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Review

Current comprehensive assessment and management of women at increased risk for breast cancer

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Abstract

The potential for reducing the risk of breast cancer through selective estrogen receptor modulators, aromatase inhibitors, and surgery has generated interest in the use of quantitative models of risk assessment. With the addition of ductal lavage cytology to traditional epidemiologic risk factors, a discovery of cellular atypia can result in refinement of assigned risk values, while simultaneously optimizing patient selection for selective estrogen receptor modulators utilization. In view of increasing complexity in this arena, a Risk Assessment Working Group was formed to outline management strategies for the patient at an elevated risk for the development of breast cancer. No longer a statistical exercise, quantitative risk assessment is part of basic breast care and comprehensive management includes a discussion of the following: ductal lavage for improved risk stratification, multiple options for risk reduction, and high risk surveillance strategies that might incorporate investigational imaging protocols.

Keywords: Breast cancer; Risk assessment; Ductal lavage; Hormone replacement therapy; Risk management strategy; Chemoprevention; Magnetic resonance imaging

Attempting to gauge a woman's risk for the development of breast cancer was largely speculative at the clinical level for many years, while the epidemiologists and statisticians worked toward objectivity. When the Gail model of breast cancer risk assessment was chosen for use in the Breast Cancer Prevention Trial (NSABP P-1) [1], the era of quantitative risk assessment in clinical breast care was launched. The success of that trial in achieving a 49% risk reduction in the development of breast cancer reinforced the utility of objective measures of risk.

As other interventional strategies such as preventive mastectomy [2] or preventive oophorectomy [3,4] were found effective in reducing breast cancer risk, the need for individual counseling to objectify personal risk levels over a defined period of time became even more apparent. Heightened surveillance guidelines for high-risk patients, including the potential use of magnetic resonance imaging, added yet another role for quantitative risk assessment.

Recently, the introduction of ductal lavage as a means of sampling duct epithelium has brought cytologic atypia into the arena of risk stratification [5]. This development has magnified the importance of clinicians being grounded in the burgeoning science of breast cancer risk assessment. In order to facilitate awareness of quantitative approaches, as

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well as interventional and surveillance strategies, the Breast Cancer Risk Assessment Working Group was established, presenting an initial report herein.

Risk factors

Factors that are known to affect the chances of developing breast cancer can be roughly divided by the degree to which they elevate risk. Many factors that are linked to hormone exposure (early menarche, late menopause, hormone replacement therapy, body mass index, alcohol intake) elevate risk only slightly [6–10]. Positive family history carries a greater degree of risk, especially in women with a first-degree relative with premenopausal breast cancer, or with two or more relatives with breast cancer [11,12]. The increased risk in nulliparous women or women experiencing a first live birth after the age of 30 may result from the absence or delay in undergoing the final epithelial differentiation that occurs during the first full-term pregnancy and lactation. It has been suggested that epithelial stem cells may be less susceptible to carcinogenesis after this differentiation [13]. Radiation exposure (eg, multiple chest fluoroscopies, atomic bomb survivors) has been known for many years to increase the risk of breast cancer. Clemons et al [14] reviewed 17 studies that tracked the incidence of breast cancer in patients who had received radiotherapy for the treatment of Hodgkin's disease. At follow-up times ranging from 5 to more than 20 years, the median relative risk for breast cancer was 5 (range 1.4 to 75.3).

Three types of histology—ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), and atypical hyperplasia (AH)—are associated with a high risk of invasive breast cancer. Ductal carcinoma in situ is believed to be a preinvasive condition, often resulting in invasive ductal carcinoma over time. In a study by Page et al [15], 28% of women who were diagnosed with DCIS on biopsy but received no subsequent treatment developed invasive disease over a period of 15 years. Unlike DCIS, LCIS is not generally considered as a preinvasive condition. It is largely asymptomatic, and usually found incidentally during biopsy for other reasons. In women found to have LCIS, there is a 10% to 15% chance in each breast of developing invasive cancer within 20 years after initial diagnosis [16].

A model of breast carcinogenesis suggests that atypical hyperplasia of either the lobular or ductal type is an early developmental stage in the process that transforms normal cells into cancerous ones [17]. Whether all or even most cancers follow this developmental pathway, it has nonetheless been demonstrated that histological AH is a strong risk factor for future breast cancer development. Dupont et al [18] have shown that women with biopsy-proven atypia have 5.3 times the risk of women with no proliferative disease, and 2.8 times the risk of women who show proliferative disease without atypia. At especially high risk (relative risk = 11) are women with AH who also have a first-degree family history of breast cancer.

Although the connection between atypia and increased breast cancer risk was first demonstrated by histologic examination of breast biopsy specimens, similar findings have been reported in studies examining cytologic abnormalities. Wrensch et al [19] reported an increased risk of breast cancer associated with abnormal cells found in nipple aspiration fluid (NAF) in 2,701 cancer-free women 25 to 54 years of age. At an average follow-up time of 12.7 years, they found that women with cytologically atypical cells were 4.9 times more likely to develop breast cancer than those in whom no NAF could be obtained. In those with atypical cells and a positive family history of breast cancer, this risk increased to 18-fold compared with women with no NAF and a negative family history, though confidence intervals were wide (4.6 to 70.2) due to the small number of subjects in this category.

Fabian et al [20] performed random periareolar fine-needle aspiration (FNA) cytology on 480 high-risk women. At an average follow-up of 45 months, they found that women with atypical cells had a fivefold increased risk of developing breast cancer, though this risk may actually be understated in light of the fact that controls (no atypia) had other risk factors for the development of breast cancer. In all three approaches above (one histologic and two cytologic), the estimated increase in risk was surprisingly similar (fourfold to fivefold). Nonetheless, there are conflicting reports about whether histologic atypia is the biologic equivalent of cytologic atypia. King et al [21] detected atypical hyperplasia in NAF in 67% of cases with an underlying malignancy, a finding that correlated significantly with the histologic presence of atypical proliferative disease. In contrast, Krishnamurthy et al [22] were able to detect atypical or malignant cells in only 23% of NAF samples taken from patients with biopsy-proven malignancies from whom adequate samples were available. From the standpoint of risk stratification, however, cytologic atypia seems to be comparable with histologic atypical hyperplasia.

Until recently, the main focus in breast cancer has always been on detection and treatment. We now have an opportunity to significantly influence both patient outcome and health-care costs in this country by shifting our focus to risk assessment and prevention.

Hormone replacement and breast cancer risk

The relationship between exogenous hormones and breast cancer risk has long been a source of controversy. This is, in part, related to the variety of estrogen preparations and combinations of estrogen and progesterone that are encompassed by the term hormone replacement therapy (HRT), as well as the potential impact of variable durations of use on risk. A national sample of postmenopausal women conducted in 1995 indicated that 38% of postmenopausal

women aged 50 to 74 years were current users of HRT [23], making this an important public health issue.

Several recent studies have provided some clarity on this issue. A meta-analysis of 51 epidemiological studies (90% of the total done) included 53,865 postmenopausal women, 17,830 (33%) of whom had used HRT at some time. Of those who had ever used HRT, approximately one third had done so for more than 5 years [24]. The relative risk (RR) of breast cancer development for women using HRT for 5 years or more was 1.35 (95% confidence interval [CI] 1.21 to 1.493, $P = 0.00001$). For women who had discontinued HRT more than 5 years ago, no increase in risk was noted. Overall, risk increased by a factor of 1.023 (95% CI 1.011 to 1.036) per year of use. The effect of HRT use was noted to be greater in women of lower weight or body mass index. These findings translate as 2 excess breast cancers per 1,000 women who use HRT for 5 years, 6 excess cancers after 10 years, and 12 excess cancers after 15 years of use [24].

Several studies have suggested that the combination of estrogen and progesterone increases breast cancer risk more than estrogen alone [25,26]. Schairer et al [25] performed a cohort study of 46,355 postmenopausal women in the Breast Cancer Detection and Demonstration Project. In this group the relative risk of breast cancer increased by 0.01 (95% CI 0.002 to 0.03) for each year of estrogen-only use compared with 0.08 (95% CI 0.02 to 0.16) for each year of estrogen and progesterone use. Ross and et al [26] also observed a significant increase in risk for the combination of estrogen and progesterone compared with estrogen alone, with odds ratios of 1.24 (95% CI 1.07 to 1.45) and 1.06 (95% CI 0.97 to 1.15), respectively, after 5 years of use.

The most compelling data on the relationship between breast cancer risk and combined estrogen and progesterone therapy comes from the Women's Health Initiative [27]. This randomized trial included 16,608 postmenopausal women aged 50 to 79 who were randomly allocated to receive conjugated equine estrogen 0.625 mg per day plus medroxyprogesterone acetate 2.5 mg per day or placebo. The primary outcomes of the study were the incidence of invasive breast cancer and the incidence of coronary heart disease. The trial was stopped after a mean follow-up of 5.2 years because the incidence of invasive breast cancer exceeded the stopping rules for the trial. The hazard ratio for invasive breast cancer development was 1.26 (95% CI 1.00 to 1.59), an excess of 8 cases per 10,000 woman-years of follow-up. Of note, women taking the hormone replacement therapy experienced a 29% increase in the risk of cardiovascular events, a 41% increase in the risk of stroke, and a doubling of venous thromboembolic episodes. The increases in the risk of breast cancer and cardiovascular disease were seen across age groups and racial/ethnic groups, and these increases were not dependent on the presence of underlying risk factors. The study did confirm the beneficial effect of hormone replacement therapy in reducing the risk of osteoporotic fracture, but a global index of risk and benefit indicated more harmful outcomes in the estrogen plus progesterone group than in the placebo group.

At this time it seems clear that hormone replacement therapy increases the risk of breast cancer development, and this risk is greatest in women receiving combined estrogen and progestin therapy. The level of risk increases with the duration of therapy. Whether breast cancer mortality is increased is uncertain. Case-control and observational studies have not shown an increased mortality among users, but these studies are confounded by differences in screening behavior among users and nonusers. Gapstur et al [28], in a population-based study, found that the excess in breast cancer risk was confined to cancers of favorable histologic subtype such as tubular or mucinous, which are associated with a lower risk of breast cancer death. This finding was not confirmed by Schairer et al [25]. However, the findings of the Women's Health Initiative have eliminated the rationale for the long-term use of hormone replacement therapy for health maintenance. Short-term use for relief of menopausal symptoms is associated with a small increase in the risk of breast cancer development that appears to be reversible after discontinuation of therapy. The lack of overall health benefit for combined estrogen-progestin therapy makes the results of ongoing studies of selective estrogen receptor modulators (SERMS) of particular interest. If these agents are proven to reduce the risk of cardiovascular disease, they will, in fact, have a positive impact on three major causes of morbidity and mortality in postmenopausal women—breast cancer, osteoporosis, and heart disease—making them the health maintenance therapy of choice [29].

Quantitative risk assessment

Managing increased risk of breast cancer begins with identification of the target population. The first step is to define risk as the probability that a harmful event will occur [30]. A risk ratio is the ratio of two incidence rates, which many physicians (and certainly most patients) do not fully understand. The absolute risk, though, is the probability that an event will occur within a specific time interval. Quantitative risk assessment is, therefore, measuring the contribution of individual risk factors and their interactions to the likelihood that an adverse event will occur.

Patients who should undergo risk assessment include those who have one or more first-degree relatives with breast or ovarian cancer, have multiple familial generations affected, have first-degree relatives with either bilateral breast cancer or breast and ovarian cancer, or have additional primary malignancies such as lymphoma and brain tumors.

In addition to these presentations, quantitative risk assessment clarifies the power of the aforementioned risks, such as women with just one first-degree relative affected with breast cancer (ie, a mother, daughter, or a sister). Women with a history of a benign breast biopsy are also

members of a group that is at higher risk [31]. Twenty percent of American women over age 40 are nulliparous, and that factor alone doubles the lifetime risk of breast cancer [32]. Similarly, if first full-term pregnancy occurs after age 30, a woman's lifetime risk of breast cancer is doubled. Women taking hormone replacement therapy, as noted in the previous section, are also at increased risk [27].

Mitchell Gail published a landmark study in 1989 that used data from more than 270,000 women in the Breast Cancer Detection and Demonstration Project (BCDDP) [12]. Baseline hazard rates for breast cancer were available from the study, and an estimate of both the relative and absolute risks predicted the likelihood that a woman with a given risk factor profile would develop invasive breast cancer, ductal carcinoma in situ, or lobular carcinoma in situ over a defined interval of time. These estimates were restricted to women having annual mammographic screening.

Age, age at menarche, family history of breast cancer in first-degree relatives, history of benign breast biopsies, age at first live birth (or nulliparity), and race are the factors needed to calculate Gail model risk. If a woman has cellular atypia, her risk is doubled. The risk factors that are used in the Gail model can be ascertained in the clinic in approximately 2 minutes. The modified model projects the absolute risk of invasive breast cancer [33].

The age-specific incidence rates used in the model are obtained from the National Cancer Institute SEER programs so that the baseline rates are population based. The attributable risks (the proportion of women in the population who have a given risk factor and the contribution of that risk factor to overall risk) are also obtained from SEER data.

The first validation of the Gail model was conducted using data from the 1987 Texas Breast Screening Project in which 64,000 women had mammograms, and approximately 40,000 of them provided risk factor information [34]. More than 3,100 of those women had at least one first-degree relative with breast cancer at the time of their screening. There was 91% follow-up of those 3,100 women 5 years later in 1992. If a model such as Gail is accurate, the model's expected number of cases should match the observed number of cases that occur over time in a cohort of women. If the observed and expected numbers are close to each other, their ratio will be 1. Bondy et al [34] found the ratio to be 1.01 and published their confirmatory data in 1994.

Subsequently, there were 6,700 women in the placebo arm of the Breast Cancer Prevention Trial (BCPT) who received no intervention. All women entering the study had baseline Gail model risk assessments and were followed prospectively for 4.5 years until the trial was unblinded. Additional validation studies have also been done in the Cancer and Steroid Hormone Study [35] and in the Nurses' Health Study [36]. Table 1 shows four different studies: BCDDP, the Cancer and Steroid Hormone Study (CASH), the Nurses' Health Study (NHS), and the BCPT. Using data from each of the trials gives some variation among the risk estimates for women with two or more affected relatives, but for those with one or two relatives, the Gail model performed well. The model slightly overestimates the risk of breast cancer in women with AH, and in those with two or more relatives but no AH. In women aged 50 years and older, the model performed very well. The observed-to-expected ratio was 0.93 for women under age 49 in the Breast Cancer Prevention Trial, 1.13 for perimenopausal women, and 1.05 for older postmenopausal women [33].

Table 1
Comparison of four studies assessing the validity of the Gail model

Feature	Study [reference]			
	BCDDP [12]	CASH [35]	NHS [36]	BCPT [33]
Number of breast cancers	2,852	4,715	2,396	204
Age range (years)	31–81	20–54	29–61	35–79
Study years	1973–1980	1980–1982	1976–1988	1992–1998
Mammography frequency	Annual	Rare	Not specified	Annual

BCDDP = Breast Cancer Detection and Demonstration Project; CASH = Cancer and Steroid Hormone Study; NHS = Nurses' Health Study; BCPT = Breast Cancer Prevention Trial.

Women with elevated Gail model risk scores should be considered as candidates for risk reduction. However, the initial challenge is recognizing that a woman with any one of the Gail model risk factors should trigger a quantitative risk assessment, allowing the potential for risk reduction. The NCI risk disk, or more properly, the Breast Cancer Risk Assessment Tool, or the web-site, http://bcra.nci.nih.gov/brc/ can be used to generate risk model estimates.

Another useful model, based entirely on family history, comes from Claus [37] and is derived from the CASH study that included approximately 4,700 women, and almost 4,700 controls. It considers both autosomal dominant maternal and paternal inheritance. The Claus model applies to women with at least one affected first-degree relative, and it takes into account second-degree relatives (that is, aunts and grandmothers) as well as their ages at diagnosis.

It is possible to use the Claus paper to look up the current age of a woman having risk assessment, her affected relatives with respective ages at diagnosis, and then to estimate the likelihood that she will develop breast cancer in her lifetime, or during shorter intervals as desired. (Using a personal data assistant [PDA], one can also go to http://www.palm.com and using the software search engine, type in "breast cancer," and download a Gail and Claus risk assessment tool for a PDA.)

In families where there is both breast and ovarian cancer, referral to medical genetics counselors is appropriate to estimate risk. These counselors have models available, other than Gail and Claus, that estimate the likelihood that a woman carries a significant mutation in one of the BRCA genes.

The Couch model was one of the earliest models that

attempted to calculate the probability that a woman harbors a BRCA1 mutation [38]. Shattuck-Eidens [39] was a refinement on Couch because this model considered women with multiple breast cancers or both breast and ovarian cancer. A third model is the Frank model, which considers both BRCA1 and BRCA2 genes, calculates the probabilities of a mutation based on the number of relatives diagnosed with breast cancer, their ages at diagnoses, along with the presence of ovarian cancer [40]. These models are designed to estimate the probability of carrying BRCA mutations, not the likelihood of developing breast cancer. After genetic testing has been completed, a skilled counselor must then address the risk for developing breast (or ovarian) cancer within the context of an individual's family history.

The model used most often by genetic counselors to quantify risk is the BRCAPRO model [41], which can be obtained from the University of Texas Southwestern Medical Center (available at: http://www3.utsouthwestern.edu/cancergene/cancergene.htm). One can enter information about a particular family, including the ages of relatives and whether they are affected with breast or ovarian cancer. The model also accommodates male breast cancers. Once the pedigree information has been entered, one can ask the model to perform a variety of calculations. BRCAPRO will calculate the probabilities of either carrying a mutation or of developing breast or ovarian cancer by a given age. Convenient graphics that demonstrate age-related risks over time assist the genetic counselor in patient education.

In summary, several tools are now available that perform validated quantitative risk assessment. At least over the short term of 5 years or so, these models give us accurate estimates of breast cancer risk. This evolving science is explained in greater detail in a recent book [42]. Prospective quantification of breast cancer risk can now be offered with an accuracy that allows this service to become part of routine clinical management of breast cancer risk.

Ductal lavage cytology as a risk stratifier

Given that the vast majority of breast cancers arise from the epithelial lining of the ductolobular system of the breast [43], it follows that a great deal of attention has been focused recently on ductal lavage, a method of sampling this system. The end component of the ductolobular system, called the terminal ductal lobular unit (TDLU), is considered the nidus for the development of both ductal and lobular carcinoma. Exfoliated epithelial cells lie within the ductolobular system, along with ductal fluid, allowing this cellular-rich material to be analyzed by a variety of methods, the most clinically useful at present being cytology. Cytologic atypia, whether discovered in NAF [19] or by FNA [20], confers an elevation in risk comparable with histologic atypical hyperplasia where RR ranges from 2.85 [44] to 5.3 [18].

The concept of ductal lavage was proposed as a means to increase the cellular yield that is often inadequate in NAF alone for the detection of atypia. In a multicenter study of women at elevated risk for breast cancer reported by Dooley et al [45] comparing ductal lavage to NAF cytology, 84% of participants had fluid-yielding ducts that served as sites for lavage. Of the patients successfully lavaged, 23% were found to have atypia (17% mild and 6% marked atypia), 54% had benign cytology, and 2 patients (less than 1%) had frankly malignant cells. Inadequate specimens for cytology were more common in the traditional NAF approach (73%) versus ductal lavage (22%). NAF had a median cell yield of 120 per breast, whereas ductal lavage demonstrated a median yield of 13,500 cells per duct. Most importantly, ductal lavage demonstrated threefold sensitivity in the detection of atypia.

If ductal lavage has improved sensitivity for the detection of cellular atypia in the breast, a convenient tool will be established that could serve to stratify risk in the management of patients with preexisting epidemiologic risk factors. In addition, the 86% risk reduction observed in women with atypical ductal hyperplasia in the Breast Cancer Prevention Trial [1] allows clinicians who are using ductal lavage to identify a subset of patients in whom favorable risk:benefit ratios of tamoxifen chemoprevention are more clearly defined.

Ductal lavage is an office-based procedure that can be easily assimilated into a breast care practice. In the multicenter study [45], using a visual analogue pain score for lavage, participants reported a median of 24 of 100, where 0 represented "no pain," and 100 represented "most severe pain." When asked to compare the comfort of ductal lavage with the comfort of mammography, 29% considered lavage more comfortable, 20% felt it was comparable, and 51% felt it was less comfortable than mammography.

While the promise of ductal lavage (and nipple aspirate fluid) extends to both genomics and proteomics [46] as they relate to risk stratification and perhaps early detection of breast cancer, current indications for ductal lavage are based on the entry requirements of the multicenter study: (1) Gail model 5-year risk assessment of 1.7% or greater, (2) patients with a prior history of breast cancer, and (3) women who harbor a BRCA 1/2 mutation. The Risk Assessment Working Group recommends extending these indications to include women in the elevated (high) risk and very high risk categories (to be described in the next section), especially if outcome would alter management decisions.

If results of ductal lavage show insufficient cellularity (insufficient cellular material for diagnosis [ICMD]), ductal lavage should be repeated once initially, then every 1 to 3 years [5,47]. With a "benign" report, the patient's quantitative risk assessment is unchanged, as no negative predictive power has yet been established that would allow a reduction in calculated risk. A follow-up study can be performed in 1 to 3 years, depending on the clinical situation. For "mild to moderate atypia," no further diagnostic work-up is required, but the quantitative risk assessment must now be altered to

account for this new risk factor. Given the comparable risk imparted by cytologic atypia and histologic atypical hyperplasia, it is reasonable to use the Gail model for quantifying risk, entering a "biopsy that showed atypical hyperplasia" into the calculator or software. Risk reduction with tamoxifen, or through entry into the STAR chemoprevention trial, will have a larger net benefit and subjects will be more likely to adopt a drug intervention risk reduction strategy.

For either "marked atypia" or "malignant cells," further diagnostic work-up is required. After confirming normal mammography and examination, ductography or ductoscopy should be performed, with biopsy of any abnormality. If the ductal visualization study is normal, then breast magnetic resonance imaging (MRI) should be performed, again with biopsy of any abnormality. If the work-up is still negative, the patient should be completely reevaluated in 3 months, or consideration can be given to a segmental resection of the cannulated duct that yielded the suspicious cells. It is also reasonable to more strongly consider tamoxifen or entry in the STAR trial.

Cytologic findings, regardless of the methodology used for sampling, can provide both patient and clinician with pertinent information to formulate management decisions. Every general surgeon practicing breast surgery, as well as any physician focusing on breast disease, should be fully cognizant of the importance of quantitative risk assessment as a prelude to discussing risk reduction strategies. Ductal lavage is an important new clinical tool to aid in this process. Random FNA cytology serves a similar purpose, and comparative studies will define whether these two approaches are interchangeable or complimentary.

Risk management strategy

The Breast Cancer Risk Assessment Working Group has developed a breast cancer risk assessment schema for the purpose of identifying women who are at an "elevated risk" as distinct from those at a "very high risk" of developing breast cancer, and to facilitate the clinical management of women at these increased levels of risk. Three risk strata have been delineated: average risk, elevated or high risk, and very high risk.

Average risk

Women at average risk for developing breast cancer are those whose risk factors confer no greater than a 1.5-fold relative risk of developing breast cancer, eg, history of a breast biopsy showing usual epithelial hyperplasia [18] and women who have a 5-year Gail risk of less than 1.7% [12].

Elevated or high risk

Women at elevated or high risk of developing breast cancer are those who have a relative risk between 1.5-fold and 4-fold to 5-fold. Women in this group include those with a 5-year Gail risk greater than 1.7% [12]; those with a finding of atypical ductal or lobular hyperplasia on breast biopsy [48]; women with cellular atypia on examination of nipple aspirate fluid (NAF) [19,49], FNA [20] or ductal lavage specimen [45]; women with two or more second-degree premenopausal relatives affected with breast cancer [37]; and women who have been taking combined estrogen and progesterone hormone replacement therapy (HRT) for more than 10 years [25,27,50].

A large prospective study by DuPont and Page [48] has demonstrated that women with biopsy-proven atypical ductal or lobular hyperplasia have a fourfold to fivefold increased risk of developing breast cancer in the ensuing 20 years, while the aforementioned studies of cytologic atypia show comparable risk [19,20]. Women with a 5-year Gail risk greater than 1.7% have at least a twofold greater risk than women at average risk, and this may be considerably higher depending on the number of first-degree relatives affected, and whether the woman is known to have atypical hyperplasia [1,12]. Claus tables [37] indicate that women with two or more second-degree relatives (both of whom are either maternal or paternal) who developed premenopausal breast cancer have an approximately twofold or greater relative risk of breast cancer, depending on the age of breast cancer onset in the relatives.

Long-term users of HRT are also placed in this elevated or high risk category based on the data provided in a previous section of this review—Hormone replacement and breast cancer risk.

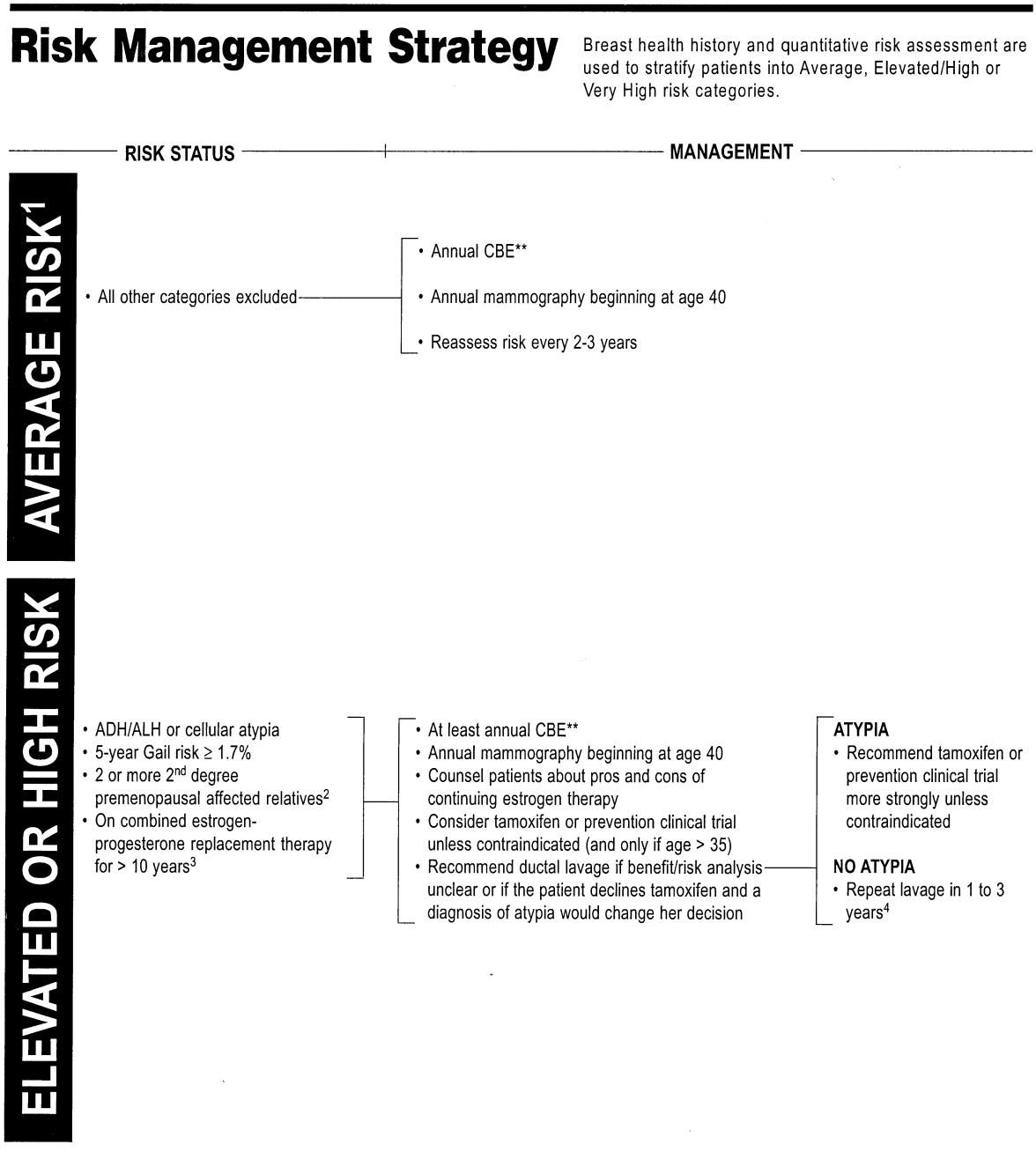
Very high risk

There are four groups of women who are considered to be at very high risk for the development of breast cancer with relative risks generally greater than fourfold to fivefold. Women with a personal history of invasive breast cancer, ductal carcinoma in situ, or lobular carcinoma in situ have more than a fourfold to fivefold increased risk of developing a new primary breast cancer [1,51,52]. Women who have a personal history of cellular atypia on ductal lavage, FNA, or NAF, or a breast biopsy that has shown atypical ductal or lobular hyperplasia, and who have a first-degree affected relative with breast cancer are at 11- to 18-fold increased risk of developing breast cancer [20,48]. Women with a known BRCA 1/2 germline mutation are at very high risk for developing breast cancer, with lifetime risk estimates between 40% and 80% [53]. Lastly, women who have undergone breast irradiation before age 20 (eg, mantle irradiation for Hodgkin's disease) have relative risks for breast cancer elevated 40-fold or higher [54].

Clinical management of breast cancer risk

Average risk

Women who are at average risk for developing breast cancer should undergo annual clinical breast examination



*IBC = Invasive Breast Cancer **CBE = Clinical Breast Exam

1 More than half of women diagnosed with breast cancer have no known risk factors.
2 If both relatives are either maternal or paternal. For more accurate risk assessment of mixtures of 1st and 2nd degree relatives consult the Claus model.
3 Women on combined hormone replacement therapy for greater than 10 years have approximately twice the risk of age-matched women who have never used hormone replacement therapy.
4 These patients should also be considered for prevention clinical trials.

Fig. 1. Management strategy for women determined to be at average risk or elevated/high risk for breast cancer.

and annual mammography beginning at age 40 (Fig. 1) [55]. Reassessment of a woman's breast cancer risk should be undertaken every 2 to 3 years or whenever there is a change in a significant risk factor such as a breast biopsy or family history of breast cancer. Postmenopausal women who are at average risk for breast cancer who take raloxifene for 3

years for the treatment or prevention of osteoporosis will realize a 70% reduction in their breast cancer risk [56]. The optimal duration of raloxifene treatment and the durability of the reduction in risk once raloxifene is stopped are not yet known. Longer follow-up on the Multiple Outcomes of Raloxifene Evaluation study and the results of the Study of Tamoxifen and Raloxifene (STAR) will provide insights into these important questions [57].

Elevated or high risk

In addition to annual clinical breast examination and annual mammography beginning at age 40, women at elevated or high risk for developing breast cancer are excellent candidates for consideration of treatment with a risk reduction agent such as tamoxifen or participation in the STAR trial (Fig. 1) [58]. Women at elevated or high risk who have been taking combined HRT for 2 years or more should be counseled about the risks and benefits of continuing HRT [27]. In general, stopping HRT should be considered to prevent a further increase in breast cancer risk [59]. A reanalysis of the aggregate data from the major case control and cohort studies of HRT has shown that the elevation in breast cancer risk that accompanies prolonged HRT use is significantly decreased 5 years after stopping HRT [24].

The Breast Cancer Risk Assessment Working Group recommends consideration of ductal lavage for women who are at elevated risk for breast cancer based on a 5-year Gail risk greater than 1.7%, two or more affected second-degree, premenopausal relatives, or use of combined HRT for more than 10 years if a finding of cytologic atypia would alter decision-making. Women with biopsy-proven atypical ductal or lobular hyperplasia are unlikely to benefit from ductal lavage because a finding of cellular atypia would not further increase risk, and because a strong recommendation for tamoxifen therapy can be made based on tamoxifen's established effectiveness in reducing risk in women with atypical hyperplasia [1]. However, a finding of cellular atypia in a woman in any of the other three categories of elevated/high risk would double that woman's 5-year Gail risk score, placing her into a considerably higher risk category. In such women, the finding of atypia can provide valuable information to facilitate decision-making about HRT and antiestrogen therapy [5].

Very high risk

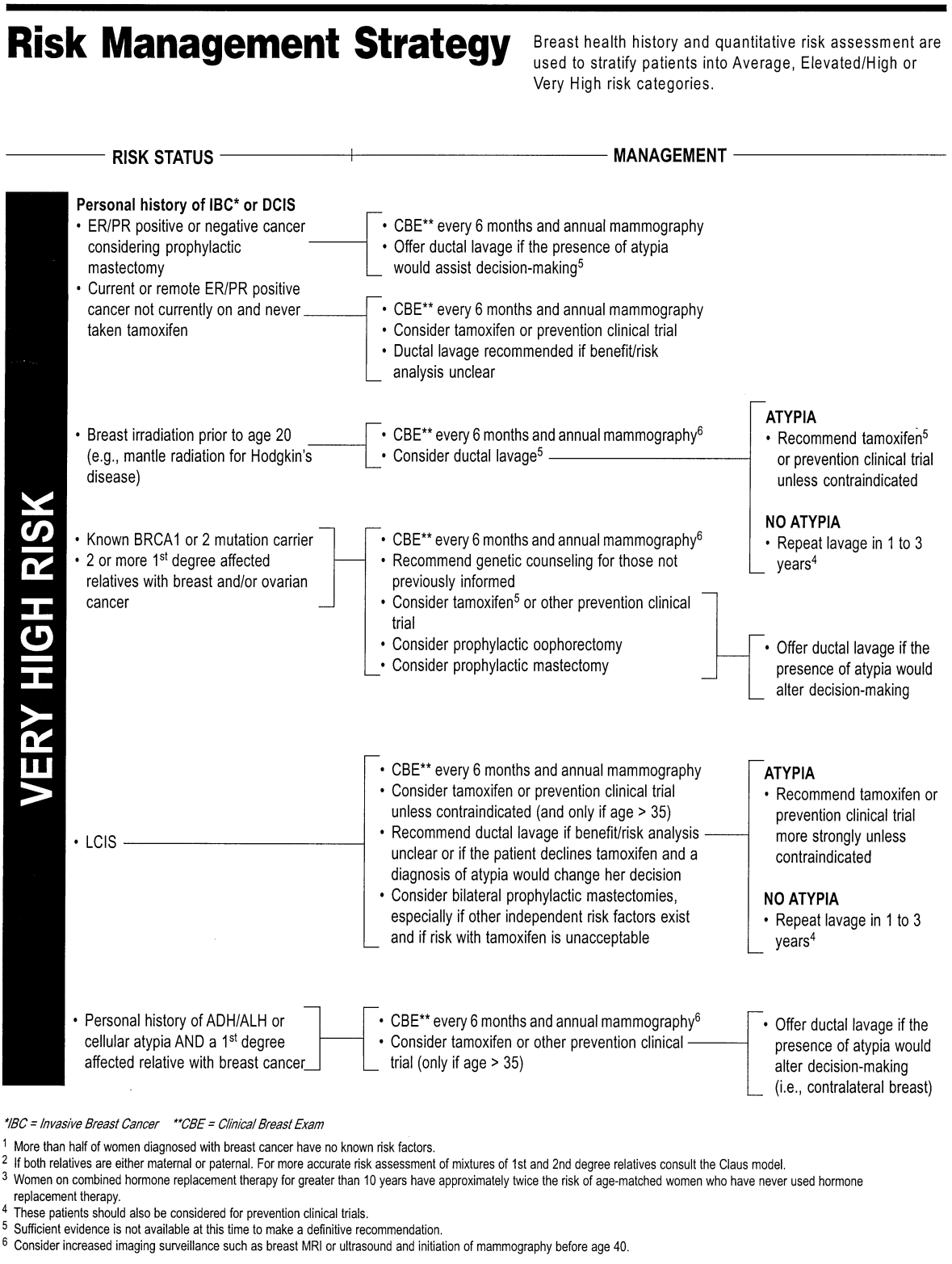
In women at very high risk for developing breast cancer, a clinical breast examination is recommended every 6 months in addition to annual mammography (Fig. 2) [60]. Women who are suspected of being BRCA 1/2 mutation carriers should undergo genetic counseling and consideration of genetic testing. If risk reduction with a SERM is elected, tamoxifen is the current standard of care for patients with estrogen or progesterone receptor-positive invasive breast cancer, ductal carcinoma in situ, or lobular carcinoma in situ [58]. Likewise, tamoxifen (or participation in the STAR trial for postmenopausal women) is the established option available for women who have a first-degree affected relative with breast cancer and a personal history of cellular atypia or atypical hyperplasia on breast biopsy [61] whose risk is greater than 1.66% in 5 years using the Gail model.

The role of tamoxifen or other SERM risk reduction therapy in women who are at very high risk based on a known BRCA 1/2 mutation or due to previous breast irradiation before age 20 has not been established, though preliminary evidence suggests that patients with BRCA mutations may experience risk reduction comparable with that seen in the Breast Cancer Prevention Trial [62,63]. One report suggests this effect is limited to patients with alterations in the BRCA2 gene [62]. Prophylactic mastectomy is known to reduce breast cancer risk by at least 90% in women who are known BRCA 1/2 mutation carriers [60] and is a reasonable consideration for women at very high risk and for whom the benefit of tamoxifen is unknown. In addition, prophylactic oophorectomy in premenopausal BRCA1/2 mutation carriers reduces breast cancer risk by up to 75% [64,65] and is recommended once childbearing is completed [60].

A finding of cytologic atypia cannot further increase breast cancer risk in the four categories of women who are already at very high risk of developing breast cancer as there are no published data applicable to these situations. However, pending such information, ductal lavage or random FNA cytology can be considered on a case-by-case basis if the discovery of atypical cells would alter decision-making about prophylactic mastectomy or committing to 5 years of tamoxifen risk reduction therapy.

Imaging the high-risk patient

Nine thousand new cases of breast cancer each year are associated with a genetic predisposition for the disease [66–68]. Mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 account for greater than 60% of hereditary cases of breast cancer [69]. By age 50 years, approximately 50% of BRCA1/2 carriers will develop breast cancer, necessitating screening strategies that begin at an early age [69,70]. The only known effective interventions for preventing breast cancer in BRCA-positive women are prophylactic mastectomy [2,71,72] and oophorectomy [64,65], although tamoxifen may show benefit as well [62,63]. As an alternative to prophylactic surgery and as a complement to tamoxifen, intensive screening with conventional mammography and clinical examination are recommended starting at age 25, despite the concern that this strategy may not have sufficient sensitivity to alter breast cancer mortality, and that radiation from mammography may foster BRCA-related breast carcinogenesis. In addition,



*IBC = Invasive Breast Cancer **CBE = Clinical Breast Exam

1 More than half of women diagnosed with breast cancer have no known risk factors.
2 If both relatives are either maternal or paternal. For more accurate risk assessment of mixtures of 1st and 2nd degree relatives consult the Claus model.
3 Women on combined hormone replacement therapy for greater than 10 years have approximately twice the risk of age-matched women who have never used hormone replacement therapy.
4 These patients should also be considered for prevention clinical trials.
5 Sufficient evidence is not available at this time to make a definitive recommendation.
6 Consider increased imaging surveillance such as breast MRI or ultrasound and initiation of mammography before age 40.

Fig. 2. Management strategy for women determined to be at very high risk for breast cancer.

breast cancer may be more difficult to detect by mammography in premenopausal women due to denser breast tissue. Screening breast MRI is not limited by dense breast tissue, does not use ionizing radiation, and should be strongly considered as an additional screening modality in high-risk women.

Breast screening mammography and MRI for women at high genetic risk of breast cancer

As a diagnostic tool, contrast-enhanced MRI has demonstrated very high sensitivity (95%) for the detection of invasive breast cancer, while reported specificity ranges from 37% to 97% [73–75]. Breast lesions on contrast-enhanced MRI are assessed for malignancy based on morphologic and pharmacokinetic patterns of enhancement. Morphologic features of malignancy include spiculated borders and rim enhancement. Pharmacokinetic features of malignancy include a rapid rate of contrast uptake and a rapid rate of contrast washout. The specificity of MRI for invasive disease can be low because benign proliferative breast disease can share these features. The mechanism of enhancement is believed to be related to processes associated with tissue perfusion and vascular permeability. It appears that invasive cancer and some types of benign breast disease share these processes. These shared factors contribute to the observed low specificity and result in additional imaging and biopsy procedures. Thus, screening breast MRI should be reserved for women at very high risk for developing breast cancer.

The high sensitivity of MRI in the detection of invasive cancer has prompted five international pilot trials for prospectively screening high-risk women, resulting in four published studies to date. These studies confirm the ability of contrast enhanced MRI to detect mammographically occult breast cancer [76–79]. Tilanus-Linthorst et al [76] detected 3 invasive cancers among a population of 109 women with normal physical examinations and negative mammograms, while Kuhl et al [77] detected invasive cancer in 7 BRCA1/2 carriers, whereas mammography failed to detect these lesions in 5 patients. Warner et al [79] compared mammography, MRI and ultrasound in high-risk women and detected six invasive breast cancers with MRI while mammography and ultrasound only detected two and three cancers, respectively. The four cancers that were missed by mammography were located in dense breasts as determined by quantitative density analysis. All cancers screen-detected by MRI in these studies were T1 lesions, demonstrating that MRI can detect invasive cancer at early stages in high-risk women. In a retrospective analysis of 179 high-risk women, 7 of 13 breast cancers were not detected by mammography, while all 13 breast cancers were detected by MRI [80]. These studies strongly support the use of breast MRI as part of a screening protocol for high-risk women.

There are few data on the role of breast MRI in the detection of DCIS and the incidence of DCIS in women who carry BRCA1/2 mutations. More data are needed to determine the role of screening breast MRI for the detection of DCIS.

The appropriate screening interval for women at high genetic risk for developing breast cancer is currently unknown. Warner et al [81] detected one interval cancer on MRI after 4 annual rounds of screening. Due of the high cost of MRI and uncertainty of the efficacy of less than 1-year intervals, current screening guidelines should include annual examinations.

A comprehensive imaging breast cancer screening protocol for women at high genetic risk for developing breast cancer should include monthly self-breast examination, clinical breast examination three to four times a year, annual mammography and breast MRI in the setting of a clinical trial. More data are needed to identify appropriate screening intervals and cohorts of women who will benefit from screening breast MRI.

Practical applications of risk assessment

The primary care provider is the first professional along the health care continuum who has the opportunity to discuss and initiate risk assessment. This is an opportunity not only to identify those women who are at an elevated risk, but also to educate and counsel them about their personal risk and appropriate options. Women at high/elevated risk or very high risk should be referred to a risk assessment clinic or specialist in this area for further evaluation. Many women are not waiting for their physician to refer them, but are initiating referrals themselves.

Breast cancer risk assessment in office practice is a process that necessitates a conversation between the clinician and the patient. Like all conversations, both parties bring different talents and abilities to the table. And, like all conversations, the outcome depends upon the manner in which information is communicated and the manner in which it is received.

To begin the process of risk assessment, documentation of the patient's risk factors, derived from family history and personal history, should be performed, and then included as part of the permanent medical record. The information should also be updated as appropriate.

This core risk assessment database is important when encountering both symptomatic and asymptomatic individuals. For the symptomatic patient, an increased background risk for breast cancer might alter the threshold to biopsy an indeterminate lesion, and could have an impact on the treatment choices should breast cancer be diagnosed. For the asymptomatic patient, a review of her breast cancer risk should be part of the summary and conclusion of a routine office visit so that appropriate plans for follow up can be made.

Quantitative risk assessment tools are invaluable to the clinician because they yield estimates of the probability that the patient will develop breast cancer within a defined period of time and, if helpful, over a lifetime. This temporal

framework helps make the level of risk real and understandable to the patient. Ductal lavage cytology may add a valuable data point, particularly as the yield of atypical cytology appears to indicate risk that is likely to be realized in the near term, which is more readily appreciated by the patient.

Every patient will understand her risk in a unique and individual way, depending largely on her personality characteristics. That is to say, some individuals are extremely risk averse, while others may tolerate high levels of risk in general. In addition, a patient's perceived threat of a breast cancer diagnosis may be influenced by the positive and negative experiences of her friends and family members.

After communication of the level of risk discerned by the clinician, the discussion should move to strategies to manage that risk. Available approaches may be grouped into three categories: enhanced surveillance, chemoprevention, and prophylactic surgery. A thorough discussion of all three should be conducted. Enhanced surveillance, possibly involving participation in a high-risk program, should be recommended to all patients, regardless of active risk reduction interventions. At this time, prophylactic surgery mainly appears to be the province of known (or putative) mutation carriers, or selected very high risk patients as outlined in Fig. 2.

The surgical approach provides dramatic risk reduction, but certainly constitutes a major life-altering event for the patient. Chemoprevention has, to date, proved to be an unappealing choice to the majority of women who are offered this strategy. Patients' concerns regarding side effects are well known. Other issues, including effects on fertility and duration of the risk reduction benefit also come into play in decision-making. The discussion of breast cancer risk management and risk reduction strategies should be an open dialogue, and may be reviewed at each office encounter to allow patients and clinicians to reevaluate decisions.

As we develop more accurate approaches for estimating risk in individual patients, the problem becomes how to effectively educate patients about those risks, as well as their options in dealing with them. As described by Prochaska [82], patients progress through recognizable stages in this process. As many as 40% of patients may tend to underestimate their chances of developing cancer while overestimating the risks involved in different treatment options. These patients are at a psychological stage where they do not understand the impact of their risk factors. With appropriate education and additional data (quantitative risk assessment, ductal lavage cytology), they can progress to the point where they are ready to consider a preventive strategy [83]. Active enrollment into a clinical trial can be effective at this point, but only after suitable groundwork has been laid in the earlier stages. Once patients are enrolled into a trial, it is important to provide an infrastructure (frequent contact, patient networks, annual celebrations) that supports them in maintaining compliance.

There are significant obstacles to the practical performance of breast cancer risk assessment in office practice. Patients have concerns regarding the confidentiality of information, particularly the results of genetic testing. We have inadequate information about the meaning of risk as well as the "best" management strategy for various subsets of high risk patients. And for the practitioner, the process of assessing a patient's breast cancer risk and discussing the management of that risk is time consuming and open-ended.

Risk is an inherently difficult concept for the clinician to communicate as no matter how high the calculated danger might be, no level of risk is completely predictive of a patient's future outcome. Also, while physicians may view risk assessment data as objective and reproducible, patients will understand and interpret that data based on their ages, attitudes, beliefs and experiences, and make their management decisions accordingly.

Perhaps the most important concept in this area is that breast cancer risk is fluid. It changes with time. Therefore, breast cancer risk assessment should be repeated periodically to allow the patient the benefit of updated information, as well as the opportunity to change the risk management strategy she previously employed.

Future directions

Risk assessment for the development of breast cancer will continue to evolve, both in improved quantification through mathematical modeling as well as improved prediction through increasing reliance on actual abnormalities in ductal cells, ductal fluid, or serum-based strategies. At the same time, risk reduction approaches will continue to unfold with the use of newer SERMs, pure antiestrogens, and conceived biologic weapons that work through hormonally independent pathways. These improvements in prediction and prevention are so intertwined that it is easy to imagine a day when specific abnormalities in breast cells pinpoint the best pharmacologic option available for risk reduction, analogous to antibiotic sensitivity testing.

And while prediction and prevention are the ultimate goals, the interim is filled with a strong need to diagnose breast cancer earlier and more reliably. The technology platform that will most likely allow major diagnostic improvements through its sensitivity is breast MRI. Breast MRI is impractical for screening the general population, however, emphasizing once again the importance of quantitative risk assessment methods that properly select patients for this modality.

It is the mission of the Risk Assessment Working Group to monitor these developments and to construct guidelines to assist practitioners in this new and exciting arena.

Appendix

Risk assessment working group

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References

[1] 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.

[2] 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.

[3] Rebbeck TR. Prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2000;18(suppl):100–3.

[4] Grann VR, Jacobson JS, Thomason D, et al. Effect of prevention strategies on survival and quality-adjusted survival of women with BRCA 1/2 mutations: an updated decision analysis. J Clin Oncol 2002;20:2520–9.

[5] O'Shaughnessy JA, Ljung BM, Dooley WC, et al. Ductal lavage and the clinical management of women at high risk for breast carcinoma. Cancer 2002;94:292–8.

[6] Brinton LA, Schairer C, Hoover RN, Fraumeni JF. Menstrual factors and risk of breast cancer. Cancer Investigation 1988;6:245–54.

[7] Trichopoulos D, MacMahon B, Cole P. Menopause and breast cancer risk. J Natl Cancer Inst 1972;48:605–13.

[8] Ursin G, Tseng C-C, Paganini-Hill A, et al. Does menopausal hormone replacement therapy interact with known factors to increase risk of breast cancer? J Clin Oncol 1992;20:699–706.

[9] Tretli S. Height and weight in relation to breast cancer morbidity and mortality: a prospective study of 570,000 women in Norway. Int J Cancer 1989;44:23–30.

[10] Longnecker MP, Berlin JA, Orza MJ, Chalmers TC. A meta-analysis of alcohol consumption in relation to risk of breast cancer. JAMA 1988;260:652–6.

[11] Sattin RW, Rubin GL, Webster LA, et al. Family history and the risk of breast cancer. JAMA 1985;253:1908–13.

[12] 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.

[13] Sharpe CR. A development hypothesis to explain the multicentricity of breast cancer. Can Med Assoc J 1998;159:55–9.

[14] Clemons M, Loijens L, Goss P. Breast cancer risk following irradiation for Hodgkin's disease. Cancer Treat Rev 2000;26:291–302.

[15] Page DL, Dupont WD, Rogers LW, Landenberger M. Intraductal carcinoma of the breast: follow-up after biopsy only. Cancer 1982;751–8.

[16] Hutter RV. The management of patients with lobular carcinoma in situ of the breast. Cancer 1984;53:2–798.

[17] Singletary SE. A working model for the time sequence of genetic changes in breast tumorigenesis. J Am Coll Surg 2002;194:202–16.

[18] Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med 1985;312:146–51.

[19] Wrensch MR, Petrakis NL, King EB, et al. Breast cancer incidence in women with abnormal cytology in nipple aspirates of breast fluid. Am J Epidemiol 1992;135:130–41.

[20] Fabian CJ, Kimler BF, Zalles CM, et al. Short-term breast cancer prediction by random periareolar fine-needle aspiration cytology and the Gail risk model. J Natl Cancer Inst 2000;92:1217–27.

[21] King EB, Chew KL, Petrakis NL, Ernster VL. Nipple aspirate cytology for the study of breast cancer precursors. J Natl Cancer Inst 1983;71:1115–21.

[22] Krishnamurthy S, Sneige N, Thompson PA, et al. Nipple aspirate fluid cytology in breast cancer. Cancer 2003;99:97–104.

[23] Keating NL, Cleary PD, Rossi AS, et al. Use of hormone replacement therapy by postmenopausal women in the United States. Ann Intern Med 1999;130:545–53.

[24] Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350:1047–59.

[25] Schairer C, Lubin J, Troisi S, et al. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA 2000;283:485–91.

[26] Ross RK, Paganini-Hill A, Wan PC, Pike NC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. J Natl Cancer Inst 2000;92:328–32.

[27] Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal

women. Principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.
[28] Gapstur SM, Morrow M, Sellers TA. Hormone replacement therapy and breast cancer with a favorable pathology. JAMA 1999;281: 2091–7.
[29] Jordan VC, Morrow M. Editorial. Raloxifene as a multifunctional medicine? BMJ 1999;319:331–2.
[30] Vogel VG. Assessing potential risk of developing breast cancer. Oncology 1996;10:1451–61.
[31] London SJ, Connolly JL, Schnitt SJ, et al. A prospective study of benign breast disease and the risk of breast cancer. JAMA 1992;267: 941–4.
[32] Vogel VG. High-risk populations as targets for breast cancer prevention trials. Prev Med 1991;20:86–100.
[33] 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.
[34] Bondy ML, Lustbader ED, Halabi S, et al. Validation of a breast cancer risk assessment model in women with a positive family history. J Natl Cancer Inst 1994;86:620–5.
[35] Claus E, Risch N, Thompson WD. The calculation of breast cancer risk for women with a first degree family history of ovarian cancer. Breast Cancer Res Treat 1993;28:115–20.
[36] Rockhill B, Spiegelman D, Byrne C, et al. Validation of the Gail et al model of breast cancer risk prediction and implications for chemoprevention. J Natl Cancer Inst 2001;93:358–66.
[37] Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer 1994;73:643–51.
[38] Couch FJ, DeShano ML, Blackwood A, et al. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. N Engl J Med 1997;336:1409–15.
[39] Shattuck-Eidens D, McClure M, Simard J, et al. A collaborative survey of 80 mutations in the BRCA1 breast and ovarian cancer susceptibility gene: implications for presymptomatic testing and screening. JAMA 1995;273:535–41.
[40] Frank TS, Deffenbaugh AM, Hulick M, et al. Hereditary susceptibility to breast cancer: significance of age of onset in family history and contribution of BRCA1 and BRCA2. Dis Markers 1999;15:89–92.
[41] Berry DA, Iversen ES, Gudbjartsson DF, et al. BRCAPRO validation, sensitivity of genetic testing of BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes. J. Clin Oncol 2002;20:2701–12.
[42] Vogel VG, editor. *Management of Patients at High Risk for Breast Cancer*. Malden, MA: Blackwell Science, 2001.
[43] Wellings SR. A hypothesis of the origin of human breast cancer from the terminal ductal lobular unit. Pathol Res Pract 1980;166:515–35.
[44] Hutchinson WB, Thomas DB, Hamlin WB, et al. Risk of breast cancer in women with benign breast disease. J Natl Cancer Inst 1980;65:13–20.
[45] Dooley WC, Ljung BM, Veronesi U, et al. Ductal lavage for detection of cellular atypia in women at high risk for breast cancer. J Natl Cancer Inst 2001;93:1624–32.
[46] Petricoin EF, Ornstein DK, Paweletz CP, et al. Serum proteomic patterns for detection of prostate cancer. J Natl Cancer Inst 2002;94: 1576–8.
[47] Morrow M, Vogel V, Ljung BM, O'Shaughnessy JA. Evaluation and management of the woman with an abnormal ductal lavage. J Am Coll Surg 2002;194:648–56.
[48] Page DL, Dupont WD, Rogers LW, et al. Atypical hyperplastic lesions of the female breast: a long-term follow-up study. Cancer 1985;55:2698–708.
[49] Wrensch MR, Petrakis NL, Miike R, et al. Breast cancer risk in women with abnormal cytology in nipple aspirates of breast fluid. J Natl Cancer Inst 2001;93:1791–8.
[50] Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to factor status: data from the Nurses' Health Study. Am J Epidemiol 2000;152:950–64.
[51] Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomized controlled trial. Lancet 1999;353: 1993–2000.
[52] Fisher B, Costantino J, Redmond C, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. N Engl J Med 1989;320:479–84.
[53] Easton DF, Ford BP, Bishop DT, and the Breast Cancer Linkage Consortium. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Am J Hum Genet 1995;56:265–71.
[54] van Leeuwen FE, Klokman WJ, Hagenbeek A, et al. Second cancer risk following Hodgkin's disease: a 20-year follow-up study. J Clin Oncol 1994;12:312–25.
[55] Smith RA, Cokkinides V, von Eschenbach AC, et al. American Cancer Society guidelines for the early detection of cancer. CA Cancer J Clin 2002;52:8–22.
[56] 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.
[57] Vogel VG, Costantino JP, Wickerham DL, et al. The study of tamoxifen and raloxifene: preliminary enrollment data from a randomized breast cancer risk reduction trial. Clin Breast Cancer 2002;3:153–9.
[58] Chlebowski RT, Col N, Winer EP, et al. American Society of Clinical Oncology technology assessment of pharmacologic interventions for breast cancer risk reduction including tamoxifen, raloxifene, and aromatase inhibition. J Clin Oncol 2002;20:3328–43.
[59] Fletcher SW, Colditz GA. Failure of estrogen plus progestin therapy for prevention. JAMA 2002;288:366–8.
[60] Eisen A, Rebbeck TR, Wood WC, Weber BL. Prophylactic surgery in women with a hereditary predisposition to breast and ovarian cancer. J Clin Oncol 2000;18:1980–95.
[61] Kinsinger LS, Harris R, Woolf SH, et al. Chemoprevention of breast cancer: a summary of the evidence for the U.S. Prevention Services Task Force. Ann Intern Med 2002;137:59–67.
[62] King MC, Wieand S, Hale K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) breast cancer prevention trial. JAMA 2001;286:2251–6.
[63] Narod SA, Brunet JS, Gharirian P, et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case control study. Hereditary Breast Cancer Clinical Study Group. Lancet 2000;356:1876–81.
[64] Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2002;346:1609–15.
[65] Rebbeck TR, Lynch HT, Neuhausen SL, et al, and the Prevention and Observation of Surgical End Points Study Group. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 2002;346:1616–22.
[66] Weinreb JC, Newstead G. MR imaging of the breast. Radiology 1995;196:593–610.
[67] Harms SE. Breast magnetic resonance imaging. Semin Ultra-sound CT MR 1998;19:104–20.
[68] Lynch HT, Albano WA, Danes BS, et al. Genetic predisposition to breast cancer. Cancer 1984;53:612–22.
[69] 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.
[70] Struewing JP, Hartage 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.

[71] 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.

[72] Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst 2001;93:1633–7.

[73] Harms SE, Flamig DP. MR imaging of the breast. J Magn Reson Imaging 1993;3:277–83.

[74] Kaiser WA, Zeitler E. MR imaging of the breast: fast imaging sequences with and without Gd-DTPA. Preliminary observations. Radiology 1989;170:681–6.

[75] Orel SG, Schnall MD, Powell CM, et al. Staging of suspected breast cancer: effect of MR imaging and MR-guided biopsy. Radiology 1995;196:115–22.

[76] Tilanus-Linthorst MM, Obdeijn IM, Bartels KC, et al. First experiences in screening women at high risk for breast cancer with MR imaging. Breast Cancer Res Treat 2000;63:53–60.

[77] Kuhl CK, Schmutzler RK, Leutner CC, et al. Breast MR imaging screening in 192 women proved or suspected to be carriers of a breast cancer susceptibility gene: preliminary results. Radiology 2000;215:267–79.

[78] Brown J, Buckley D, Coulthard A, et al. Magnetic resonance imaging screening in women at genetic risk of breast cancer: imaging and analysis protocol for the UK multicentre study. UK MRI breast Screening Study Advisory Group. Magn Reson Imaging 2000;18:765–76.

[79] Warner E, Plewes DB, Shumak RS, et al. Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. J Clin Oncol 2001;19:3524–31.

[80] Stoutjesdijk MJ, Boetes C, Jager GJ, et al. Magnetic resonance imaging and mammography in women with a hereditary risk of breast cancer. J Natl Cancer Inst 2001;93:1095–102.

[81] Warner E, Plewes DB, Hill K, et al. Three year results of annual breast magnetic resonance imaging (MRI) and ultrasound (US) in addition to mammography and clinical breast examination for surveillance of women at high risk for hereditary breast cancer. Proc Am Soc Clin Oncol 2002;21:1704.

[82] Prochaska JO. Treating entire populations for behavior risks for cancer. Cancer J 2001;7:360–8.

[83] Vogel VG, Costantino JP, Wickerham DL, Cronin WM. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2002;94:1504.