

# The Estimation and Use of Absolute Risk for Weighing the Risks and Benefits of Selective Estrogen Receptor Modulators for Preventing Breast Cancer

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**ABSTRACT:** In order to weigh the risks and benefits of intervention with selective estrogen response modifiers for preventing breast cancer, one needs to consider the effects of intervention on several health outcomes. For example, tamoxifen was shown to reduce the risks of breast cancer and hip fracture while increasing the risks of endometrial cancer and cardiovascular end points, including stroke. One approach to weighing risks and benefits is to estimate the net effect of the intervention on the absolute risk of each of the relevant health outcomes. To estimate this net effect, one needs to know not only the relative risk from the intervention, but also the absolute risk of the health outcome in the absence of intervention. Intervention trials yield unbiased estimates of intervention relative risks, but data are usually too limited to estimate these relative risks precisely for subgroups or for rare health outcomes. Moreover, intervention trials are usually too small to provide data for developing a model for estimating the individualized absolute risk of various health outcomes in the absence of intervention. The model of Gail *et al.* for projecting the individualized risk of breast cancer, as modified for use in the Breast Cancer Prevention Trial, has been validated. To weigh various risks and benefits of interventions, there is a need for research to develop such models for a range of health outcomes.

**KEYWORDS:** risks, benefits, breast cancer prevention, SERMs

The decision to use selective estrogen receptor modulators (SERMs) to prevent, treat, and reduce the risk of breast cancer is complicated by the fact that SERMs influence many health outcomes. For example, the Breast Cancer Prevention Trial (BCPT), also known as P-1,<sup>1</sup> demonstrated that tamoxifen reduced the risks of invasive and noninvasive breast cancer and of hip fractures, while increasing the risks of endometrial cancer, stroke, pulmonary embolism, and deep vein thrombosis. A woman deciding whether to take tamoxifen needs to weigh the various risks she faces in the presence and the absence of tamoxifen. An essential ingredient in this decision process is an estimate of the absolute risks of the various outcomes in the presence and the absence of tamoxifen. In this paper we discuss the role of absolute

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**TABLE 1.** Numbers of events expected in five years in a population of 10,000 40-year-old white women with a projected risk of breast cancer of 2% in the absence of tamoxifen

	Expected without tamoxifen $I_j \times 10^4$	Expected with tamoxifen $R_j I_j \times 10^4$	Prevented (or caused) by tamoxifen $I_j(1 - R_j) \times 10^4$
Invasive breast cancer	200	102	98
Hip fracture	2	1	1
Endometrial cancer	10	26	(16)
Stroke	22	35	(13)
Pulmonary embolism	7	22	(15)

risk and its estimation. Although we illustrate these ideas with data from the BCPT and rely heavily on a publication aimed at measuring the risks and benefits of tamoxifen,<sup>2</sup> our comments apply more broadly to the evaluation of SERMs and to other interventions to prevent or reduce the risk of disease.

The absolute risk of developing breast cancer over a period of five years, for example, is just the probability that a woman who is free of breast cancer at age "a" will be observed to develop breast cancer at or before age "a + 5." Suppose that there are "J" adverse health outcomes of interest, "j = 1, 2, ..., J." Suppose that, in the absence of tamoxifen, outcome "j" has a 5-year absolute risk " $I_j$ ." We call " $I_j$ " the baseline absolute risk of outcome "j." Suppose the effect of tamoxifen is to multiply this risk by a relative risk factor " $R_j$ ," which is less than one for a protective effect of tamoxifen and greater than one for an adverse effect of tamoxifen. Then, to a good approximation, the net effect of tamoxifen is to reduce (or increase) the absolute risk of outcome "j" by the net amount

$$I_j - R_j I_j = I_j(1 - R_j), \quad (1)$$

which is positive when tamoxifen is beneficial and negative otherwise. More complicated expressions are needed for longer time periods in which competing risks from the various health outcomes and other causes of death must be taken into account,<sup>2-3</sup> but Eq.(1) is quite adequate for 5-year time intervals.

BCPT was a randomized intervention study and provided excellent estimates of relative risks  $R_j$  for various health outcomes, including those in TABLE 1. Estimates of " $I_j$ " are more problematic, as we shall discuss in subsequent sections, and often must be based on data sources outside a particular intervention trial.

To make the idea of absolute risk easier to understand, we tabulate the number of women expected to have a given event in a population of 10,000 women followed for five years (TABLE 1). Thus, in the absence of tamoxifen, an absolute risk of breast cancer of 0.02 or 2% over five years would correspond to an expected  $0.02 \times 10,000 = 200$  women who develop breast cancer in that population.

In such a population of white women, data from the BCPT indicate<sup>1,2</sup> that tamoxifen would prevent 98 invasive breast cancers and one hip fracture, while causing an additional 16 endometrial cancers, 13 strokes, and 15 pulmonary embolisms (TABLE 1). In counseling, each woman might react to these data differently, depend-

ing on her concerns about the various health outcomes. In putting these numbers in perspective, it might be useful to note that 92 white women would be expected to die from any cause in this population during this 5-year period. Gail *et al.*<sup>2</sup> presented a more elaborate version of TABLE 1 with more health outcomes, and they summarized the benefits and losses from tamoxifen by taking the weighted average of the various net outcomes (column 4, TABLE 1). But whether one summarizes the results in TABLE 1 or discusses each outcome separately, the basic ingredients in the decision include the absolute risks in columns 2 and 3 of TABLE 1, the net effect of intervention on each outcome (column 4) and the importance the woman attaches to each outcome. In implementing this approach to assessing risks and benefits, we found that there is substantial uncertainty, not only concerning  $R_j$ , but also especially concerning  $I_j$ . We discuss these uncertainties in the following sections.

### UNCERTAINTIES IN THE ESTIMATION OF TREATMENT RELATIVE RISKS, $R_j$

A carefully designed and conducted randomized intervention trial is an ideal study to estimate treatment relative risks,  $R_j$ . Randomization protects against selection bias and yields unbiased estimates of the relative risk associated with treatment. Even a large and well-executed study such as the BCPT will often provide only limited information on  $R_j$  for some of the rarer outcomes, however. For example, the BCPT was designed to yield precise results for the effects of tamoxifen on invasive breast cancer. The relative risk for invasive breast cancer, based on 264 events in the trial, was  $R = 0.51$  with 95% confidence interval (CI) 0.39–0.66, indicating a substantial protective effect. Data on endometrial cancer were comparatively sparse; the relative risk for endometrial cancer was 2.53 with a fairly wide 95% CI of 1.35–4.97 based on 51 events. For stroke, the relative risk was 1.59 with 95% CI 0.93–2.77 based on 62 events. Thus, although the BCPT yielded unbiased estimates of  $R_j$  for various outcomes, the precision of the estimates varied, depending on how rare or common the outcome was.

The data from BCPT are too limited to permit reliable estimates of tamoxifen effects for small subgroups of the population. One usually assumes that the treatment effects are homogeneous across subgroups, unless there is evidence to the contrary. Indeed, Fisher *et al.*<sup>1</sup> found very consistent effects of tamoxifen on the risk of invasive breast cancer in subgroups defined by baseline predicted breast cancer risk, age, history of carcinoma *in situ*, and number of first-degree relatives with breast cancer. Only 1.7% of the women in BCPT were African American. Thus, there is little power to demonstrate whether tamoxifen's effects differ between African-American women and other trial participants. In practice, one will often be forced to assume that treatment effects observed for the entire trial population apply to various subgroups of the population.

### ESTIMATING ABSOLUTE RISKS $I_j$ IN THE ABSENCE OF TAMOXIFEN

Absolute risk, in the absence of tamoxifen, depends strongly on a number of individual characteristics such as age, medical history, ethnicity, and selection factors

used to define eligibility for participation in an intervention study. In counseling a woman on her risk of breast cancer in the absence of tamoxifen, it is important to individualize the risk projection to the extent possible. Data from an intervention trial, such as the BCPT, will usually be insufficient to define baseline absolute risk within subgroups defined by age and various medical factors. For example, only 89 women in the placebo arm of the BCPT developed invasive breast cancer; thus it would not be feasible to estimate baseline risk precisely, even in subgroups defined only by age. Instead, one must rely on larger studies to provide information on baseline absolute risk.

To project baseline risk for invasive breast cancer for BCPT, statisticians Stewart Anderson and Carol Redmond of the University of Pittsburgh modified the model for projecting breast cancer risk developed by Gail *et al.*,<sup>3</sup> which was based on data from the Breast Cancer Detection Demonstration Project (BCDDP). Gail *et al.* analyzed case-control data from BCDDP of 2,852 white women who developed breast cancer and 3,146 white women without breast cancer to develop a multivariate relative risk model that took into account age, age at menarche, age at first live birth, number of previous breast biopsies, the presence of atypical hyperplasia on any biopsy, and the number of first-degree relatives (mothers and sisters) with breast cancer. Gail *et al.* showed how to combine this relative risk information with age-specific breast cancer incidence rates from the entire BCDDP population of 243,221 white women to estimate the absolute risk of developing disease over particular time intervals, such as a 5-year age interval, for a woman with a given age and set of risk factors. Drs. Anderson and Redmond modified the calculations by substituting for BCDDP age-specific rates the age-specific incidence rates from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program. They also adapted the model to project risks for African-American women, as described in Costantino *et al.*<sup>4</sup>

This modification of the model by Gail *et al.*<sup>3</sup> was used to characterize women who were eligible for the BCPT. Indeed, women under age 60 who had a projected 5-year risk less than 1.66% were ineligible. The predictions from this model for women in various age groups proved to be quite accurate, as was seen by comparing expected and observed cancer incidence in subgroups of the placebo arm of the BCPT.<sup>4</sup> A recent validation analysis on data from the Nurses Health Study confirmed the good calibration of this model.<sup>5</sup> This model is available at the National Cancer Institute's web site [http://cancernet.nci.nih.gov/genetics\\_prevention.html](http://cancernet.nci.nih.gov/genetics_prevention.html).

Thus, one has a well-calibrated model for projecting the 5-year risk of breast cancer for white women with particular risk factors. The net benefits of tamoxifen for preventing invasive breast cancer depend directly on the level of baseline absolute risk, as indicated in Eq. 1. For example, if a woman with particular risk factors has a baseline risk  $I = 0.02$ , as in TABLE 1, her net benefit is  $0.02 (1-0.51) \times 10,000 = 98$ . In contrast, a woman with more risk factors and a higher baseline risk of  $I = 0.04$  stands to benefit by  $0.04 (1-0.51) \times 10,000 = 196$  events. This calculation illustrates the importance of having individualized estimates of baseline incidence rates,  $I_j$ , for each of the health outcomes of interest.

Unfortunately, models to project individualized absolute risk are not available for many important health outcomes. This is because registries are not available to gather data on the incidence of many of these diseases and because few investigators have published data on individualized absolute risk from cohort studies.

As an important example, Gail *et al.*<sup>2</sup> estimated the age-specific risk of stroke in white women from population-based studies in Rochester, Minnesota.<sup>6</sup> Rochester, Minnesota probably has lower incidence rates than rates in other parts of the United States, however. Indeed, age-adjusted stroke mortality rates for white women were 69.8 per 10<sup>5</sup> woman-years for women aged 35–84 years in Olmstead County, Minnesota, compared to a rate of 92.2 for the United States. In addition, these data could not be used directly to obtain individualized estimates depending on medical factors such as blood pressure, weight, and the presence of a cardiac arrhythmia. Incidence data were not even available on ethnicity, because Rochester, Minnesota has a predominantly white population. Yet it is known that African-American women have stroke mortality rates considerably higher than white women in the U.S., and, as reviewed by Gail *et al.*,<sup>2</sup> the literature indicates similar elevation in stroke incidence among African-American women. Thus, Gail *et al.*<sup>2</sup> individualized stroke baseline incidence rates for age and ethnicity, but were unable to find validated models for absolute risk that incorporated important features of the medical history. This can be problematic when advising a black woman, for example, who is in excellent physical condition and has no health problems. Her baseline risk of stroke may be considerably lower than the average black woman in her age group, and she may therefore have a lower risk of stroke than one would find in tables individualized only for age and ethnicity, such as Table 3 in Gail *et al.*<sup>2</sup>

To project individualized absolute risk in the absence of tamoxifen, one needs a multivariate relative risk model to take various prognostic factors into account, and one needs to obtain absolute rates from following a cohort or from registry data.<sup>3</sup> Cohort or case-control studies can be used to estimate the multivariate relative risk function, but only cohorts or registries provide the additional ingredients needed to compute individualized absolute risk. Many analyses of cohort studies have focused on the relative risk features of the model, which may be applicable in various populations, rather than on modeling individualized absolute risk. For whatever reason, there is a dearth of validated individualized models for absolute risk for most health outcomes, and there is a need to develop such models. Large cohorts, such as the Women's Health Initiative cohort, can provide valuable information on absolute risk. Volunteers for such studies, however, tend to be healthier than the general population and to have lower incidence and mortality rates from cardiovascular diseases.

## DISCUSSION

The assessment of intervention with SERMs to prevent breast cancer is complicated by their effects on multiple health outcomes. The important role of individualized absolute risk in the absence of intervention, as well as the treatment relative risk from intervention, in assessing the net gains and losses from intervention for each health outcome affected by intervention has been highlighted. These gains and losses can be examined individually (TABLE 1) or can be summarized to assist in decision making. Although unbiased estimates of treatment relative risks can be obtained from randomized intervention studies, there will typically be insufficient information to estimate treatment effects precisely within subgroups or for uncommon health outcomes. To permit more reliable assessment of the risks and benefits of pre-

ventive interventions, there is a pressing need for research to develop models for projecting individualized absolute risks of various health outcomes in the absence of intervention.

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