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E6. How do we choose candidates for breast cancer prevention?

Steven R. Goldstein*

Professor of Obstetrics & Gynecology, New York University School of Medicine, 530 First Avenue, Suite 10N, New York, NY 10016, USA

Prospective studies have found that the risk of breast cancer rises with increases in endogenous oestradiol levels. Recently published data from the placebo group of the multiple outcomes of raloxifene evaluation (MORE) trial showed that the postmenopausal osteoporotic women with highest circulating levels of oestradiol within a menopausal range had the greatest risk of developing breast cancer through four years. Additionally the greatest reduction in breast cancer in the raloxifene-treated group was seen in the highest risk group, whereas the lowest risk group had no reduction. If confirmed by future studies, sensitive measurements of oestradiol levels, at least in postmenopausal women, may be an appropriate way to assess breast cancer risk for those patients considering chemoprevention.

In the United States, breast cancer is the second most common cancer in women, only recently surpassed by lung cancer There are more 180 000 new cases diagnosed annually and more than 45 000 deaths. The emotional and psychological ramifications of developing breast cancer and the concomitant fear of the disease is overwhelming for many women. Tamoxifen, long used to treat women with breast cancer, is now approved by the FDA for breast cancer risk reduction in women at high-risk. This was based on data supplied from the national surgical adjuvant breast and bowel project (NSABP)-P1 Trial (BCPT) [1]. Raloxifene, a benzothiophene selective oestrogen receptor modulator (SERM), significantly lowers new onset invasive breast cancer in osteoporotic women through 4 years of exposure [2]. Currently, study of tamoxifen and raloxifene (STAR) is ongoing, but it appears likely that, ultimately, raloxifene too, will be approved for chemoprevention of breast cancer. Thus, the assessment of breast cancer risk is important and will only become more so in the future in order to decide which women are appropriate candidates for such chemoprevention.

In the past, isolated risk factors for breast cancer have been assigned a Relative Risk or Odds Ratio. Such factors with varying Relative Risks include early menarche, late menopause, obesity, alcohol use, hormone-replacement therapy (HRT), first-degree relative with breast cancer, first live birth after age 35 years, as well as any gene mutations (*BRCA-1 or BRCA-2*) or pre-invasive breast lesions. Relative Risks or Odds Ratio of the specific characteristic gives the likelihood of a group of women with that characteristic developing breast cancer compared with a group of women without that characteristic. This is of limited value to an individual woman. Developing models that estimate absolute risk of developing breast cancer taking into consideration various risk factors, seems to be a better way to counsel patients. One such model was developed by Gail [3]. Based on 2852 detected cancers (10% *in situ*), and 3146 controls between 1973 and 1980 at 28 centres as part of the Breast Cancer Detection Demonstration Project (BCDDP), a model to predict an individual woman's risk of developing breast cancer in the next 5 years and within her lifetime was developed. Oral contraceptives, methyl xanthenes and cigarette smoking had no relationship with the development of breast cancer. Alcohol, long-term HRT use and height caused an increased risk, but the number of women with these risk factors was limited, so these variables were ultimately not included. The model was later modified for invasive breast cancer only and incorporated data from SEER (Surveillance, Epidemiology, and End Results) to include non-Caucasian women. This final version gives a risk based on age, age at menarche, age at first live born (if any), number of first-degree relative with breast cancer, number of previous breast cancer biopsies, and if any were hyperplastic.

Rockhill and colleagues [4] applied the Gail model to almost 100 000 women in the Nurses Health Study between 1992 and 1997. E/O (expected to observed) ratios

* Tel.: +1 2122637416; fax: +1 2122636259.
E-mail address: steven.goldstein@med.nyu.edu.

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were close to 1. Thus, the model was accurate in predicting risk in a population. However the discriminatory accuracy for an individual was only 0.58. When a 5 year cut-off point of 1.66% risk of developing breast cancer (the level used in the BCPT) was used to define "high-risk", only 44% of 13 054 women who developed breast cancer had a score >1.67%. In other words, most of the women who developed breast cancer had a 5 year risk <1.67%. Another shortcoming of the Gail model is that of "breast biopsies". In the original description, there was no mention of what is a "breast biopsy". This data was derived between 24 and 33 years ago. Today, numerous less invasive techniques for breast tissue sampling have emerged, including fine-needle aspiration, core biopsy, and stereotactical mammographic-guided biopsy. Ultrasound-guided biopsy and, most recently, in 1993, the introduction of the Mammotome® biopsy system (Biopsys Medical Instruments, San Juan Capistrano, California). Thus, the number of "biopsies" women are undergoing is increasing dramatically and this has a tremendous effect on an individual's assessment of risk by the Gail model. For instance, a hypothetical 50-year Caucasian woman who is nulliparous with menarche at age 11 years and no first-degree relative with breast cancer and no previous breast biopsies yields a Gail score of 1.2% risk over the next 5 years i.e. low-risk. If the same woman had 3 previous breast "biopsies" none of which were hyperplasic her Gail score rises to 1.8% making her a candidate for chemoprevention.

Other shortcomings of the Gail model include that it is not appropriate for risk assessment in women less than 35 years of age, women with a history suggestive of hereditary breast cancer, a personal history of earlier breast cancer, lobular carcinoma *in situ* (LCIS) or ductal carcinoma *in situ* (DCIS), and women not undergoing annual screening.

Ultimately, assessment of risk based on an individual's own findings rather than population-based characteristics would be desirable. Examples might include things like a patient's breast density on imaging study or ultra-sensitive measurements of her circulating endogenous hormones, such as oestradiol, oestrone, and even testosterone.

Harvey and colleagues [5] published a meta-analysis of 12 studies. Breast density was quantitated by visual assessment or planimetry. Increased mamographic density is an independent risk factor for breast cancer with Odds Ratios ranging from 1.8–6.0 (average 4.0). Possible explanations for the association of increased density and risk of breast cancer include development of premalignant lesions, elevated growth factors, overactive aromatase causing increased oestrogen within the breast and possibly even a hereditary basis for breast density. Furthermore, density is hormonally-responsive and is influenced by alcohol intake and diet.

Prospective studies have found that the risk of breast cancer rises with an increase in endogenous oestrogens. Toniolo and colleagues [6] was the first to confirm the link between circulating oestrogens in breast cancer risk in a large prospective epidemiological study. Of 130 cancers in 260 matched controls through 5 1/2 years of study on stored serum specimens, women with higher levels of oestrone, and total and free oestradiol had a higher rate of breast cancer.

Cauley and colleagues [7] published a prospective case-cohort study from 4 centres for an average of 3.2 years involving 97 women with cancer and 244 controls. Women with the highest concentration of bioavailable oestradiol had a RR = 3.6 (95% CI, 1.3–10.0). In addition, the concentration of free testosterone had a RR = 3.3 (95% CI, 1.1–10.3).

Recently published data from the multiple outcomes of raloxifene evaluation (MORE) trial [8] may offer promise of a type of risk assessment that can be expected for the future. This was an osteoporosis treatment trial. All patients were postmenopausal i.e. serum oestradiol < 20 pmol/l. However, using an ultrasensitive assay for oestradiol, they were able to stratify these patient's quantitative oestradiol levels. In the placebo group the Relative Risk of developing invasive breast cancer for undetectable levels, levels between 0 and 5 pmol/l, between 5–10 and 10–20 pmol/l was 0.6, 1.2, 1.8 and 3.0, respectively. In other words, the postmenopausal women with the highest circulating levels of oestradiol within a menopausal range had the greatest risk. Additionally, the greatest reduction in breast cancer in the raloxifene group was seen in the highest risk group, whereas the lowest risk group had no reduction.

In summary, the assessment of breast cancer risk is important and will only become more so in the future. Methods to determine an individual woman's risk of developing breast cancer will be important to assess those patients who are considering chemoprevention.

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