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Clinical management of women at increased risk for breast cancer

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Summary

A large number of women in the population are at risk for the development of breast cancer. Methods now exist to accurately assess risk and to provide quantitative estimates of the chance of a woman developing breast cancer in her lifetime. Histologic assessment of premalignant breast pathology aids in the evaluation of risk. The availability of primary chemoprevention clinical trials reduces the number of indications for prophylactic mastectomy. Women at risk for breast cancer and women who have had a malignant lesion at another anatomic site have an increased risk for new cancers at multiple sites. We propose screening strategies based on epidemiologic information about the risks of these diseases and on the predictive value of the available screening tests. The merits and inadequacies of specific management strategies are considered. We review the risks and benefits of estrogen replacement therapy for women at increased risk for breast cancer and consider the ethical implications of both risk assessment and the various interventions.

Introduction

Physicians are being asked with increasing frequency to counsel women who may be at increased risk for breast cancer, and a number of issues in the management of such women confront the practicing clinician. An emerging body of literature provides guidelines for making medical decisions in these patients. The tasks to be accomplished in the clinical encounter include assessing who is at risk, quantifying that risk, communicating the risk to the patient and her family in a nonthreatening context, and recommending and selecting interventions that minimize risk while providing the greatest benefit to health.

Table 1 lists the issues we will discuss to guide the clinician toward optimal management of the growing number of women at increased risk for breast cancer.

Risk assessment

Family history

Other than age, a history of breast cancer in first-degree relatives (mother, sisters, daughters) is the most important risk factor for breast cancer [1,2]. Early age at disease onset and bilateral disease both increase patient risk [3]. The occurrence of breast cancer in a pre-menopausal patient is an indication to conduct a careful family history with

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Table 1. Management issues in women at increased risk for breast cancer

Obtaining a risk factor profile
Assessing premalignant breast pathology
Quantifying risk
Prescribing a screening regimen for breast cancer for other sites
Recommending primary prevention prophylactic mastectomy Breast Cancer Prevention Trial
Using estrogen replacement therapy
Communicating with family members
Dealing with dietary concerns
Screening for cancer at other sites
Wrestling with ethical considerations

elaboration of the nuclear pedigree. Families with two or more affected women provide evidence of possible familial clustering. When nearly half the women at risk for breast cancer in a family are affected before age 50, especially with bilateral disease, genetic predisposition to the disease is likely. Careful attention must also be directed toward the possibility of paternal transmission in affected families [4]. The reliability of the family history is high in affected families [5], and careful histories should be obtained from newly diagnosed breast cancer patients to identify both familial syndromes and unaffected family members at increased risk [6].

Proliferative benign breast disease

Benign breast disease that is serious enough to warrant a biopsy of breast tissue increases the patient's risk of developing breast cancer subsequent to the biopsy [7]. Nonproliferative disease (which includes fibroadenoma, cysts, duct ectasia, apocrine metaplasia, and mild hyperplasia) does not increase the risk of developing breast cancer [8]. Proliferative disease without atypia (intraductal papilloma, radial scar, sclerosing adenosis, moderate or florid ductal hyperplasia) increases the risk of developing breast cancer by 1.5 to 4-fold. The risk increases in the presence of a family history of breast cancer, but this finding is not consistent across studies [9]. Atypical hyperplasia (ductal or lobular) increases the risk of developing breast cancer 3 to 4-fold; if atypical hyperplasia is associated with a family history of breast cancer in first-degree relatives, the increase in risk of breast cancer can be as much as 8 times the baseline rate [10]. There is disagreement among pathologists about the classification of atypical hyperplasia, with some observers classifying it as ductal carcinoma *in situ*. This classification error will not adversely affect risk assessment, however, because women who are diagnosed with carcinoma *in situ* become "cases" and are no longer "at risk."

Total burden of increased risk

A substantial number of women are at increased risk for breast cancer, and prospective epidemiologic studies indicate that approximately 8% of women in the general population have at least one first-degree relative with breast cancer. Nearly 14% of patients with breast cancer report a family history of the disease; therefore, at least 6 million white women in the United States have first-degree relatives with breast cancer [11]. Published data indicate that 17% of women undergo breast biopsy by age 50 years [12]. Of these women, approximately one fourth will have proliferative benign breast disease. Thus, it is likely that more than 1.5 million white women in the United States age 50 or older have this disease. As many as 14% of those women also have first-degree relatives with breast cancer.

Lobular carcinoma in situ

A diagnosis of lobular carcinoma *in situ* (LCIS) increases an individual's risk for breast cancer 10-

to 20-fold [13-15]. The combination of LCIS *and* a family history of breast cancer further increases that risk [16]. Patients diagnosed with LCIS must be carefully advised that although the malignancy is not invasive, the histologic abnormality predisposes the patient to the subsequent development of breast cancer. The risk is bilateral, with both breasts equally at risk. In the past, women with LCIS who had two or more first-degree relatives with breast cancer were offered prophylactic mastectomy [17]. This may not be appropriate, because the published studies cited above show the risk of invasive breast cancer to be 20% to 25% (at maximum) in the 20 years following a diagnosis of LCIS. Therefore, prophylactic mastectomy for LCIS is unnecessary in at least 75% of cases. Careful screening or participation in investigational prevention trials are now more appropriate management options.

Ductal carcinoma in situ

Ductal carcinoma *in situ* (DCIS), like LCIS, increases an individual's risk for the subsequent development of invasive malignancy [18]. While LCIS may be managed locally with excision alone, such therapy may not be adequate for DCIS [17]. Many clinicians prefer breast irradiation with or without tamoxifen therapy for patients with DCIS. The preferred treatment in such women with a family history of breast cancer is less certain, however. We can infer from the data on benign breast disease that a histologic diagnosis of DCIS further increases the risk of breast cancer in a woman already at increased risk because of her family history. Additional data are needed on the magnitude of the additive risk of a family history in the setting of DCIS. A woman with DCIS who also has a family history of breast cancer should be encouraged to participate in randomized treatment trials because the best management strategy is not yet defined.

Mammographic parenchymal pattern

An abnormal parenchymal pattern seen on mammography increases a woman's risk of breast cancer by approximately 1.5 times baseline; women with a family history of breast cancer *and* an abnormal parenchymal pattern have relative risks for breast cancer as high as 3 times baseline [19-24]. The breast parenchyma of young women is more dense than that of older women. Figure 1 shows an example of a screening mammogram in a 39 year-old woman whose mother and sister both had breast cancer. Because of the dense parenchyma, early detection of breast cancer in such patients is difficult or impossible. However, blind fine-needle aspiration or fine-needle core biopsy can yield histologic and biological information about these women that can be useful in risk management [25-27]. For example, if the fine-needle core biopsy specimen of such a woman shows atypical hyperplasia, a more objective discussion about prophylactic mastectomy is possible. In younger women, histologic findings also may determine eligibility for participation in primary chemoprevention trials.

Additional risk factors

Other factors associated with an increased risk for breast cancer include early age at menarche, age at first live-birth, and parity status [28-30]. The relative risks associated with these factors are small, however. Numerous other factors (including the use of oral contraceptives, thyroid supplements, cigarette smoking, and consumption of methylxanthines) do not appear to increase an individual's risk of breast cancer, although epidemiologic studies have implicated some of them. The possibility exists that there is a publication bias favoring positive results even when the study population is small, and multivariate analyses of breast cancer risk factors have failed to confirm the importance of many risk factors published individually [7]. Furthermore, prospective studies have shown that some risk

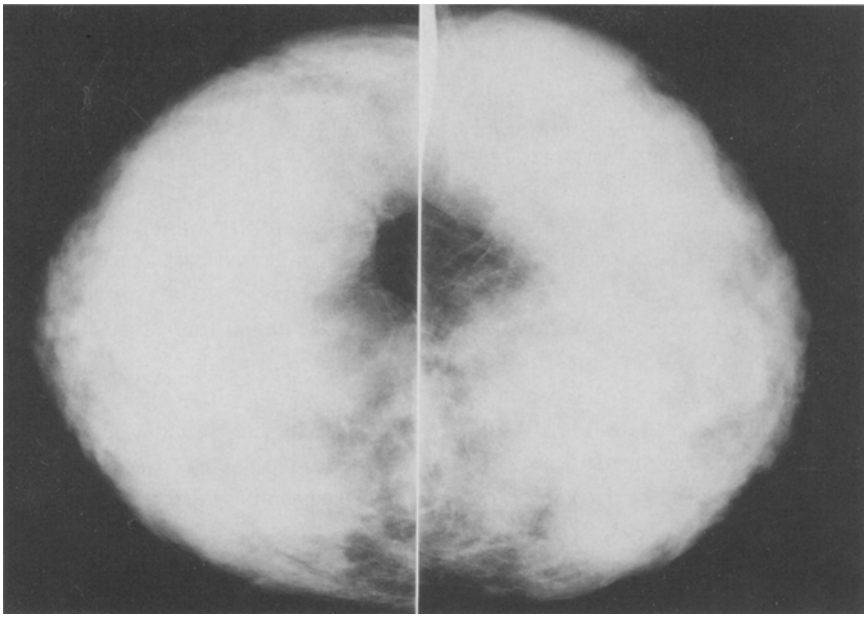

Figure 1. Bilateral film screen mammograms of a 39 year-old asymptomatic woman whose mother and sister both were diagnosed with invasive breast cancer. The severe degree of glandular density makes reliable mammographic screening difficult.

factors identified singly in case-control epidemiologic research (e.g. alcohol) have only a modest impact (if any) on risk [31].

Quantifying risk

Quantification of risk is possible using multivariate regression models [7]; the available models may not accurately reflect, however, the degree of risk experienced by women who are members of affected families. Simply counting affected first-degree relatives is not, by itself, an adequate assessment of the magnitude of familial risk because of the strong likelihood of vertical genetic transmission with more second-degree than first-degree relatives having breast cancer. Affected second-degree relatives (grandmothers, aunts, cousins) increase risk substantially without directly affecting quantitative risk assessments that merely count first-degree relatives [32,33].

Women at increased risk for breast cancer can be identified using individual risk factors one at a time, but the availability of multivariate risk models allows the additional determination of a composite relative risk for breast cancer and the calculation of a cumulative lifetime risk of cancer adjusted for competing causes. There are, however, limitations to the generalization of risk estimates from multivariate models because of selection biases in the studied populations. Published data are largely from studies restricted to white women, and the generalizability of those data to other racial and ethnic groups is uncertain. While there is no reason to suspect a differential effect of family history by race or ethnicity, multivariate risk models derived from minority populations have not been published.

The model developed by Gail et al. [7] is the most widely used method of quantifying risk to assist clinicians in counseling women about their probability of developing breast cancer. The model allows estimation of the likelihood that a woman of a given age with certain risk factors will develop breast cancer over a specified interval. Risk factors include age at menarche,

age at first live birth, number of previous breast biopsies, and the number of first degree relatives with breast cancer. The presence of atypical hyperplasia doubles the risk. Coefficients were estimated using logistic regression and are converted to a composite relative risk for each individual's profile. Figure 2 illustrates an example of the application of the model in the clinical setting.

The limitations of multivariate risk models must be considered. First, available models may not accurately estimate the degree of risk as noted above. One must use caution in generalizing the results of regression models to women seeking risk information since the data used to develop the models were derived from case-control and screening studies, and inherent selection biases in the populations studied must be recognized. Validation studies of multivariate risk models are important for ensuring accurate results. A recent validation study of the model of Gail et al. that examined incident breast cancer occurring over five years following mammographic screening and risk profiling in a group of healthy volunteers indicates that the observed number of breast cancers agrees very closely with the number predicted by the model (Bondy ML et al, submitted for publication). Additional validation studies are needed before the model is applied widely in clinical counseling.

Diagnosis of previous malignancy

Patients at highest risk for breast cancer are women with a prior diagnosis of breast, colon, endometrial, or ovarian carcinomas [34,35]. The risk for development of contralateral breast cancer among women with a first primary breast cancer is approximately 0.5% to 0.75% annually [36]. That is, there is a 10% to 15% cumulative risk at 20 years for the development of a second contralateral breast primary tumor. Among women from families with inherited multi-site cancers, those with prior colon, endometrial, or ovarian cancer are at increased risk for breast cancer

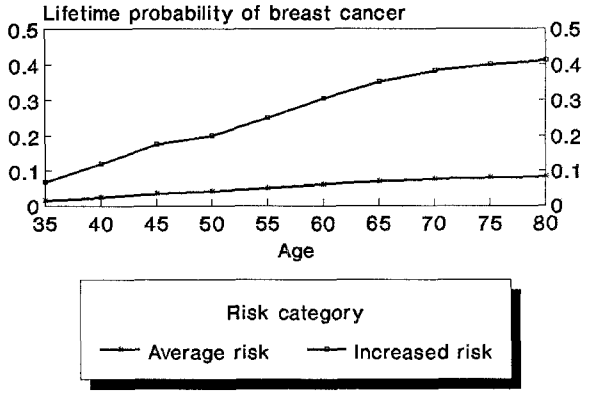

Figure 2. Cumulative lifetime probability by age of developing invasive breast cancer. Lower curve is for a 35 year-old woman at average risk followed until age 80. Upper curve is for a 35 year-old woman with a relative risk of 5.

[37,38]. Those pedigrees often contain multiple individuals, each of whom is affected with a single site-specific malignancy, thus suggesting an increased risk for breast cancer among all women in the family.

Management strategies

Women at increased risk for breast cancer regularly seek counseling for appropriate management of their risks. An effective, prospectively validated management strategy remains to be devised, but prudent recommendations can be derived from available data. These recommendations, summarized in Table 2, must be modified to clarify optimal management decisions as additional data become available.

Mammographic screening prescriptions

Women who have one first-degree relative affected with premenopausal breast cancer and women who have two affected first-degree relatives of any age can be defined as being at increased risk. Similar degrees of risk exist for women whose multivariate risk scores are 5 or greater. For example, a 30-year-old woman whose relative risk

Table 2. Management strategies for women at increased risk for breast cancer

- Risk should be quantified and discussed with the patient in terms of probability of disease developing in a given interval.
- Annual mammographic screening should begin at age 30 or at the completion of childbearing, whichever is later.
- Patients at increased risk should be encouraged to enter clinical prevention trials studying tamoxifen, dietary fat reduction, estrogen-progestin replacement therapy, LHRH agonists, retinoids, or other preventive strategies.
- Fine-needle aspiration or fine-needle core biopsy can yield histologic information that is useful in making management decisions in women at increased risk.
- Increased risk for breast cancer is not an absolute contraindication for estrogen replacement therapy.
- Clinicians must be aware of the risk for cancer at other anatomic sites, but they must recognize the limitations of available screening strategies for colon, ovarian, and endometrial malignancies.
- The patient's right to full disclosure, confidentiality, autonomy, and beneficence must be foremost in all clinical encounters and decisions.

for breast cancer is greater than 5 has an annual risk of breast cancer approximately equal to that of a woman age 45. That is, the relative risk can be thought of as a multiplier of the annual incidence of breast cancer.

How should these women be screened? For women no longer actively attempting to conceive children, annual mammographic screening should begin at age 30 if their relative risk for breast cancer is 5 or greater or they have at least two affected first-degree relatives. This argument is based on consideration of the efficacy of screening mammography (with known sensitivity and specificity) in a defined population with an increased prevalence of disease: the predictive value of a positive mammogram in a 30-year-old woman with a 5-fold increase in her risk of breast cancer should be identical to the positive predictive value of a screening mammogram in a 40-year-old woman at usual risk [39]. Two-thirds of young women who are at increased risk for breast cancer have mammographic images of normal density that are amenable to usual radiologic interpretation (Vogel VG, Higginbotham E, unpublished data). It is also possible, though, that mammographic screening will not decrease mortality from breast cancer in women younger than 50 years [40]. Only a prospective study of screening mammography in young women at increased risk will resolve the existing uncertainty. Until the issue is resolved, annual screening of high-risk women offers the potential of decreased mortality. Mammographic screening should be suspended during pregnancy and lactation in women at increased risk.

Because adequate mammographic visualization can be very difficult in young women with dense breasts [41], ultrasonography should accompany screening mammography to distinguish the frequent cystic lesions that occur in these young women from the solid lesions that require biopsy for diagnosis. This strategy will minimize the number of biopsies performed in young women who receive regular screening.

Prophylactic mastectomy

Prophylactic mastectomy for women at increased risk for breast cancer must be recommended cautiously and advisedly [42]. The considerations listed in Table 3 should be addressed and discussed openly and frankly with the patient before prophylactic mastectomy is undertaken.

A prophylactic mastectomy is an operation that removes the total breast, the tail of Spence, lower lymph nodes, areola, and nipple [43]. Theoretically, a total mastectomy as a prophylactic

Table 3. Considerations in the decision for prophylactic mastectomy

- The extended nuclear pedigree must be examined for evidence of an autosomal dominant syndrome involving either the breast alone or multiple anatomic sites.
- In the absence of a clearly autosomal dominant syndrome, the multivariate risk score should be 10 or greater.
- Women at increased risk who have had repeated breast biopsies with breasts that are difficult to examine due to nodularity and who have diffuse mammographic densities may consider prophylactic mastectomy an acceptable alternative.
- Carriers of BRCA1 may wish to consider prophylactic mastectomy.
- In most women at increased risk, discussions about prophylactic mastectomy should be initiated *only* at the patient's request and *only* after discussion of other management options.
- Breast biopsy or fine needle aspiration showing proliferative changes, especially atypia, is an indication to consider prophylactic mastectomy in women who have two or more first-degree relatives with premenopausal breast cancer and who are not willing to consider primary chemoprevention trials.
- Women who are eligible for participation in primary chemoprevention studies should be offered participation in the trial with a clear understanding that they may receive placebo therapy.
- If the patient's fear and anxiety about breast cancer interfere with her quality of life, if she can cope with the possibility of a poor cosmetic result, and if she has explored these issues with her husband or significant other, she is a candidate for prophylactic mastectomy.

measure prevents the possibility of invasive disease. However, the benefit from this procedure is questionable since long-term outcome data related to the physical and psychological sequelae from women who have had this procedure are not available. Subcutaneous mastectomy is a procedure in which only part of the breast tissue is removed. This is not acceptable surgery because breast tissue is left behind in the areola, nipple, axillary, and supraclavicular areas, and behind any biopsy scar. Invasive breast cancers have been reported in the remaining breast tissue following subcutaneous mastectomies [44-47]. Because of the controversies surrounding silicone breast implants and the moratorium on their use [48], reconstruction should be accomplished using a rectus abdominus flap or saline implants. Women at increased risk should be counseled not to undergo breast augmentation procedures because of the difficulty in reading screening mammograms in augmented breasts.

Fine-needle aspiration (FNA) of nodular areas of the breast or of areas of severe mammographic density can be used to evaluate women at increased risk who are potential candidates for a prophylactic procedure. FNA has a sensitivity for breast cancer greater than 90% and a specificity of at least 98%, and can distinguish histologic subsets of proliferative benign breast disease [49]. Women who have proliferative changes with or without atypia in the presence of an increased relative risk for breast cancer are candidates for prophylactic mastectomy [50]. Women who have normal histologic findings on aspiration or biopsy specimens must be counseled that this does not offer assurance against the development of breast cancer in the future. The diagnosis of invasive breast cancer in a young woman with a family history of the disease should lead to considerations of bilateral mastectomy, particularly when other family members have been affected with bilateral premenopausal breast cancer, or the contralateral breast demonstrates proliferative changes or atypia.

Prophylactic mastectomy is aggressive, and even with reconstruction, may be more disfiguring than a lumpectomy for early stage disease. Also, the pleasurable sensation derived from stimulation of the nipple during sexual foreplay is not possible after surgery. The procedure is rarely

indicated and is reserved for women who are at exceptionally high risk for the disease.

Breast Cancer Prevention Trial

After extensive use worldwide in adjuvant treatment trials, tamoxifen is known to reduce the incidence of contralateral breast cancer by approximately 40% [51], making it a candidate for use in the primary prevention of breast cancer [52]. Tamoxifen also reduces total cholesterol [53] and preserves bone mineral density in postmenopausal women [54]. These beneficial effects strengthen the argument for tamoxifen, but its side effects (including endometrial malignancy) [55] and safety considerations limit its use to clinical trials in women at increased risk for breast cancer.

A portion of women at increased risk for breast cancer are eligible for the Breast Cancer Prevention Trial [56]. For these women, participation in this trial will obviate prophylactic surgery, especially in those with a diagnosis of lobular carcinoma *in situ*. Because of the trial design, half of the enrolled subjects will receive placebo but will remain under intensive surveillance. Participants must understand the possibility of receiving placebo therapy. Physicians treating women with breast cancer should do histories for the nuclear pedigree to identify relatives at risk so that they can be offered the opportunity to participate in the trial.

Estrogen replacement therapy

The risk of breast cancer among women using replacement estrogen therapy after menopause is the subject of controversy and conflicting data in the medical literature [57].

It is generally accepted that endogenous estrogens play some role in the causation of breast cancer [28,29], yet it has been difficult to prove that exogenous estrogens given at the time of menopause have a similar effect. Most studies that have evaluated estrogen replacement therapy and its possible role in the development of breast cancer found no overall increase in risk [58-63], though several studies demonstrated a modest overall increase [64-65].

Such studies may be confounded, however, by a bias in treatment selection that denies hormone replacement therapy to women with a family history of breast cancer [66]. If physicians are less likely to prescribe estrogen for women with a family history of breast cancer, a lack of association or a spurious inverse relationship between estrogen use and breast cancer risk may appear. Nevertheless, the relative risk in published studies is related to the dose and duration of estrogen administration [61].

The association of estrogen administration with the development of breast tumors is derived largely from *in vitro* or animal studies [67]. No prospective randomized trials have addressed the risks and benefits of estrogen replacement therapy in women at increased risk for breast cancer. However, retrospective review does suggest an increased risk of breast cancer among women with a family history of that disease who take replacement estrogen therapy for longer than 5 years [68]. The risk is greatest among premenopausal women exposed to estradiol.

Three meta-analyses to determine the effect of noncontraceptive estrogen replacement therapy on breast cancer risk [68-70] have been published. Two of the analyses did not find a positive association between estrogen replacement therapy and breast cancer in high-risk women, which included subjects with a positive family history [69,70]. One meta-analysis [69] included only American studies while the other [70] included 27 American studies and one European study. Steinberg et al [68] found that women with a family history of breast cancer who had ever used estrogen replacement had a significantly increased risk (relative risk = 3.4; 95% CI 2.0–6.0). The increased risk among women with a family history in the latter analysis may be due to the difference in preparations of estrogen used in the United States and Europe.

Based upon the results of these numerous and large epidemiologic studies, there is not definitive evidence that hormone replacement therapy with low-dose conjugated estrogens increases the risk of breast cancer, including therapy in high-risk women. The possibility remains that the risk may be moderately increased with long durations of use (>15 years) and at higher doses, especially with unconjugated estrogens (e.g. estradiol). There is no published clinical trial investigating the role of estrogens in increasing breast cancer risk. Only a randomized, prospective clinical trial can address the question of a causal relationship.

In some studies, no apparent increase in the risk of breast cancer is seen when estrogen replacement therapy is given to women with surgically induced menopause, women with intact ovaries, or women with benign breast disease and a family history of breast cancer [63]. It is not known whether supplemental estrogen replacement therapy affects the risk of recurrence or the development of metastases in postmenopausal patients with a history of breast cancer, but pregnancy (a condition that profoundly stimulates estrogen production) does not adversely affect women previously diagnosed with breast cancer [71].

Most studies of oral contraceptive use show no associated increase in the risk of breast cancer [72-74], and at least one study has suggested a reduced risk in oral contraceptive users [75].

Estrogen replacement therapy in women at increased risk for breast cancer

The morbidity and mortality associated with estrogen deficiency in postmenopausal women is substantial [76]. Estrogen deficiency causes hot flashes, genital atrophy with resultant dyspareunia, and mood swings. More importantly, the risk of death from cardiovascular disease increases 18-fold after menopause and is directly linked to estrogen deficiency [76]. Elevated levels of total cholesterol and low-density lipoprotein (LDL) cholesterol have been causally related to an increased risk of coronary vascular disease. The use of estrogen replacement therapy after menopause has a favorable influence on high-density lipoproteins, LDL, and total cholesterol levels. Estrogen supplementation reduces the risk for coronary heart disease [77], and estrogen replacement therapy has been reported to have a vascular protective effect [78].

Numerous studies have demonstrated that all-cause mortality and mortality form coronary heart disease and cerebrovascular disease is reduced in women who have ever used estrogen replacement therapy [79]. Estrogen supplementation can reduce or prevent trabecular bone loss and the development of osteoporosis, and it can also reduce or prevent morbidity and mortality associated with osteoporosis [80,81]. Other treatments for osteoporosis, including calcium supplementation, exercise, and fluoride administration, may not, when used alone, prevent osteoporosis.

Contrary to these arguments for the use of replacement estrogen therapy, there are substantial data showing that breast cancer risk is lower among women who experience menarche at a later age, who have fewer ovulatory menstrual cycles during their lifetimes, or who are younger at menopause, whether the menopause is natural or surgical [82,83]. Anovulatory menstrual cycles and early menopause extract a price, however, through reduced bone mineral density and a higher risk of fracture [84]. Despite these observations, the lower risk of breast cancer among women who have lower endogenous estrogen levels does not necessarily imply an increased risk of breast cancer in women who receive replacement estrogen therapy at menopause.

In light of the published benefits of estrogen replacement therapy with regard to quality of life and reduction of cardiovascular morbidity and mortality as well as reduction of morbidity and mortality attributable to osteoporosis, estrogen replacement therapy must be considered even in women known to be at increased risk for breast cancer [85]. It is unreasonable to reject such therapy as inappropriate for all women at increased risk [86]. In women who have undergone

oophorectomy prior to natural menopause, low-dose estrogen replacement prevents the occurrence of stroke or myocardial infarction during an increased number of years at risk following premature menopause. In families where the BRCA1 gene is present, 72% of women with the gene develop breast cancer by age 55 [87]. Therefore, among women with a family history of breast cancer who reach natural menopause without having developed breast cancer, the likelihood of developing breast cancer in the remaining years of life is largely determined by rising age-specific incidence rather than by genetic factors. To deny these women estrogen replacement therapy is to ignore the substantial competing risks of osteoporosis and heart disease that both rise exponentially following menopause. Estrogen replacement therapy should be offered to these women after a careful discussion of the potential risks and known benefits [79,88].

Communicating results from risk assessments

Strategies for counseling women about the risk of breast cancer are now well developed and have been reviewed [87,89]. Risk assessment and counseling for women at increased risk for breast cancer include collection of family history data, calculation of cancer risks, communication of risk status, and education to reduce the risk of morbidity and mortality. Published data indicate that women at increased risk for breast cancer are misinformed about their risks and are not screened adequately [90]. The poor screening histories among these women are indications for increased counseling efforts. Unfortunately, there are potentially adverse effects of communicating breast cancer risks [89]. Upon learning of their increased risk, some women experience an increased sense of denial, low self-esteem, anxiety, and guilt. Thus, both the patient's desire for information and the level at which the patient chooses to control decision-making must be considered in the counseling process.

Women at increased risk for breast cancer tend to overestimate that risk [91]. Providing them with accurate information about their risk heightens awareness while reducing anxiety. Although information about relative risk is useful to epidemiologists and perhaps to clinicians, formulating risk information in this way will be ambiguous for the woman at risk because the public does not routinely deal with comparative risk assessments [92]. A more useful strategy is to use lifetime probability of disease (Figure 2), expressing risk as a proportion of women affected among a hypothetical group at similar risk over a fixed period of time (e.g., 10 or 20 years). Proper communication of risk results in diminished anxiety and improved compliance with screening recommendations [93].

Dietary modification

The evidence linking dietary fat to the risk of breast cancer is controversial [94], and there is no published prospective study that demonstrates a reduction in breast cancer incidence through a reduction in dietary fat intake. Most studies show no relationship between dietary fat intake and the risk of breast cancer [95-97]. Other dietary components, including fiber, retinoids and carotenoids, trace elements, and antioxidants, may reduce the risk for breast cancer [98], but more data are needed.

For the woman at increased risk for breast cancer, a more important consideration supervenes: the presence of genetic or other predispositions for the development of breast cancer will likely overwhelm and outweigh any effects of lifestyle on breast carcinogenesis. Thus, if a woman is a member of a pedigree in which the predisposition for the development of breast cancer is transmitted as an autosomal dominant trait, dietary fat modification or increased consumption of antioxidants or trace elements may have no impact upon her risk of developing breast cancer.

The psychological implications of advising a woman at increased risk for breast cancer to

reduce her dietary fat intake are potentially serious. If such a recommendation is made with the hope of reducing the risk of breast cancer, a woman who rigorously adheres to a reduced-fat diet and then develops breast cancer anyway may experience profound feelings of frustration, guilt, or betrayal when she recognizes that these actions did not affect her risk of developing disease. These feelings may place the physician-patient relationship in serious jeopardy by destroying trust.

This is not to suggest that on a population basis, reduction of dietary fat will *not* have an effect on breast cancer incidence. However, physicians who counsel women at increased risk as a result of genetic predisposition must be cautious about placing emphasis on the importance of possible (but unproven) environmental causative factors, including diet.

Screening for cancer at other sites

Genetic syndromes that place women at risk for malignancy at multiple anatomic sites (including breast, colon, endometrium, and ovary) are well described [33-35,38]. Although screening mammography can reduce breast cancer mortality by 30% in postmenopausal women, the ability of other screening tests to reduce cancer mortality at other anatomic sites is less certain. We review three of those sites below.

Ovary. Screening for ovarian cancer can be accomplished with transvaginal pelvic ultrasound and CA-125 antigen testing. CA-125, a marker widely used for monitoring the progress of epithelial ovarian malignancy, is recognized by a murine monoclonal IgG^1 immunoglobulin raised against a cell line of ovarian serous cyst adenocarcinoma [99]. It has not yet been incorporated into population screening for ovarian malignancy because it is no more specific for ovarian malignancy than bimanual pelvic examination [100], and its sensitivity is poor for each stage of disease [101]. False-positive elevations occur in a variety of gynecological conditions, especially uterine leiomyomata and endometriosis [102,103].

The sensitivity and specificity of either ultrasound or CA-125 done as a screening procedure in healthy women are uncertain. Although the risks for developing ovarian cancer can be considerable among women from affected families, the lack of specificity of CA-125 antigen and pelvic ultrasound will result in some unnecessary invasive procedures in a group of screened women [104]. A difficult clinical situation arises when a woman at increased risk is screened with an imperfect screening test. A questionable mass noted on a vaginal ultrasound or an elevated level of CA-125 obligates the clinician to investigate the abnormality further, particularly in the setting of increased risk. Because benign ovarian cysts, endometriosis, and other gynecologic abnormalities can lead to spurious elevations in the CA-125 antigen and because vaginal ultrasound cannot distinguish between benign and malignant ovarian cysts, caution must be used in the broad application of a screening strategy that incorporates these tests.

Colon. Despite the fact that tens of thousands of women in the United States each year develop breast cancer, there is no consensus regarding endoscopic screening for those with a previous diagnosis of breast cancer. Few epidemiologic studies have investigated the effect of a breast cancer diagnosis on the subsequent risk of colon cancer, although one study suggested a 3-fold increase in that risk among Israeli women [105]. Because the risk of colon cancer increases among women age 50 years and older who have never had breast cancer, it reasonable to recommend a baseline flexible sigmoidoscopic or colonoscopic screening examination for asymptomatic women with a history of breast cancer [106]. Indeed, recent studies indicate mortality reduction from colorectal cancer using either fecal occult blood testing [107] or flexible sigmoidoscopy [108] in individuals at usual risk for colorectal malignancy. Additional research is needed to determine the optimal screening strategy for colon

cancer among women with a previous diagnosis of breast cancer.

A more difficult dilemma involves colon cancer screening in women whose relatives have had breast cancer but not colon cancer. In families with a history of Lynch Type II disease, regular colonoscopic screenings should begin at an early age in all members at risk [38]. Patients from families with familial clustering of breast cancer but no definite genetic syndromes that include colon cancer should be screened at minimum with annual flexible sigmoidoscopy, beginning at age 40.

Endometrium. The risk of endometrial malignancy increases in women with a history of breast cancer [109]. Few published studies address the appropriate screening strategy for women at increased risk for endometrial cancer. Annual endometrial aspiration biopsy is indicated for women who have received or are receiving adjuvant tamoxifen therapy [110] and for women receiving estrogen replacement therapy [111]. Using available techniques, endometrial samples can be obtained with minimal discomfort to the patient [112].

An endometrial screening strategy for women who have no prior diagnosis of malignancy but whose genetic histories place them at increased risk is not well defined. Women from Lynch Type II disease families should have annual endometrial screening beginning at age 35 if they are no longer actively attempting to conceive.

Interventions with other family members

Clinicians who identify breast cancer patients with family members at increased risk for breast or other malignancies should notify those family members of their increased risks. Such notification of family members results in improved compliance with recommendations for screening mammography [113]. Counseling is difficult when family members live at a distance from the index case and cannot visit the clinic for personalized screening, but informational letters can be an effective mechanism for educating family members. The optimal strategy also involves notification of their family members' attending physicians with recommendations for appropriate screening interventions. When family members live in proximity to one another, family counseling visits are an effective means for transmitting information about risks and for outlining possible preventive interventions.

Ethical implications

Ethical issues arise in the management and counseling of women at increased risk for breast cancer [89]. The patient's comprehension of the risk information and the physician's disclosure to the patient of genetic testing data of uncertain significance create situations wherein harm is possible. Women at increased risk for breast cancer are understandably anxious, and they seek information (for example, genetic) that can assist them in modifying their risk and managing their clinical situations. However, preliminary results of genetic and molecular epidemiologic studies often appear in the press before the implications of the genetic abnormality are completely understood. The clinician is then faced with the patient's questions about the use of preliminary genetic information (e.g., loss of the p53 suppressor gene [114] on the development of malignancy). Complicating the clinical situation further is the need to collect research data from women who go to clinics that evaluate risk. Genetic information may be derived from blood specimens or tissues obtained from these women for research purposes, and ethicists are debating whether genetic information collected necessarily translates into genetic knowledge that the clinician is obligated to share with the patient. The obligation to fully disclose preliminary and incomplete genetic information remains to be completely defined. Active participation of multidisciplinary institutional review boards in genetic research programs is encouraged to

maintain patient rights and to protect research subjects from potential harm.

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