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ORIGINAL REPORT

Benefit/Risk Assessment for Breast Cancer Chemoprevention With Raloxifene or Tamoxifen for Women Age 50 Years or Older

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ABSTRACT

Purpose
The Study of Tamoxifen and Raloxifene (STAR) demonstrated that raloxifene was as effective as tamoxifen in reducing the risk of invasive breast cancer (IBC) in postmenopausal women and had lower risks of thromboembolic events, endometrial cancer, and cataracts but had a nonstatistically significant higher risk of noninvasive breast cancer. There is a need to summarize the risks and benefits of these agents.

Patients and Methods
Baseline incidence rates of IBC and other health outcomes, absent raloxifene and tamoxifen, were estimated from breast cancer chemoprevention trials; the Surveillance, Epidemiology and End Results Program; and the Women's Health Initiative. Effects of raloxifene and tamoxifen were estimated from STAR and the Breast Cancer Prevention Trial. We assigned weights to health outcomes to calculate the net benefit from raloxifene compared with placebo and tamoxifen compared with placebo.

Results
Risks and benefits of treatment with raloxifene or tamoxifen depend on age, race, breast cancer risk, and history of hysterectomy. Over a 5-year period, postmenopausal women with an intact uterus had a better benefit/risk index for raloxifene than for tamoxifen. For postmenopausal women without a uterus, the benefit/risk ratio was similar. The benefits and risks of raloxifene and tamoxifen are described in tables that can help identify groups of women for whom the benefits outweigh the risks.

Conclusion
We developed a benefit/risk index to quantify benefits from chemoprevention with tamoxifen or raloxifene. This index can complement clinical evaluation in deciding whether to initiate chemoprevention and in comparing the benefits and risks of raloxifene versus tamoxifen.

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INTRODUCTION

Chemoprevention trials in the United States and Europe have evaluated selective estrogen receptor modulators to prevent breast cancer in high-risk women.[1-4] The Breast Cancer Prevention Trial (BCPT) demonstrated that tamoxifen produced a 49% reduction in invasive breast cancer (IBC) in US women at increased risk.[1] The US Food and Drug Administration (FDA) subsequently approved tamoxifen for breast cancer chemoprevention among women age 35 years or older with a 5-year breast cancer risk of 1.67% or higher. Because tamoxifen use is associated with adverse events such as endometrial cancer and stroke, a previous analysis[5] developed a benefit/risk index to identify levels of breast cancer risk for which benefits outweighed risks.

Raloxifene, another selective estrogen receptor modulator, reduced IBC risk in studies for the prevention and treatment of other conditions in postmenopausal women.[6] The Multiple Outcomes Raloxifene Evaluation trial for osteoporosis[7] and the Raloxifene Use for the Heart trial[8] both demonstrated a substantial reduced risk of IBC in postmenopausal women. These trials provided the scientific basis for the National Cancer Institute (NCI) to initiate the National Surgical Adjuvant Breast and Bowel Project (NSABP) Study of Tamoxifen and Raloxifene (STAR) in 1999.[9] STAR did not include a placebo group but directly compared tamoxifen with raloxifene in a population of US postmenopausal women at increased risk of breast cancer. Over a mean follow-up of 3.9 years, STAR demonstrated that raloxifene was as effective as

Table 1. Incidence Rates per 1,000 Woman-Years by Race

Type of Event	Incidence Rates for Women (by age groups, in years)								
	White			Black			Hispanic		
	50-59	60-69	70-79	50-59	60-69	70-79	50-59	60-69	70-79
Hip fracture*	0.43	1.41	4.84	0.22	0.3	1.9	0.25	0.61	1.32
Endometrial cancer†	0.92	1.80	1.70	0.53	1.48	1.11	0.5	0.71	0.86
Stroke*	0.83	2.22	5.49	2.03	3.69	6.19	0.75	2.56	5.14
Pulmonary embolism*	0.56	0.86	1.08	0.82	0.8	1.43	0.0	0.1	0.95
Deep vein thrombosis*	0.66	1.28	2.04	0.99	1.47	2.28	0.25	0.89	0.96
Colles fracture*	0.97	1.34	1.64	0.32	0.35	0.49	0.64	1.13	2.0
Spine fracture*	0.98	2.13	4.40	0.26	0.3	0.83	0.59	1.01	1.62
Cataracts‡	15.91	52.18	98.49	15.91	52.18	98.49	15.91	52.18	98.49

*Age-specific incidence rates for stroke, pulmonary embolism, deep vein thrombosis, and fractures of the proximal femur (hip), vertebra (spine), and distal forearm (Colles fractures) were obtained from the placebo arm of the Women's Health Initiative.[15]

†We based estimates of endometrial cancer incidence rates on age- and race-specific incidence rates from the Surveillance, Epidemiology and End Results (SEER) Program for 1998 through 2002. To predict risk for women with a uterus, SEER rates were divided by the estimated age-specific prevalence of having a uterus by using data from the 2000 National Health Interview Survey.[16]

‡Baseline estimates of cataract incidence were calculated from data in the placebo arm of the Breast Cancer Prevention Trial because this cohort reflects current ophthalmologic practice and is the largest cohort with reports on cataracts in women.[1]

tamoxifen in reducing risk of IBC. Raloxifene also resulted in lower risk of endometrial cancer, thromboembolic events, and cataracts, but a nonstatistically significant higher risk of noninvasive breast cancer. The risk of fractures, ischemic heart disease, and stroke were similar for raloxifene and tamoxifen.

In 2007, FDA approved the use of raloxifene to reduce the risk of IBC in postmenopausal women with osteoporosis or at high risk of IBC.[10] Several cancer networks and professional societies have issued guidelines on the use of these chemopreventive agents in breast cancer risk reduction.[11-13] A recent systematic review compared the effectiveness and safety of several breast cancer chemopreventive agents but reached limited conclusions.[14] Relying on data from the BCPT and STAR trials and on methods for weighing risks and benefits in Gail et al,[5] we produced tables of benefit/risk indices to compare raloxifene with no treatment (placebo) and tamoxifen with no treatment. Our tables and results can be used for counseling postmenopausal women regarding the use of these agents.

PATIENTS AND METHODS

To compute net benefit/risk indices, we assigned weights to various health outcomes and used background incidence rates for relevant health outcomes in the absence of raloxifene and tamoxifen (Table 1) and relative risk (RR) estimates of the effects of raloxifene and tamoxifen on these incidence rates from BCPT and STAR (Table 2). Net benefit/risk indices were calculated for raloxifene as the difference in the sums of weighted expected events in the absence and presence of raloxifene. Analogous indices were computed for tamoxifen.

Projecting Risks in the Absence of Raloxifene and Tamoxifen

To calculate the projected 5-year risk of IBC for white and Hispanic women with particular risk factors but with no history or current evidence of

Table 2. Computed RRs for Events for Raloxifene Versus Placebo on the Basis of BCPT and STAR

Type of Event	No. of Events in BCPT			No. of Events in STAR			RR for BCPT × RR for STAR (raloxifene *v* placebo)	
	Placebo/ Tamoxifen	RR	95% CI	Tamoxifen/ Raloxifene	RR	95% CI	RR	95% CI
Invasive breast cancer	175/89	0.51	0.39 to 0.66	181/212	1.16	0.95 to 1.42	0.59	0.43 to 0.82
Hip fracture	22/12	0.55	0.25 to 1.15	26/23	0.88	0.48 to 1.60	0.48	0.20 to 1.16
Endometrial cancer							1.14*	0.65 to 1.98
All women	15/36	2.53	1.35 to 4.97	36/23	0.62	0.35 to 1.08		
Women age ≥ 50 years	7/27	4.01	1.70 to 10.90	35/23	0.65	0.37 to 1.13		
Stroke	24/38	1.59	0.93 to 2.77	53/51	0.96	0.64 to 1.43	1.53	0.81 to 2.85
Pulmonary embolism	6/18	3.01	1.15 to 9.27	54/35	0.64	0.41 to 1.00	1.93	0.74 to 5.07
In situ breast cancer	69/35	0.50	0.33 to 0.77	57/80	1.40	0.98 to 2.00	0.70	0.41 to 1.18
Deep vein thrombosis	22/35	1.60	0.91 to 2.86	87/65	0.74	0.53 to 1.03	1.18	0.64 to 2.19
Colles fracture	23/14	0.61	0.29 to 1.23	27/23	0.85	0.46 to 1.53	0.52	0.22 to 1.20
Spine fracture	31/23	0.74	0.41 to 1.32	53/52	0.98	0.65 to 1.46	0.73	0.38 to 1.38
Cataracts	507/574	1.14	1.01 to 1.29	394/313	0.79	0.68 to 0.92	0.90	0.75 to 1.09

Abbreviations: RR, relative risk; BCPT, Breast Cancer Prevention Trial; STAR, Study of Tamoxifen and Raloxifene.
*Based on analysis of raloxifene versus placebo studies by Nelson et al.[14]

IBC, ductal carcinoma in situ, or lobular carcinoma in situ, we used the breast cancer risk assessment model developed by Gail et al,[17] modified by Costantino[18] and by Anderson et al,[19] and recently modified for African American women.[20] We estimated the risk for in situ breast cancer as 0.22 times the estimated IBC risk. This ratio was obtained from the three placebo arms of the Women's Health Initiative (WHI) trial.[15,21]

We based estimates of endometrial cancer incidence rates on age- and race-specific incidence rates from the Surveillance, Epidemiology and End Results (SEER) Program for 1998 through 2002. To predict risk for women with a uterus, SEER rates were divided by the estimated age-specific prevalence of having a uterus with data from the 2000 National Health Interview Survey.[16] For white, black, and Hispanic women, the age-specific incidence rates for stroke, pulmonary embolism, deep vein thrombosis (DVT), and fractures of the proximal femur (hip), vertebra (spine), and distal forearm (Colles fractures) were obtained from the three placebo arms of WHI.[15,21] Detailed eligibility criteria and recruitment methods for WHI have been published.[22] Baseline estimates of cataract incidence were calculated from the placebo arm of BCPT[1] (Table 1).

Projecting Risks With Raloxifene and Tamoxifen

Fisher et al[1] described the RRs comparing tamoxifen to placebo in BCPT. Protective RRs were found for IBC, in situ breast cancer, and hip fracture (Table 2). Adverse RRs were found for endometrial cancer, stroke, pulmonary embolism, DVT, and cataracts. Vogel et al[9] described RRs of raloxifene compared with those for tamoxifen in STAR. RRs favored raloxifene for endometrial cancer, pulmonary embolism, and DVT, but tamoxifen was more effective in preventing in situ breast cancer than raloxifene (RR, 1.40; 95% CI, 0.98 to 2.00; Table 2). For IBC, we used the estimated RR of 1.16 (95% CI, 0.95 to 1.42) from recent STAR data.[23]

There was no statistically significant evidence of heterogeneity of RRs for IBC or in situ breast cancer in either trial across groups defined by age, number of affected first-degree relatives, projected 5-year risk of IBC, or lobular carcinoma in situ status. Therefore, we assumed that the RRs for IBC and in situ breast cancer are uniform across all subgroups.

Because STAR did not include a placebo group, it did not provide an RR compared with no treatment. To estimate the RR of raloxifene compared with placebo, we multiplied the RR estimates from STAR by the RR estimates from BCPT (Table 2). We used log-normal approximations to construct 95% CIs on RRs. The variance of the log-RR estimate for raloxifene versus placebo was the sum of the corresponding variances from both trials. RRs for raloxifene versus placebo (Table 2) were 0.59 (95% CI, 0.43 to 0.82) for IBC, 0.48 (95% CI, 0.2 to 1.16) for hip fracture, 1.53 (95% CI, 0.81 to 2.85) for stroke, 1.93 (95% CI, 0.74 to 5.07) for pulmonary embolism, 0.70 (95% CI, 0.41 to 1.18) for in situ breast cancer, and 1.18 (95% CI, 0.64 to 2.19) for DVT. For endometrial cancer, we used an RR of 1.14 (95% CI, 0.65 to 1.98) that was based on several studies comparing raloxifene to placebo.[14] This RR was used instead of $4.01 \times 0.65 = 2.60$ from Table 2 because intensive follow-up in the tamoxifen arm in STAR with hysterectomies for conditions such as endometrial bleeding and atypical hyperplasia biased the RR comparing raloxifene to tamoxifen (0.65) upward. Our raloxifene-to-placebo RRs (Table 2) are similar to those in trials of raloxifene for osteoporosis.[6]

Benefit/Risk Comparisons for Women Age 50 Years or Older

Although BCPT included pre- and postmenopausal women age 35 years and older, we confined our benefit/risk analyses to women age 50 years and older because only postmenopausal women were eligible for STAR. Few women in STAR were younger than age 50 years, and raloxifene is not approved for reduction of breast cancer risk in premenopausal women.

As in Gail et al,[5] we considered eight non–breast cancer conditions whose rates were potentially influenced by raloxifene (Tables 1 and 2). We grouped these outcomes plus IBC and in situ breast cancer into the categories "life-threatening events," "severe events," and "other events." Life-threatening events included invasive breast cancer, hip fracture, endometrial cancer, stroke, and pulmonary embolism. Severe events included in situ breast cancer and DVT. Other events included Colles and spine fracture and cataracts.

To summarize risks and benefits in an index, we assigned weight 1.0 for life-threatening events, 0.5 for severe events, and 0.0 for other events. We

5-Year Projected Risk of IBC (%)	Tamoxifen *v* Placebo (with uterus) 50-59	60-69	70-79	Raloxifene *v* Placebo (with uterus) 50-59	60-69	70-79
1.5	-133	-310	-325	21	-11	-15
2.0	-105	-283	-298	43	11	7
2.5	-78	-255	-271	65	33	29
3.0	-51	-228	-244	86	55	51
3.5	-25	-202	-217	108	76	71
4.0	3	-175	-190	128	97	93
4.5	29	-148	-164	150	119	115
5.0	56	-121	-137	172	140	136
5.5	83	-95	-111	193	161	157
6.0	109	-69	-84	214	183	179
6.5	135	-42	-58	236	204	199
7.0	162	-15	-32	256	225	221

Strong evidence of benefits outweighing risks

Moderate evidence of benefits outweighing risks

Benefits do not outweigh risks

5-year projected risk of IBC is ≥ 1.67%.

Using BCPT data and WHI baseline rates

Combining RR from BCPT and STAR using WHI baseline rates

Fig 1. Benefit/risk indices for tamoxifen and raloxifene chemoprevention by level of 5-year projected risk for invasive breast cancer (IBC) for white non-Hispanic women with a uterus, by age group. On the basis of a woman's risk factors (age, ethnicity, breast cancer risk, and whether she has a uterus), one can calculate her probability of having a health event in 5 years in the absence or presence of chemoprevention. To summarize risks and benefits in a single index, we assigned weights of 1.0 for life-threatening events (IBC, hip fracture, endometrial cancer, stroke, and pulmonary embolism) and 0.5 for severe events (in situ breast cancer and deep vein thrombosis). The net benefit index is the expected number of life-threatening equivalent events in 5 years without chemoprevention in 10,000 such women minus the expected number of life-threatening equivalent events if chemoprevention is used. (A severe event is regarded as equivalent to half a life-threatening event). For example, in this table, among 10,000 non-Hispanic white women with a uterus, age 50 to 59 years, and with a 5-year IBC risk of 3.5%, one expects that 108 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is strong evidence ($P > .9$; blue) that the benefits of taking raloxifene outweigh the risks. If tamoxifen were used instead, we estimate chemoprevention would result in 25 excess life-threatening events ($P < .6$, gray). BCPT, Breast Cancer Prevention Trial; WHI, Women's Health Initiative; RR, relative risk; STAR, Study of Tamoxifen and Raloxifene.

defined the expected number of life-threatening equivalent events in a population of 10,000 women followed for 5 years as the life-threatening events plus half the severe events. On the basis of a woman's risk factors, one can calculate her probability of having each of the health outcomes in 5 years in the absence of chemoprevention and in the presence of chemoprevention. The net benefit index is the expected number of life-threatening equivalent events without chemoprevention in 10,000 such women minus the expected number of events with chemoprevention. To assess variability, we used a Bayesian bootstrap. The posterior distribution of RR for each event from each trial is a constant times an F distribution.[5] In each bootstrap replication, we resampled the RRs in both trials,[5] and the RR of raloxifene versus placebo was calculated as the product of the RR estimates from both trials. The expected number of adverse events in each treatment group and the net benefit were recalculated in 100,000 independent bootstrap replications. We defined "strong evidence" of a positive net benefit of a chemoprevention group versus placebo if the net benefit was positive in 90% or more of the replications (coded blue in Figs 1 through 4), and "moderate evidence" if the net benefit was positive in 60% to 89.99% (coded gold). If the probability was less than 60%, the cell was coded gray in Figures 1 through 4. The net benefit index is also shown in each cell. Some gray cells have positive net benefit indices. The 95% CIs on the difference in net benefits comparing raloxifene to tamoxifen were based on the 2.5th and 97.5th percentiles of the bootstrap distribution. In sensitivity analyses, we examined other choices of weights.

RESULTS

In Figure 1, we show benefit/risk indices for tamoxifen versus placebo and for raloxifene versus placebo by age group and level of 5-year IBC risk for non-Hispanic white women with a uterus. Figure 2 gives such results for white women without a uterus, and Figures 3 and 4 give results for black women. Appendix Figures A1 and A2 (online only) give these results for Hispanic women. From Figure 1, among 10,000 non-Hispanic white women with a uterus, age 50 to 59 years, with a 5-year IBC risk of 3.5%, one expects that 108 life-threatening equivalent events would be prevented in 5 years by taking raloxifene; there is strong evidence ($P \geq .9$; blue) that benefits outweigh risk. If tamoxifen were used instead, we estimate chemoprevention would result in 25 excess life-threatening events (negative index). The direct comparison between raloxifene and tamoxifen indicates 108 + 25 = 133 (95% CI, −28 to 352) fewer life-threatening equivalent events on raloxifene. A similar pattern is seen for black women with an intact uterus and 5-year projected IBC risk of 3.5% (Fig 3).

For non-Hispanic white women age 50 years or older with a uterus, raloxifene displayed a better benefit/risk profile than tamoxifen overall (Fig 1). For tamoxifen, women age 50 to 59 years with a 5-year IBC risk of 4.5% to 6.5% showed moderate evidence (gold) of net positive benefit, and women with IBC risk of 7.0% or higher showed strong evidence (blue). For women age 50 to 59 years with a 5-year IBC risk less than 4.0%, the risks outweighed the benefits (gray cells with negative net benefit indices). The risks outweighed the benefits for women age 60 years or older, regardless of IBC risk. In contrast, for raloxifene, there was strong evidence (blue) that benefits outweighed risks, compared with placebo, for women age 50 to 59

5-Year Projected Risk of IBC (%)	Tamoxifen *v* Placebo (without uterus) 50-59	60-69	70-79	Raloxifene *v* Placebo (without uterus) 50-59	60-69	70-79
1.5	3	-53	-93	27	2	-4
2.0	31	-26	-66	49	23	18
2.5	57	2	-39	71	45	40
3.0	84	29	-12	92	67	62
3.5	111	56	15	114	88	82
4.0	138	83	42	134	109	104
4.5	164	109	69	156	131	126
5.0	191	136	96	178	152	147
5.5	218	163	121	199	173	168
6.0	244	189	148	220	195	190
6.5	270	215	175	242	216	210
7.0	297	242	201	262	237	232

Strong evidence of benefits outweighing risks
Moderate evidence of benefits outweighing risks
Benefits do not outweigh risks

5-year projected risk of IBC is ≥ 1.67%.
Using BCPT data and WHI baseline rates
Combining RR from BCPT and STAR using WHI baseline rates

Fig 2. Benefit/risk indices for tamoxifen and raloxifene chemoprevention by level of 5-year projected risk of invasive breast cancer (IBC) for white non-Hispanic women without uterus, by age group. On the basis of a woman's risk factors (age, ethnicity, breast cancer risk, and whether she has a uterus), one can calculate her probability of having a health event in 5 years in the absence of chemoprevention and in the presence of chemoprevention. To summarize risks and benefits in a single index, we assigned weights of 1.0 for life-threatening events (IBC, hip fracture, endometrial cancer, stroke, and pulmonary embolism) and 0.5 for severe events (in situ breast cancer and deep vein thrombosis). The net benefit index is the expected number of life-threatening equivalent events in 5 years without chemoprevention in 10,000 such women minus the expected number of life-threatening equivalent events if chemoprevention is used. (A severe event is regarded as equivalent to half a life-threatening event). For example, in this table, among 10,000 non-Hispanic white women without a uterus, age 50 to 59 years, and with a 5-year IBC risk of 3.5%, one expects that 114 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is strong evidence ($P > 0.9$; blue) that the benefits of taking raloxifene outweigh the risks. If tamoxifen were used instead, we estimate chemoprevention would also result in the prevention of 111 life-threatening events ($P < 0.9$; blue). Among 10,000 non-Hispanic white women without a uterus, age 70 to 79 years, and with a 5-year IBC risk of 3.0%, one expects that 62 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is moderate evidence ($P \geq 0.6$ but < 0.9; gold) that the benefits of taking raloxifene outweigh the risks. If tamoxifen were used instead, we estimate chemoprevention would result in 12 excess life-threatening events ($P < 0.6$; gray). BCPT, Breast Cancer Prevention Trial; WHI, Women's Health Initiative; RR, relative risk; STAR, Study of Tamoxifen and Raloxifene.

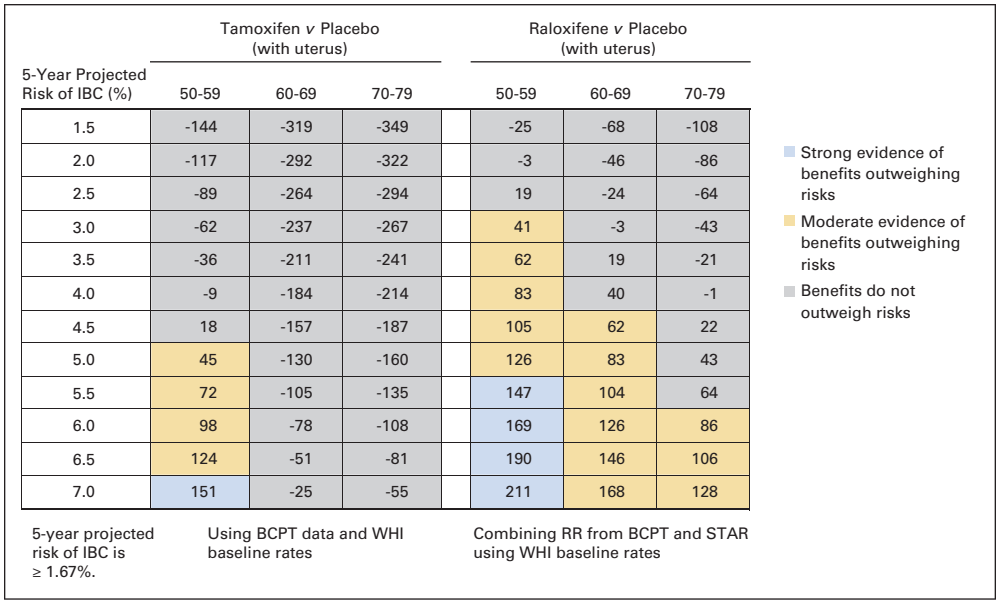

Fig 3. Benefit/risk indices for tamoxifen and raloxifene chemoprevention by level of 5-year projected risk of invasive breast cancer (IBC) for black women with uterus, by age group. On the basis of a woman's risk factors (age, ethnicity, breast cancer risk, and whether she has a uterus), one can calculate her probability of having a health event in 5 years in the absence of chemoprevention and in the presence of chemoprevention. To summarize risks and benefits in a single index, we assigned weights of 1.0 for life-threatening events (IBC, hip fracture, endometrial cancer, stroke, and pulmonary embolism) and 0.5 for severe events (in situ breast cancer and deep vein thrombosis). The net benefit index is the expected number of life-threatening equivalent events in 5 years without chemoprevention in 10,000 such women minus the expected number of life-threatening equivalent events if chemoprevention is used. (A severe event is regarded as equivalent to half a life-threatening event). For example, in this table, among 10,000 black women with a uterus, age 50 to 59 years, and with a 5-year IBC risk of 3.5%, one expects that 62 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is moderate evidence ($P \geq 6$ but < 0.9; gold) that the benefits of taking raloxifene outweigh the risks. If tamoxifen were used instead, we estimate chemoprevention would result in 36 excess life-threatening equivalent events ($P < .6$; gray). BCPT, Breast Cancer Prevention Trial; WHI, Women's Health Initiative; RR, relative risk; STAR, Study of Tamoxifen and Raloxifene.

years with a 5-year IBC risk of 3.5% or higher and for women age 60 to 69 years with an IBC risk of 6.5% risk or higher. There was moderate evidence (gold) of a net benefit for women age 50 to 59 years with a 5-year IBC risk of 2.0% to 3.0%, women age 60 to 69 years with a 5-year IBC risk of 3.0% to 6.0%, and women age 70 to 79 years with a 5-year IBC risk of 4.0% or higher. For postmenopausal black and Hispanic women with a uterus, raloxifene also displayed a better benefit/risk profile than tamoxifen and in a similar pattern to that for whites (Fig 3 and Appendix Table A1). Net benefit indices tended to be larger in Hispanic women and smaller in black women than in white women, however.

For non-Hispanic white women age 50 years or older without a uterus, the benefit/risk ratios were similar for raloxifene and tamoxifen (Fig 2). For tamoxifen, there was moderate or strong evidence for benefits outweighing risks among women age 50 to 59 years with an IBC risk of 2.0% or more, women age 60 to 69 years with a risk of 3.0% or more, and women age 70 to 79 years with a risk of 4.5% or more. For raloxifene, there was moderate or strong evidence for benefits outweighing risks among women age 50 to 59 years with a projected 5-year IBC risk of 1.5% or more, women age 60 to 69 years with a risk of 2.5% or more, and women age 70 to 79 years with a risk of 3.0% or more. Direct comparison of raloxifene with tamoxifen showed that the 95% CI on the difference in benefit indices usually included zero (data not shown). For postmenopausal black women without a uterus, both tamoxifen and raloxifene also displayed a benefit/risk profile pattern similar to that of white women (Fig 4). Similar results were found for postmenopausal Hispanic women without a uterus, (Appendix Table A2), except among women age 50 to 59 years in whom tamoxifen had a better benefit/risk profile. Net benefit indices were smaller for black women than for white women, but Hispanic and white women without a uterus had similar indices.

In sensitivity analyses with weights ranging from 0.5 to 1.0 for severe events and from 1.0 to 0.25 for other events, the patterns of evidence for benefit were similar to those in Figures 1 through 4 and Appendix Tables A1 and A2 (data not shown). However, putting more weight on other events favored raloxifene, primarily because tamoxifen is associated with increased risk of cataracts (Table 2), which are common (Table 1), whereas raloxifene is not associated with risk of cataracts.

DISCUSSION

The benefit/risk indices in this article indicated that raloxifene is better than tamoxifen for women age 50 years or older with a uterus. For women without a uterus, the benefit/risk profile for raloxifene is similar to that for tamoxifen. Our tables can help physicians and patients summarize the benefits and risks of tamoxifen and raloxifene for chemoprevention. By using NCI's Breast Cancer Risk Assessment Tool (BCRAT) to estimate the projected 5-year risk of IBC,[24] a health care provider can obtain a benefit/risk index from the corresponding table entries. By combining this information with information on clinical features and personal preferences, the health care provider and patient can make an informed decision.

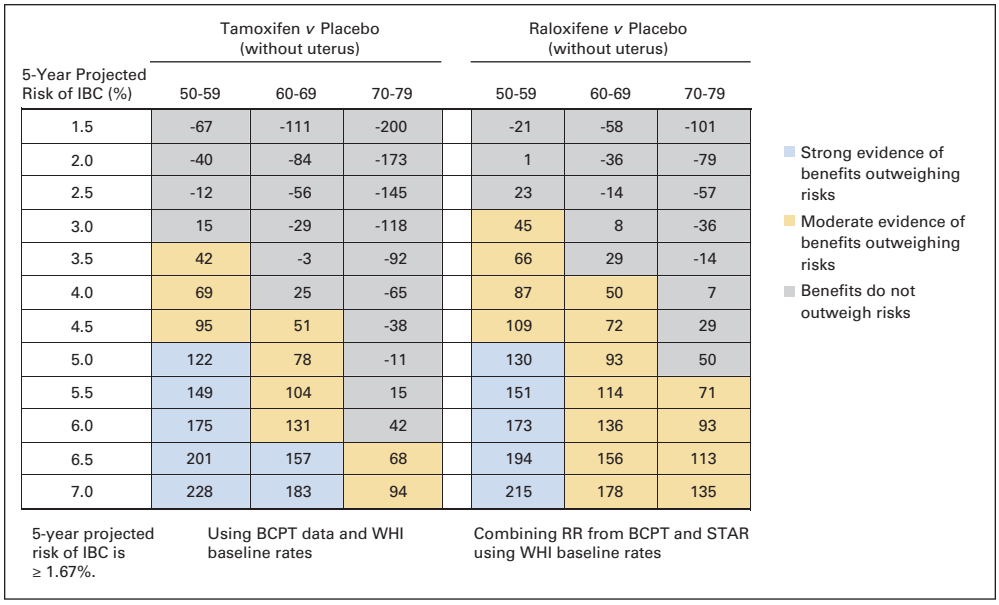

Fig 4. Benefit/risk indices for tamoxifen and raloxifene chemoprevention by level of 5-year projected risk of invasive breast cancer (IBC) for black women without uterus, by age group. On the basis of a woman's risk factors (age, ethnicity, breast cancer risk, and whether she has a uterus), one can calculate her probability of having a health event in 5 years in the absence of chemoprevention and in the presence of chemoprevention. To summarize risks and benefits in a single index, we assigned weights of 1.0 for life-threatening events (IBC, hip fracture, endometrial cancer, stroke, and pulmonary embolism) and 0.5 for severe events (in situ breast cancer and deep vein thrombosis). The net benefit index is the expected number of life-threatening equivalent events in 5 years without chemoprevention in 10,000 such women minus the expected number of life-threatening equivalent events if chemoprevention is used. (A severe event is regarded as equivalent to half a life-threatening event.) For example, in this table, among 10,000 black women without a uterus, age 50 to 59 years, and with a 5-year IBC risk of 3.5%, one expects that 66 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is moderate evidence ($P > 6$ but < 0.9; gold) that the benefits of taking raloxifene outweigh the risk. If tamoxifen were used instead, we estimate chemoprevention would result in 42 life-threatening equivalent events being prevented, with moderate evidence of the benefits outweighing the risks ($P > 0.6$ but < 0.9; gold). BCPT, Breast Cancer Prevention Trial; WHI, Women's Health Initiative; RR, relative risk; STAR, Study of Tamoxifen and Raloxifene.

We revised benefit/risk tables for tamoxifen compared with no treatment (placebo) previously developed by Gail et al[5] by using baseline incidence rates from WHI. We confined our analysis to women age 50 years and older because raloxifene is approved only for postmenopausal women. However, net benefits of tamoxifen are greater in younger women with high risk of breast cancer for whom the earlier tables[5] are still recommended.

We produced tables of indices to weigh the benefits and risks of raloxifene compared with no treatment by combining data from STAR and BCPT. This innovation improves the usefulness of STAR data in deciding whether to use raloxifene for chemoprevention because the STAR trial did not have a placebo arm.

Our tables are appropriate for the general population of women age 50 years or older without previous breast cancer. However, women with high risks for certain conditions in Tables 1 and 2 are at additional risk from chemoprevention. For example, a woman with a history of a thromboembolic event would be at greater risk of having a DVT than the average woman. Data are insufficient on the effect of chemoprevention in women with mutations in *BRCA1* or *BRCA2* genes.[25]

Principal strengths of this article include use of data from randomized chemoprevention trials and use of WHI data on incidence rates of health outcomes in the absence of chemoprevention.

Our study has some weaknesses or points of criticism. (1) The weights chosen for life-threatening, severe, and other events affect the benefit/risk values in our tables. If more weight is assigned to a particular severe event, such as in situ breast cancer, the relative benefit of tamoxifen increases. Some women may be concerned about a particular health outcome. For such women, different weighting of the outcomes might be more appropriate. (2) To estimate the effects of raloxifene versus placebo, we multiplied RRs from BCPT and STAR. This method increased the variability of our net benefit indices for raloxifene and required the assumption that the treatment RR comparing tamoxifen with placebo in BCPT would also have been observed in the STAR population. (3) Women in WHI may have lower baseline disease rates than the general population, which could affect the indices. (4) Much of the improved performance of raloxifene compared with tamoxifen is from reduced risk of endometrial cancer. Although we used the best available data,[14] our findings in favor of raloxifene are sensitive to these estimates. (5) BRCAT does not predict the incidence of estrogen receptor–positive IBC, which is affected by tamoxifen and raloxifene, and the net index for black women may be less than that tabulated because a smaller proportion of black women have estrogen receptor–positive disease. (6) Some women who stand to gain the most from chemoprevention are younger than age 50 years,[5] and are not covered by our tables. (7) Although tamoxifen shows continued chemopreventive efficacy and reduced adverse effects for up to 20 years,[26,27] and updated data from STAR show continued efficacy in reducing breast cancer risk at 81 months of follow-up,[23] we restricted our net benefit index tables to 5 years. An analysis over extended time periods may be worthwhile and health care providers may wish to consider this continued efficacy.

In summary, we have updated and extended a benefit/risk index for raloxifene and tamoxifen, and for Hispanic and non-Hispanic white and black women age 50 years or older. By giving quantitative indices that are color-coded for strength of evidence, we hope to help

health care providers and their postmenopausal patients make better informed decisions about chemoprevention.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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