Based on information from Jemal et al., 2005.

Past History of Breast Biopsy

According to Page et al. (1978), women with a history of breast biopsy have an elevated risk of approximately twice the general population for future breast cancer development. This

is because of the underlying presence of benign breast disease, which has been found to be significantly associated with breast cancer development (Webber & Boyd, 1986). Breast biopsy history has been included in the Gail risk model as an important risk factor. Kelly (2000) argued against using the number of biopsies in a risk model because some, but not all, benign breast disease leads to biopsy, limiting its usefulness as a risk marker. Hughes, Mansel, and Webster (2000) wrote, "There is no reason to believe that the clinical presentations that induce a surgeon to perform a biopsy will be associated with high-risk pathology as most of the hyperplastic lesions with atypia are found incidentally at biopsy for a condition such as dominant nodularity" (p. 255). Is the fact that a woman had a biopsy important in risk assessment? Using the actual results of the biopsy may be more informative, but only if hyperplasia or atypical hyperplasia is present. Page et al. investigated the link between histologic changes present in breast tissue and breast cancer risk and concluded that benign breast disease is not necessarily associated with increased cancer risk; however, histologic changes defined as epithelial proliferative disease may distinguish high-risk groups from women with general population risk. Winer et al. (2001) noted that most breast biopsies result in nonproliferative disease findings. Using the number of biopsies in a risk model would lead to an overestimation of risk based on this information. Refining the concept of breast biopsy numbers is necessary for value in clinical decision making. Suggesting biopsies for large populations of at-risk women is unrealistic and cost prohibitive. Determining the presence of abnormal proliferative changes through less invasive methods that may lead to biopsy might improve the prediction value and specificity of this factor. Perhaps the incorporation of pathology findings (via biopsy, fine needle aspiration, lavage, or nipple aspiration) is more essential for enhanced risk assessment.

Family History of Breast Cancer

A family history of breast cancer is associated with a significant increase in breast cancer risk; however, only 5%–10% of breast cancers are believed to have strong hereditary origins (Winer et al., 2001). In addition, Winer et al. wrote that "family history is a heterogeneous risk factor with different implications depending on the number of relatives with breast cancer, the exact relationship, the age at diagnosis, and the number of affected relatives" (p. 1652). A person with multiple relatives diagnosed with breast cancer at an early age is at greater risk than a woman with one relative diagnosed at a postmenopausal age. Kelly (2000) listed the following indications that hereditary cancers may be present: young age at diagnosis, one person diagnosed with several different cancers, cancers present in two or more generations, and three or more cancers found in close relatives. Complicating the family history is that shared environment might contribute to disease development in all family members, independently of any inherited genetic mutation.

Two tumor suppressor genes have been identified that are associated with true genetic risk of breast cancer development. Located on chromosome 17 is *BRCA1,* and on chromosome 13 is *BRCA2* (Winer et al., 2001). Mutations in either of these genes correlate with a 50%–85% lifetime chance of developing breast cancer. Additionally, these mutations can be passed down by either the mother or father. The large size of *BRCA1* and *BRCA2* makes genetic testing prohibitively expensive and unreasonable for large populations (Winer et al.). The cost of testing for a BRCA mutation was more than $2,500 in 2000 (Kelly, 2000). Also, all *BRCA1* and *BRCA2* mutations are not the same. Researchers have been unable to determine whether mutations in different locations on the gene convey the same level of risk. At this time, a positive genetic test means that a person might be at increased risk for breast cancer development; however, a negative test cannot rule out the possibility of another unknown mutation. Counseling a woman in regard to genetic testing involves a complex and complete screening process, including the discussion of breast cancer prevention strategies available in the event of a positive test. Other considerations regarding genetic counseling include the need for privacy and availability of qualified genetic counselors to guide future decisions affected by the presence of *BRCA1* and *BRCA2* mutations.

Atypical Hyperplasia

Recent studies have demonstrated a significant relationship between the presence of atypical hyperplasia in breast tissue or fluid samples and increased breast cancer risk (Fabian et al., 2000; Wrensch et al., 2001). Cytologic and histologic attributes associated with atypical hyperplasia include (a) an increase in cellular mitotic activity, (b) nuclear enlargement, (c) irregular nuclear borders, (d) nuclear hyperchromasia, (e) involvement of two or fewer ductal sections, and (f) foci measuring less than 2 mm (Rosen, 2001). Cells may be obtained by a number of methods, including breast biopsy, fine needle aspiration, ductal lavage, and nipple aspiration; however, results may vary based on the method of cell extraction chosen. Dupont and Page (1985) reexamined breast biopsies of 3,303 women after 17 years and found that women with atypical hyperplasia had a relative risk for invasive breast cancer of 5.3, with an increased relative risk of 11 for women with atypical hyperplasia and a positive family history. Inspired by an early study (Papanicolaou, Holmquist, Bader, & Falk, 1958), Sartorius, Smith, Morris, Benedict, and Friesen (1977) developed a nipple aspiration device to obtain breast fluid from 1,706 women. Fluid was obtained in approximately 50% of the cohort, and study results indicated a significant relationship between the presence of atypia and underlying breast cancer. Fabian et al. used fine needle aspiration to examine cells for the presence of atypical hyperplasia and determined that cytomorphologic findings of atypical hyperplasia are useful in evaluating short-term breast cancer risk. In several studies. abnormal cellular cytology in breast fluid was associated with an increased risk of breast cancer (Wrensch et al., 1992, 2001; Wrensch, Petrakis, King, Lee, & Miike, 1993). King, Chew, Petrakis, and Ernster (1983) documented the high correlation between atypical hyperplasia found in nipple aspirate fluid and atypical proliferative disease found in breast biopsy. This study confirmed the feasibility of using any of the available methods (biopsy, fine needle aspiration, ductal lavage, or nipple aspiration) to examine abnormalities associated with higher breast cancer risk. If cytologic and histologic methods of obtaining cells yield equally accurate information, choosing less invasive and costly procedures (e.g., fine needle aspiration, nipple aspiration) would allow for broader use of this marker for risk assessment. Dooley et al. (2001) concluded that ductal lavage is safe and well tolerated by most women, as well as a source of many breast epithelial cells for analysis. O'Shaughnessy (2001) stated that ductal lavage was a promising risk assessment tool. In addition, a number of breast cancer specialists recommended incorporating breast fluid findings into the breast cancer risk profile (Goodman, 2002).

Current Models of Breast Cancer Risk Assessment

Overview

For the purposes of this article, a breast cancer risk assessment model refers to mathematical models that calculate actual risk of breast cancer development as well as genetic tests (e.g., BRCAPRO) that examine known breast cancer gene mutations (e.g., *BRCA1, BRCA2*). The most commonly employed breast cancer risk assessment models currently are the Gail model and the Claus model (mathematical models) and BRCAPRO, which is used to evaluate the possible presence of genetic mutations associated with increased risk of breast cancer development. The Tyrer-Cuzick model has been developed to address concerns and limitations of currently used models. This model incorporates the likelihood of the presence of genes predisposing one to breast cancer, as well as personal risk factors (Tyrer, Duffy, & Cuzick, 2004). However, this model has not been validated independently (Amir et al., 2003). Euhus (2001) stated that an understanding of the principles used in each of these models is essential for healthcare professionals engaged in risk management counseling. MacDonald (2002) suggested that all healthcare providers will come in contact with a woman who has a family history of breast cancer at some point, given the prevalence of this disease. Risk assessment models are not used uniformly in clinical practice, making the accuracy of each woman's risk assessment a function of her provider's knowledge. Regarding healthcare providers, Kelly (2000) reported, "Many have a general knowledge of breast cancer risks, but few make it their specialty, have the time to keep up with all the latest developments in this area, or are aware of all whose risk might be increased" (p. 174).

Gail Model

Gail et al. (1989) developed a mathematical model for risk assessment of invasive and in situ breast cancer using information from 284,780 Caucasian women participating in the Breast Cancer Detection Demonstration Project from 1973–1980. This was a first attempt to refine population characteristics and based risk assessment on subgroups of women with varying risk factors, including age, age at menarche, number of prior breast biopsies, age at first live birth, and number of first-degree relatives affected with breast cancer. Relative risk was calculated for each of these risk factors; those relative risks (i.e., the probability of developing breast cancer in a given population) then were used to calculate absolute risk at five years from the time of assessment and a lifetime risk up to the age of 90. This model has been modified to include African Americans as well as Caucasians and uses invasive cancer as the only defined "breast cancer event" (Euhus, Leitch, Huth, & Peters, 2002). In addition, the presence of atypical hyperplasia has been added as a risk factor (Euhus, Leitch, et al.). The modified Gail model was used to qualify women for enrollment eligibility by the NSABP to assess the effectiveness of tamoxifen in preventing breast cancer development. Women with a five-year Gail score of more than 1.7% were designated "high risk" and qualified for participation in the tamoxifen study. In addition, this model was used for selection of candidates for the Study of Tamoxifen and Raloxifene trial comparing the effectiveness of tamoxifen versus raloxifene (Euhus, 2001).

Strengths of the Gail model include its attempt to adapt risk assessment from the general population to be more applicable to specific subgroups. In a study by Euhus, Leitch, et al. (2002), the Gail model was useful in specialized clinic settings, although it is criticized widely for not accounting for adequate family history information. The Gail model was developed prior to extensive genetic testing and now is thought to be most applicable to women without a strong family history suggestive of an inherited genetic mutation (Sakorafas, Krespis, & Pavlakis, 2002).

Criticisms of the Gail model are wide and varied, but it is limited by the characteristics of the data set used for its development. Kelly (2000) reported that the Gail model was problematic because (a) relative risk is not an accurate way to obtain absolute risk, (b) the number of biopsies included in the calculation is too simplistic (the pathology information obtained from the biopsy is more informative than the fact that a biopsy was performed), (c) all relevant family history is not included (i.e., grandparents and paternal history relatives are excluded), and (d) risk is overestimated in young women. Bondy and Newman (2003) found that the model has not been validated in African American women and stated their concern relative to enrollment and recruitment of African Americans in the ongoing NSABP trials. In addition to complaints regarding lack of validation for African Americans, no attempt has been made to validate the Gail model in other ethnic populations. The addition of atypical hyperplasia may enhance model accuracy; perhaps this would replace the number of biopsies with more useful biologic information.

Claus Model

In 1993, Claus, Risch, and Thompson published information on a model that incorporated extensive family history of cancer development. These data were obtained from the Cancer and Steroid Hormone Study, consisting of interviews of 4,730 confirmed breast cancer cases and 4,688 controls. The final model included breast cancer information on not only mothers and sisters but aunts and grandmothers as well. The development of the Claus model supported the notion that inherited genetic mutations might increase the risk of breast cancer and was a hint of a genetic component that would be elucidated further in the following five years (Euhus, 2001). The Claus model also addressed an inadequacy of the Gail model. The strength of the Claus model is its ability to incorporate the age of affected family members at diagnosis into the analysis. Since the discovery of *BRCA1* and *BRCA2* mutations, this information has taken on more importance, given that a woman with early onset of the disease is more likely to carry one of these mutations. However, the Claus model does have its own limitations: It does not include known breast cancer risk factors that are unrelated to family history of breast cancer, such as those included in the Gail model (Euhus). Therefore, the Claus model cannot be used among women without a family history of breast cancer. Because of the small sample size of African Americans in the original data set, final risk assessments did not include race. Other ethnicities were not addressed, probably because of the limited amount of information available for analysis. This model may be most helpful for women with a strong family history of breast cancer. Comparisons between the Gail and Claus model are shown in Table 5.

Table 5. Variables Used in the Gail and Claus Models

Variable	Gail	Claus
Age	Yes	Yes
First-degree family history (i.e., mother, sisters, and daughters)	Yes	Yes
Second-degree family history (i.e., aunts and grandmothers)	No	Yes
Age at onset in relatives	No	Yes
Age at menarche	Yes	No
Age at first live birth	Yes	No
Number of breast biopsies	Yes	No
Atypical hyperplasia	Yes	No
Race and ethnicity	Yes	No

Note. Based on information from McTiernan et al., 2001.

BRCAPRO

Unlike the Gail and Claus models of breast cancer risk assessment, BRCAPRO is used to determine the probability of having a genetic mutation (specifically *BRCA1* or *BRCA2*) associated with an increased risk of developing breast cancer. Although other genetic risk models exist, BRCAPRO is considered the most comprehensive (Allain, Gilligan, & Redlich, 2002). It is described as mathematically "intense" and uses Bayes theorem to answer the questions: "Given this pattern of affected and unaffected relatives, what is the probability that this individual carries a mutation in one of the BRCA genes? Given this BRCA gene mutation probability, what is the probability that this individual will develop breast cancer?" (Euhus, 2001, p. 228). The reliability of the calculation grows as more information is added to the model about the age and history of relatives with breast and ovarian cancer. Euhus wrote that the key to the usefulness of this model lies in knowing the underlying frequency of mutated genes in the population to which a patient belongs (e.g., European American, Eastern European Jewish).

BRCAPRO was found to be relatively accurate in predicting the presence of BRCA mutations in samples where the probability of penetrance was either very high (> 95%) or very low (< 5%) (Berry et al., 2002). BRCAPRO is a sensitive tool, missing only 15% of mutations present; however, Berry et al. did not determine whether this tool is useful in predicting which mutation carriers will develop breast cancer. Additional studies found that BRCAPRO more accurately identified possible mutations than experienced risk counselors (Euhus, Smith, et al., 2002). Limitations of the model include its underestimation of women's risk when familial clustering is unrelated to BRCA gene mutation (Euhus, 2001). Allain et al. (2002) listed lack of verification of family history as another limitation of this tool. BRCAPRO does not evaluate risk factors unrelated to family history (e.g., reproductive risk factors, presence of atypical hyperplasia). See Table 6 for a comparison of the three breast cancer risk assessment models.

Using Atypical Hyperplasia to Enhance Assessment Models

Most women who develop breast cancer do not have a known genetic mutation that indicates increased risk for the disease. How can more specific biologic information be obtained to refine breast cancer risk assessment? Perhaps examining breast epithelial cells (via lavage, nipple aspirate fluid, or periareolar fine needle aspiration) will illuminate cellular changes leading to cancer development. Daly and Ross (2000) stated that an understanding of the biologic progression from healthy breast epithelium to malignancy has been impeded by a lack of access to at-risk tissue for surveillance. Studies show atypical hyperplasia's contribution to increased risk in breast cancer development to be four- to fivefold in atypical hyperplasia, rising to anywhere from 11- to 18-fold in women with atypical hyperplasia and family history of breast cancer (Dupont & Page, 1985; Singletary, 2003). These relative risks are higher by a substantial margin than relative risks of currently accepted breast cancer risk factors such as age at menarche or age at first pregnancy. Increased emphasis should be placed on obtaining biologic markers of breast cancer risk that will allow for more accurate assessment of who is truly at risk for disease development. O'Shaughnessy (2001) wrote that more specific tools, such as ductal lavage to obtain cytologic information, are necessary to substratify women into useful risk assessment categories. Promising studies indicate that evaluating breast epithelium may yield important clues as to who may be at great risk for breast cancer (Fabian et al., 2000; Wrensch et al., 2001). This addition to risk assessment has become more feasible because data from less invasive means (nipple aspiration) provide

Table 6. Advantages and Disadvantages of the Gail, Claus, and BRCAPRO Models

Characteristic	Gail	Claus	BRCAPRO
Advantages	Accurately predicts the number of expected cases of breast cancer in large-scale clinical trials; incorporates nonfamily risk factors	Uses information from first- and second-degree relatives; incorporates age at diagnosis of affected family members	Most comprehensive estimate of genetic mutation risk; highly sensitive
Disadvantages	All relevant family history of breast cancer is not included; the model may overestimate risk in young women.	Does not include breast cancer risk factors other than family history	Underestimates risk in women with familial clustering unrelated to *BRCA1* and *BRCA2* mutations; does not evaluate risk factors unrelated to family history of breast cancer
High-risk definition	High risk is defined as a score of more than 1.7% within a five-year time period.	–	–
Most appropriate population	Women without a strong family history of breast cancer	Women with a strong family history of breast cancer	Women with a strong family history of breast or ovarian cancer

a degree of pathologic information on par with breast biopsy (King et al., 1983). In the past, cytologic information has been available only for a limited number of at-risk women, which has made the inclusion of atypical hyperplasia information sporadic in risk assessment models. Incorporating these findings into regular risk assessment may help to further specify who requires more aggressive, invasive follow-up. At present, assessment of atypical ductal hyperplasia may be one of the risk assessment tools with the most potential.

Conclusion

The mathematical Gail and Claus models may benefit from the addition of a serum- or tissue-based biologic marker of breast cancer risk. As these models are used currently, certain women's risk of breast cancer development may be overestimated or underestimated. Risk factors used in these models are largely unmodifiable, either practically or ethically. In addition, many of the risk factors used for assessment contribute very small relative risks, making their importance in risk models questionable. The definition of who is at high risk for breast cancer development should be expanded and articulated. The development of breast cancer prevention options makes this articulation even more critical. Fisher et al.'s (1998) conclusion that tamoxifen was most beneficial in women with atypical hyperplasia suggested an important link between cytologic findings and benefit from prevention strategies. Studying cytologic and histologic proliferative patterns such as atypical hyperplasia may lead to the next step in refining risk assessment.

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