

How Many US Women Are Eligible to Use Tamoxifen for Breast Cancer Chemoprevention? How Many Women Would Benefit?

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Tamoxifen has been used by women diagnosed with breast cancer to reduce their risk of recurrence and the development of a new tumor in the contralateral breast. In 1998, the Breast Cancer Prevention Trial (BCPT) demonstrated that tamoxifen treatment produced a 49% reduction in the risk of invasive breast cancer among women at elevated risk for the disease, but with no previous history of the disease.¹ The US Food and Drug Administration (FDA) subsequently approved tamoxifen for breast cancer chemoprevention for certain subgroups of women at high risk of breast cancer (age 35 years or older with a 5-year breast cancer risk of 1.67% or higher). Unfortunately, tamoxifen use has been associated with adverse outcomes, including excesses of endometrial cancer, pulmonary embolism, stroke, deep vein thrombosis, and cataracts, and not all eligible women have a positive benefit/risk ratio.

Investigators have made several attempts to understand the implications of widespread population use of tamoxifen to prevent breast cancer. However, a full evaluation of the impact of tamoxifen

chemoprevention on public health requires that both the adverse events and proven benefits for breast cancer risk reduction be taken into account. It is particularly important to identify subsets of women in whom the tamoxifen-induced benefits of reducing the risks of breast cancer and other life-threatening or severe illnesses, such as hip fracture, outweigh the risks of serious or life-threatening tamoxifen-induced events, such as stroke, pulmonary embolism, or endometrial cancer.

To help identify these women, Gail et al² created a tool for weighing the benefits and risks of tamoxifen. They combined information collected from the BCPT on the effects of tamoxifen with information from other sources on the background rates of various health outcomes in women who were not taking tamoxifen to estimate the effect of tamoxifen on the absolute risk of each outcome over 5 years for women aged 35 to 79 years. They proposed an

overall benefit/risk index, which was computed as the net number of life-threatening events prevented (the total number of invasive breast cancers plus hip fractures

A full evaluation of the impact of tamoxifen chemoprevention on public health requires that both the adverse events and proven benefits for breast cancer risk reduction be taken into account.

For a more detailed discussion, please see the following: Freedman AN, Graubard BI, Rao SR, et al. Estimates of the number of US women who could benefit from tamoxifen for breast cancer chemoprevention. *J Natl Cancer Inst.* 2003;95:526-532.

Table 1

Relative Risks and Baseline Rates Used to Estimate the Risk of Invasive Breast Cancer in the Next 5 Years*

Risk Factor Category	Relative	Age, y	Baseline 5-Year Risk, %			
			Black	White	Hispanic	
A. Age at menarche, y						
≥14	1.00	20-24	0.003	0.003	0.006	
12-13	1.10	25-29	0.025	0.022	0.021	
<12	1.21	30-34	0.076	0.077	0.057	
		35-39	0.165	0.191	0.126	
B. No. of breast biopsies						
Age at counseling, <50 y old						
0	1.00	40-44	0.285	0.366	0.235	
1	1.70	45-49	0.343	0.540	0.378	
≥2	2.88	50-54	0.376	0.640	0.456	
Age at counseling, ≥50 y old						
0	1.00	55-59	0.474	0.788	0.537	
1	1.27	60-64	0.581	0.969	0.623	
≥2	1.62	65-69	0.592	1.135	0.727	
C. Age at first live birth, y						
No. of first-degree relatives with breast cancer						
<20	0	80-84	0.876	1.280	0.730	
	1					2.61
	≥2					6.80
20-24	0	0.876	1.280	0.730	0.730	
	1					2.68
	≥2					6.78
25-29 or nulliparous	0	0.876	1.280	0.730	0.730	
	1					2.76
	≥2					4.91
≥30	0	0.876	1.280	0.730	0.730	
	1					2.83
	≥2					4.17
D. Atypical hyperplasia						
No biopsies	1.00					
At least one biopsy and no atypical hyperplasia found in any biopsy specimen	0.93					
No atypical hyperplasia found and hyperplasia status unknown for at least one biopsy specimen	1.00					
Atypical hyperplasia found in at least one biopsy specimen	1.82					

*To compute overall relative risk, multiply four component relative risks from categories A, B, C, and D. For example, a 42-year-old white nulliparous woman who began menstruating at age 12 years, who has no affected first-degree relatives, and who has had one previous breast biopsy with specimens interpreted as benign and no evidence of atypical hyperplasia has an overall relative risk of $1.10 \times 1.70 \times 1.55 \times 0.93 = 2.70$. From the data on 5-year baseline risk, her projected 5-year risk of invasive breast cancer is $2.70 \times 0.366 = 1.0\%$.

For easier individualized breast cancer risk calculations, please refer to NCI's Breast Cancer Risk Assessment Web page: <http://cancer.gov/bcrisktool>. Baseline hazards were modified slightly to reflect data in NCI's Breast Cancer Risk Assessment Tool.

Adapted from Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *J Natl Cancer Inst.* 1999;91:1829-1846 by permission of Oxford University Press.

Table 2

Estimates of the Total Number of US Women Eligible for Tamoxifen Chemoprevention Based on FDA Guidelines,* by Race and Age Groups

Age Groups	All Women			White Women		
	Total Number	Number Eligible for Tamoxifen	Percent Eligible for Tamoxifen (95% CI)	Total Number	Number Eligible for Tamoxifen	Percent Eligible for Tamoxifen (95% CI)
35-79	65,826,074	10,232,816	15.5% (14.7% to 16.3%)	50,104,829	9,377,715	18.7% (17.8% to 19.7%)
35-39	11,384,220	8,309	0.1% (0.0% to 0.3%)	7,906,811	0	0.0% (0.0% to 0.3%)
40-49	21,092,915	960,883	4.6% (3.7% to 5.4%)	15,577,412	831,199	5.3% (4.2% to 6.4%)
50-59	14,994,216	1,979,185	13.2% (11.6% to 14.8%)	11,699,803	1,803,782	15.4% (13.5% to 17.2%)
60-69	9,988,403	3,292,131	33.0% (30.5% to 35.4%)	7,979,454	3,008,966	37.7% (34.9% to 40.6%)
70-79	8,366,320	3,992,308	47.7% (44.7% to 50.7%)	6,941,299	3,733,768	53.8% (50.5% to 57.0%)

*Five-year projected risk of invasive breast cancer (IBC) is greater than or equal to 1.67%.

†Estimates for all women includes women of other race.

Adapted from Freedman AN, Graubard BI, Rao SR, et al. Estimates of women who could benefit from tamoxifen for breast cancer chemoprevention. *J Natl Cancer Inst.* 2003;95:526-532 by permission of Oxford University Press.

minus the total number of endometrial cancers, strokes, and pulmonary embolisms) plus half the net number of serious events prevented (the number of in situ breast cancers minus the number of deep vein thromboses) over a 5-year period. The benefit/risk index for a particular woman depended on age, race, risk factors for breast cancer, and whether she had a uterus.

In this study, we used nationally representative data from the year 2000 National Health Interview Survey (NHIS) to compare the number of US women who would be eligible for tamoxifen chemoprevention, according to FDA-approved indications, with the number of women who might benefit from breast cancer chemoprevention based on a benefit/risk index.

These data can assist in evaluating the potential public health impact of tamoxifen use for breast cancer chemoprevention and may help identify subgroups of US women who would especially benefit from this strategy.

Methods

Assessing breast cancer risk. The year 2000 NHIS consisted of comput-

Tamoxifen for breast cancer chemoprevention

Black Women			Hispanic Women		
Total Number	Number Eligible for Tamoxifen	Percent Eligible for Tamoxifen (95% CI)	Total Number	Number Eligible for Tamoxifen	Percent Eligible for Tamoxifen (95% CI)
7,481,779	430,057	5.7% (4.3% to 7.5%)	5,813,012	167,485	2.9% (2.1% to 3.9%)
1,522,332	8,309	0.5% (0.1% to 2.0%)	1,309,812	0	0.0% (0.0% to 1.0%)
2,559,253	64,601	2.5% (1.1% to 5.0%)	2,081,708	13,554	0.7% (0.1% to 1.9%)
1,715,650	123,405	7.2% (4.1% to 11.6%)	1,092,643	18,659	1.7% (0.6% to 3.9%)
915,010	104,508	11.4% (6.6% to 18.1%)	823,861	80,832	9.8% (5.5% to 15.8%)
769,534	129,234	16.8% (9.6% to 26.0%)	504,988	54,440	10.8% (5.3% to 19.0%)

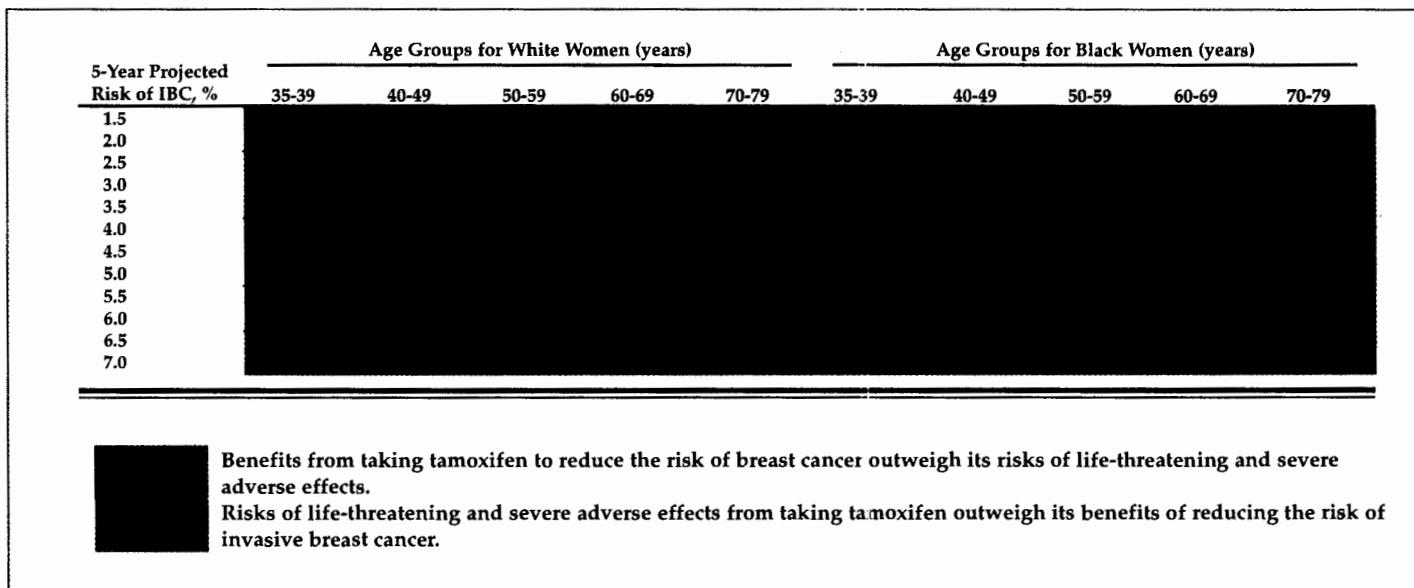
er-assisted personal interviews of a nationally representative sample of 32,374 individuals.³ The year 2000 NHIS contained an additional set of questions called the Cancer Control Module (CCM), which asked about breast cancer risk factors. Data on age, age at first live birth, age at menarche, number of first-degree relatives with breast cancer, and number of breast

biopsies were ascertained and were all part of a breast cancer predictive model developed by Gail et al⁴ (Table 1). We used this model to calculate the 5-year projected breast cancer absolute risk for our study sample, which consisted of the 11,893 women between the ages of 35 and 79 years who completed the 2000 NHIS CCM. We excluded 355 of these women from

further analysis because they reported having a diagnosis of breast cancer.

Determining tamoxifen eligibility. The FDA-approved indications for tamoxifen chemoprevention—age 35 years or older and a 5-year risk of invasive breast cancer of at least 1.67%—is based on the model by Gail et al⁴ as modified and Anderson et al⁵ and described by Costantino et al.⁶

Figure 1



Benefit/risk indices for tamoxifen chemoprevention by level of 5-year projected risk of invasive breast cancer, age group, and race for women with a uterus.

Adapted from Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *J Natl Cancer Inst.* 1999;91:1829-1846 by permission of Oxford University Press.

We calculated the number of women, by race and age, who matched these criteria and would be eligible for tamoxifen chemoprevention by applying those 5-year projected breast cancer risk estimates to the 2000 NHIS CCM data. Our calculations of the total number of US women who would be eligible for tamoxifen chemoprevention included white, black, and Hispanic women, as well as women who reported that they were of another race (Table 2). Because of small numbers, estimates for women in the "other race" category are not presented separately in the table.

Calculating Tamoxifen Benefit/Risk Index

We used data from the 2000 NHIS CCM to also estimate the number of US women who would potentially

benefit from tamoxifen chemoprevention. Women were first categorized according to their 5-year projected breast cancer risk estimates, race, age, and whether they had a uterus. We then used the net benefit/risk indices presented in the entries with at least one asterisk in Tables 10 and 11 of Gail et al² to calculate the number of white and black women, aged 35 to 79 years, in these categories who would have a positive benefit/risk index (see Figures 1 and 2). Although the FDA-approved indications for tamoxifen chemoprevention include a 5-year risk of invasive breast cancer of at least 1.67%, we included in our calculations women with a 5-year risk of invasive breast cancer of at least 1.50%. We used this lower risk cutoff to include most women aged 35

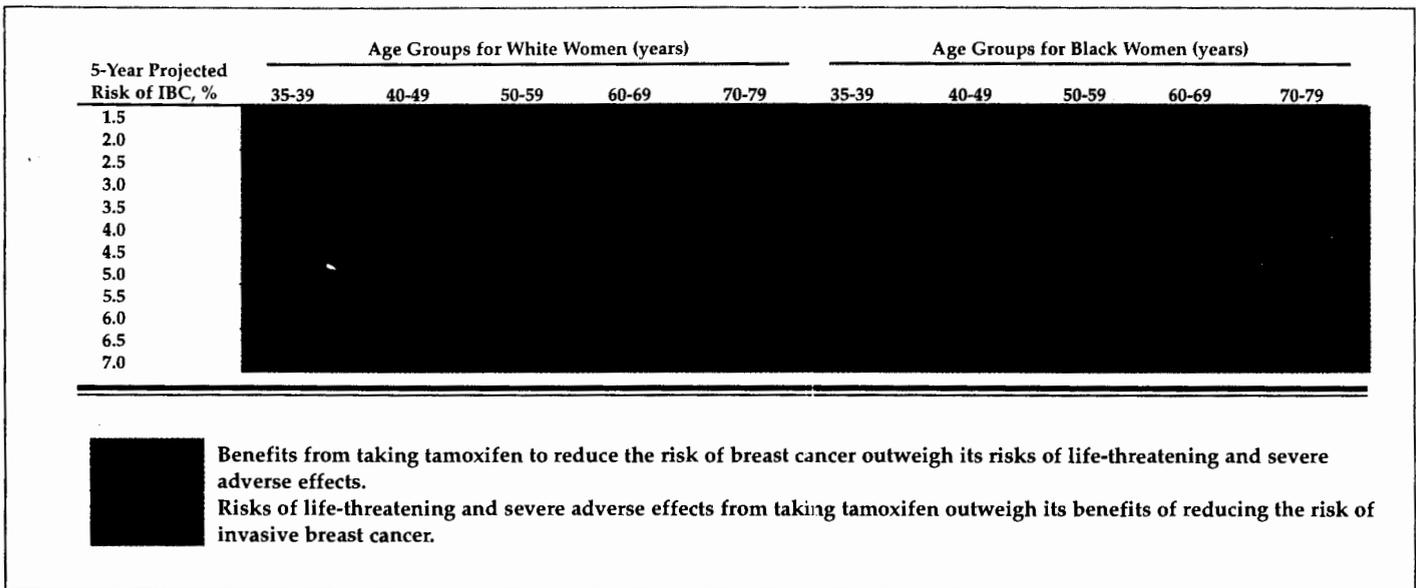
years or older who could potentially benefit from tamoxifen.

All estimates, including totals and percentages, were weighted by the NHIS sample weights to the total US population. Standard errors used to compute the 95% confidence intervals (CIs) were estimated to take into account the complex multistage probability sampling design of the NHIS.^{7,8}

Results

Table 2 shows estimates of the total number of US women, by race and age groups, eligible for tamoxifen chemoprevention according to FDA-approved indications. For all 65,826,074 women aged 35 to 79 years in the US population, 10,232,816 (15.5%, 95% CI = 14.7% to 16.3%) women would be eligible for tamoxifen chemoprevention on the basis of

Figure 2



Benefit/risk indices for tamoxifen chemoprevention by level of 5-year projected risk of invasive breast cancer, age group, and race for women without a uterus.

Adapted from Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *J Natl Cancer Inst.* 1999;91:1829-1846 by permission of Oxford University Press.

their age and breast cancer risk factors. The percentage of women eligible for tamoxifen chemoprevention increases with increasing age. Only 0.1% of women aged 35 to 39 years would be eligible, whereas 4.6% of women aged 40 to 49 years, 13.2% of women aged 50 to 59 years, 33.0% of women aged 60 to 69 years, and 47.7% of women aged 70 to 79 years would be eligible. The percentage of US women who would be eligible for tamoxifen chemoprevention varies dramatically by race, with 18.7% of white women, 5.7% of black women, and 2.9% of Hispanic women being eligible.

Table 3 shows weighted estimates of the total number of white and black US women, both with and without a uterus, who would benefit from tamoxifen chemoprevention based on evidence for a positive benefit/risk

index as calculated with the use of the benefit/risk indices presented in Gail et al.² Of the 50,104,829 white women aged 35 to 79 years, we found that 2,431,911 (4.9%, 95% CI = 4.3% to 5.4%) would benefit from tamoxifen chemoprevention. The percentage of white women who would benefit varies by age, with 0% of women aged 35 to 39 years benefiting, 8.1% of women aged 40 to 49 years benefiting, 8.5% of women aged 50 to 59 years benefiting, 2.1% of women aged 60 to 69 benefiting, and 0.1% of women aged 70 to 79 years benefiting. Absence of a uterus was an important factor in determining benefit. Overall, 59.4% (95% CI = 53.4% to 65.4%) of the white women who would benefit from tamoxifen reported having had a hysterectomy (data not shown). Among those who would benefit, the

percentage who had had a hysterectomy varied by age: 24.7% (95% CI = 16.9% to 33.9%) of women aged 40 to 49 years, 96.5% (95% CI = 93.7% to 99.3%) of women aged 50 to 59 years, and 100% (95% CI = 86.8% to 100%) of women aged 60 to 79 reported having had a hysterectomy (data not shown).

Discussion

The BCPT demonstrated a striking 49% reduction in the risk of invasive breast cancer among women at elevated risk who took tamoxifen for 5 years. Using nationally representative data, we estimate that 15.5% (N=10,232,816) of women aged 35 to 79 years in the United States would be eligible for tamoxifen chemoprevention on the basis of their age and breast cancer risk factors. Because breast cancer incidence rates increase

Table 3

Estimates of the Total Number of US White and Black Women Who Would Benefit From Tamoxifen Chemoprevention, by Age						
Age Groups	White Women			Black Women		
	Total Number	Number Benefiting From Tamoxifen	Percent Benefiting From Tamoxifen (95% CI)	Total Number	Number Benefiting From Tamoxifen	Percent Benefiting From Tamoxifen (95% CI)
35-79	50,104,829	2,431,911	4.9% (4.3% to 5.4%)	7,481,779	42,768	0.6% (0.2% to 1.3%)
35-39	7,906,861	0	0.0% (0.0% to 0.3%)	1,522,332	10,413	0.7% (0.1% to 2.1%)
40-49	15,577,412	1,263,824	8.1% (6.8% to 9.4%)	2,559,253	32,355	1.3% (0.3% to 3.7%)
50-59	11,699,803	996,231	8.5% (7.2% to 9.8%)	1,715,650	0	0.0% (0.0% to 0.9%)
60-69	7,979,454	163,667	2.1% (1.3% to 3.0%)	915,010	0	0.0% (0.0% to 1.5%)
70-79	6,941,299	8,189	0.1% (0.0% to 0.4%)	769,534	0	0.0% (0.0% to 1.8%)

Adapted from Freedman AN, Graubard BI, Rao SR, et al. Estimates of women who could benefit from tamoxifen for breast cancer chemoprevention. *J Natl Cancer Inst.* 2003;95:526-532 by permission of Oxford University Press.

with increasing age, it is not surprising that the percentage of women eligible for tamoxifen chemoprevention increases dramatically with age, with 45% of white women older than 60 years of age being eligible.

A higher percentage of women eligible for tamoxifen were white (18.7%) than were black (5.7%) or Hispanic (2.9%). These large differences are likely the result of: 1) the lower prevalence of breast cancer risk factors among blacks and Hispanics, and 2) the lower baseline incidence rates for breast cancer for blacks and Hispanics (compared with those for

whites) used in the Gail breast cancer predictive model. Our data may explain, in part, the difficulty of identifying and recruiting minority women at high risk of breast cancer for trials of breast cancer chemopreventive agents. That is, few of them have an estimated risk of invasive breast cancer high enough to make them eligible to participate in such a trial.

Although a substantial percentage of US women would be eligible for tamoxifen according to FDA-approved indications, a much smaller percentage would actually benefit from tamoxifen use (see Figure 3). In

our study, only 4.9% of white US women would benefit from tamoxifen when we weighed benefits of reducing risk of breast cancer against the risks of life-threatening and severe adverse effects to tamoxifen. Although this percentage is much smaller than the percentage of white women eligible for tamoxifen (18.7%), it nonetheless corresponds to a substantial number of women (N=2,431,911). These data also indicate that, whereas the percentage of women eligible for tamoxifen is highest among women in the 60- to 79-year age group, the proportions of white women who would benefit are

Case Studies

Women who are at increased risk of breast cancer now have the option to consider taking tamoxifen to reduce their chances of developing the disease. It is important to emphasize, however, that as with any medical procedure or intervention, the choice to take tamoxifen is an individual one in which benefits and risks must be considered in consultation with a woman's physician. The decision will depend on a woman's age, breast cancer risk factors, whether she has a uterus, family history, how she weighs the benefits and risks, and her specific lifestyle, personal values, and preferences. Tamoxifen therapy may not be appropriate for all women who are at increased risk. These case studies illustrate how a decision about tamoxifen use may differ based on the specific combination of factors involved.

On a physician's visit, a 42-year-old white woman is concerned about her risk of developing breast cancer in the future. Her physician inquires about her risk factors for breast cancer and calculates her 5-year estimated risk. Her risk factors include having her first menstrual period at age 14, giving birth to her first child at age 22, having no first-degree relatives with a history of breast cancer, and never having a breast biopsy. Using NCI's breast cancer predictive model (see Web site reference below and Table 1), her estimated risk of developing invasive breast cancer over the next 5 years is 0.5%. This patient's risk would not be high enough to qualify for the FDA-

approved indications for use of tamoxifen for breast cancer chemoprevention (aged 35 years or older with a 5-year breast cancer risk of 1.67% or higher).

Consider another 42-year-old white woman with different risk factors for breast cancer. This patient had her first menstrual cycle at the age of 12, had her first child at age 28, and has a mother and a sister who already have had breast cancer. She has never had a breast biopsy or a hysterectomy. Her estimated risk of developing breast cancer is 2.3% over the next 5 years. Based on her breast cancer risk estimate, she is eligible to take tamoxifen for breast cancer chemoprevention based on the FDA-approved indications for the drug. From Table 10 (Figure 1) from the article by Gail et al,² the benefits of taking tamoxifen to reduce this patient's breast cancer risk would outweigh the risks of adverse side events such as stroke, pulmonary embolism, or endometrial cancer.

Consider a 48-year-old black woman who is concerned about her risk of developing breast cancer in the future. Her risk factors include having her first menstrual period at age 12, giving birth to her first child at age 27, having no first-degree relatives with a history of breast cancer, and never having a breast biopsy. Using NCI's breast cancer predictive model, her estimated risk of developing invasive breast cancer over the next 5 years is 0.6%. This patient's risk would not be high enough to qualify for the FDA-approved indications for use of

tamoxifen for breast cancer chemoprevention (aged 35 years or older with a 5-year breast cancer risk of 1.67% or higher).

Consider another 48-year-old black woman with different risk factors for breast cancer. This patient had her first menstrual cycle at the age of 11, had her first child at age 27, and has a mother and a sister who already have had breast cancer. She has had a benign breast biopsy. Her estimated risk of developing breast cancer is 3.0% over the next 5 years. Based on her breast cancer risk estimate, she is eligible to take tamoxifen for breast cancer chemoprevention based on the FDA-approved indications for the drug. From Table 10 (Figure 1) from the article by Gail et al,² the benefits of taking tamoxifen to reduce this patient's breast cancer risk would outweigh the risks of adverse side events such as stroke, pulmonary embolism, or endometrial cancer.

Consider a 55-year-old white woman with several risk factors for breast cancer. She had her first menstrual cycle at age 12, had her first child at age 22, has a sister with a diagnosis of breast cancer, and has had one previous benign breast biopsy. Her estimated risk of developing breast cancer over the next 5 years is 2.9%. Her estimated risk meets the FDA-approved indications for the use of tamoxifen for breast cancer chemoprevention. However, at age 55, her benefit/risk ratio for taking the drug depends largely on whether she has a uterus, because the risk of developing

Case Studies (continued)

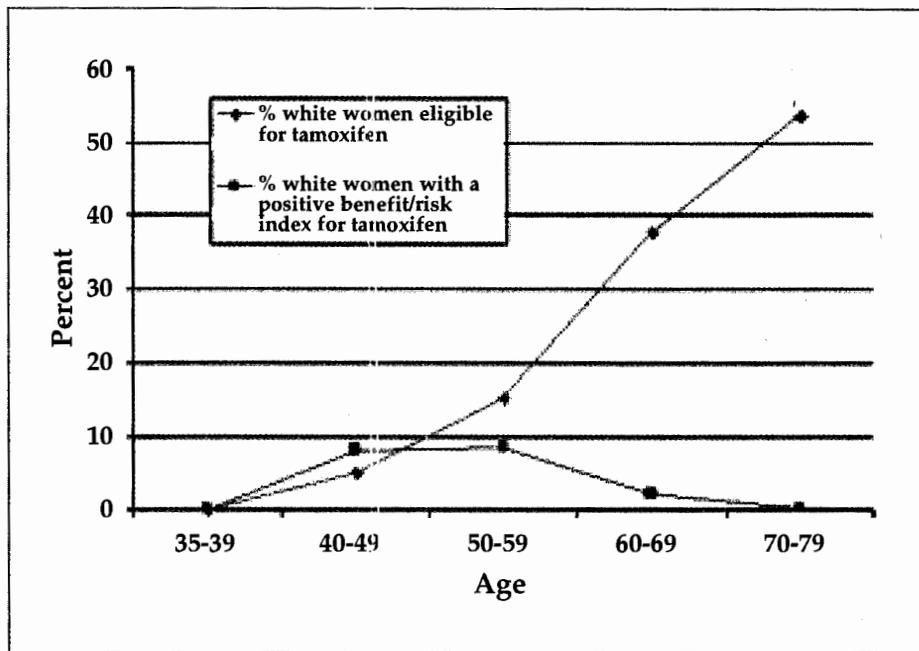
endometrial cancer with tamoxifen use increases with increasing age. This patient still has an intact uterus. Therefore, the risks of adverse events would outweigh the benefits of taking tamoxifen to reduce her risk of developing breast cancer (Figure 1).

On the other hand, a 55-year-old white woman with the exact same risk factor profile for breast cancer as the case above, but with a previous history of surgery to remove her uterus, would have a more favorable benefit/risk ratio. In her case, because the possibility of developing endometrial cancer no longer exists, the benefits of taking tamoxifen to reduce her risk of developing breast cancer would outweigh the risks of adverse events (Figure 2).

greatest in the 40- to 49-year and 50- to 59-year age groups (8.1% and 8.5% would benefit, respectively). This pattern reflects the high proportion of women aged 40 to 59 years in the current US population, and the fact that the benefit/risk index decreases with increasing age as adverse side effects associated with tamoxifen use become more common. Among women aged 50 years or older, with few exceptions, only those who had had a hysterectomy had a positive benefit/risk index. Having a hysterectomy eliminates the risk of endometrial cancer; thus, our data demonstrate the important role that endometrial cancer plays in the benefit/risk index for women aged 50 years or older.

Although FDA-approved indications specify that a 5-year invasive

Figure 3



Estimates of the percentage of white US women who would be eligible for tamoxifen and the percentage who would have a positive benefit/risk index for tamoxifen chemoprevention, by age.

breast cancer risk of 1.67% is necessary for tamoxifen chemoprevention eligibility, our data, which take into account the benefits of reducing a woman's risk of breast cancer as well as the risk of adverse events associated with tamoxifen, demonstrate that a substantial number of white women with a risk less than 1.67% but greater than 1.50% would also benefit from tamoxifen use. For example, among white women in the 40- to 49-year age group, only 5.3% would be eligible for tamoxifen according to FDA eligibility criteria, but 8.1% would benefit on the basis of the benefit/risk index. This difference reflects the substantial number of women in this age group who have a 5-year invasive breast cancer risk greater than 1.50% but less than the 1.67% defined by FDA-

approved indications. By contrast, most of the older women with a risk greater than 1.50% would not benefit from tamoxifen because of the high incidence of adverse side effects associated with its use in older women.

Although approximately 6% of black women would be eligible for tamoxifen, our analysis suggests that a very small percentage (0.6%) would derive any net benefit from its use. Proportionally fewer black women than white women in the United States have an estimated net benefit from taking tamoxifen because the estimated risk of breast cancer among black women in the general population is relatively low, and because the estimated baseline rates of stroke, pulmonary embolism, and deep vein thrombosis are higher among black

women than among white women.² Our results for black women are less stable than those for white women, however, not only because of the higher uncertainty in projecting breast cancer risk among this population, but also because the estimated beneficial and adverse effects of tamoxifen from the BCPT primarily reflect the outcomes in white women, who comprised 96.5% of the study population.

Of the 9,377,715 white US women who would be eligible for tamoxifen chemoprevention, we estimate that less than one third (N=2,431,911) would derive a net benefit from taking the drug on the basis of their age and breast cancer risk factors. We estimate that among the white women who would benefit from tamoxifen, approximately 58,148 invasive breast cancers will develop over the next 5 years. If all 2,431,911 women with an estimated net benefit/risk index took tamoxifen over the next 5 years, and if the risk reduction of 49% reported by the BCPT¹ applies, then 28,492 of these breast cancers would be prevented, or deferred, which would be a substantial achievement. However, of the 7,481,779 black US women between the ages of 35 and 79 years who would be eligible, only 42,768 (0.6%, 95% CI = 0.2% to 1.3%) would benefit from tamoxifen chemoprevention. Estimates for Hispanic US women and women of other races could not be calculated because benefit/risk indices for these races have yet to be developed.

Although the probabilities obtained from the breast cancer risk model used in these analyses⁴ have been shown to accurately predict the numbers of breast cancers in various subgroups of women over a specified period of time,⁹ the model has only limited ability to identify which women in partic-

ular will develop breast cancer and which will not.¹⁰ Some might argue that one should not recommend a course of medical management, such as taking or not taking tamoxifen, unless one is able to foretell an individual's outcome with precision. However, most clinicians weigh the risks and benefits associated with a particular treatment and recommend the course of action that has the most favorable expected net effect. For example, a doctor might recommend an antihypertensive medication for a person with only moderately elevated blood pressure, even though a moderate elevation in blood pressure cannot reliably discriminate between a person who will die from cardiovascular disease in the next 5 years and one who will not. Moreover, the clinical trials that provide evidence of a benefit of treatments such as antihypertensive agents rely on comparisons of groups of individuals. However much

one would like to have a treatment tailored to an individual, the best available evidence to guide treatment decisions is based on the resemblance of an individual to a group.

Not everyone would agree with the criteria used by Gail et al² to determine a net benefit/risk index, particularly as it pertains to counseling an individual woman on the appropriate therapy for her situation. Although a benefit/risk index is useful for making population estimates, it may not appropriately measure the net benefit for a particular woman because it does not include all health risk and protective factors for the disease, and because a particular woman may assign different weights to the various health outcomes than in Gail et al.² For example, women who exercise regularly may have lower risk of cardiovascular disease than women of the same age and ethnic group in the general population, which could mitigate

Additional information on estimating the risks and benefits of tamoxifen for breast cancer chemoprevention can be found at the following Web sites and articles.

- <http://cancer.gov/bcrisktool>—NCI's page for Risk Disk and accompanying information for calculating individualized breast cancer risk
- <http://cancer.gov/star>—NCI's page for STAR trial information
- <http://www.BreastCancerPrevention.com>—The National Surgical Adjuvant Breast and Bowel Project is conducting the STAR trial for NCI. This is their Web site about the trial
- <http://www.fda.gov/cder/news/tamoxifen/default.htm>—FDA's page about tamoxifen for breast cancer risk reduction
- <http://www.ahrq.gov/clinic/uspstf/uspstfbrpv.htm>—AHRQ page for USPHSTF recommendations on chemoprevention of breast cancer
- <http://www.nolvadex.com/>—AstraZeneca Web site for tamoxifen, which includes full labeling information and additional mandated education materials
- Gail MH, Costantino JJ, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *J Natl Cancer Inst.* 1999;91:1829-1846.

adverse outcome factors in the benefit/risk index. Such women, therefore, would have a more favorable benefit/risk index than we used in our calculations (see Table 12 in Gail et al²). Moreover, a woman might have much more concern about breast cancer than a pulmonary embolism, for example. Therefore, the tabulated benefit/risk index should not be the sole basis for decision making regarding the use of tamoxifen for breast cancer risk reduction therapy. Counseling individual women about tamoxifen chemoprevention must involve both fully informing a woman of her disease risk and benefits and considering her comorbidities, personal values, preferences, lifestyle, and specific medical situation. These issues are especially important when counseling minority women about tamoxifen chemoprevention because limited predictive information for their health risk profiles is available.

The precision of breast cancer risk prediction models and benefit/risk indices for tamoxifen chemopreven-

tion is highly dependent on the availability and quality of health outcomes data, not only those for breast cancer, but also for other outcomes, such as stroke. Efforts to collect more accurate data on various health outcomes and in various populations are needed to improve our prediction models and our assessments of the risks and benefits of health outcomes associated with tamoxifen chemoprevention. ■

References

1. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: a report of the National Surgical Adjuvant Breast and Bowel Project P-1. *J Natl Cancer Inst.* 1998;90:1371-1388.
2. Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *J Natl Cancer Inst.* 1999;91:1829-1846.
3. National Center for Health Statistics. National Health Interview Survey (NHIS). Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Available at: <http://www.cdc.gov/NCHS/nhis.htm>. Accessed July 22, 2002.
4. 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;81:1879-1886.
5. Anderson SJ, Ahnn S, Duff K. NSABP breast cancer prevention trial risk assessment program, Version 2. NSABP Biostatistical Center Technical Report. Pittsburgh, PA: Department of Biostatistics, University of Pittsburgh; August 14, 1992.
6. 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;91:1541-1548.
7. Botman SL, Moore TF, Moriarity CL, et al. Design and estimation for the National Health Interview Survey, 1995-2004. National Center for Health Statistics. Vital and Health Statistics, Series 2, No. 130, 2000.
8. Korn EL, Graubard BI. Analysis of health surveys. Sec 3.2. New York, NY: John Wiley & Sons; 1999:22-28, 64-68.
9. 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;93:358-366.
10. Rockhill B, Colditz G, Kaye J. Re: tamoxifen prevention of breast cancer: an instance of the fingerpost. *J Natl Cancer Inst.* 2000;92:657-658.

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