NANCY PRESS, PhD
Oregon Health Sciences University
Portland, Or

WYLIE BURKE, MD, PhD
University of Washington
Seattle, Wash

Eff Clin Pract. 2000;3:98-103.

If You Care about Women's Health, Perhaps You Should Care about the Risks of Direct Marketing of Tamoxifen to Consumers

Recently, a full-page advertisement for tamoxifen appeared in mass-circulation magazines. The ad reached an estimated 41,000,000 readers in its first appearance.[1] Over the back of a lovely young woman in a lacy bra, the headline reads, *"If you care about breast cancer, care more about being a 1.7 than a 36B"* (**Figure 1**).

This advertisement represents the opening salvo in a marketing strategy that also includes television spots and Web links. This new, direct-to-consumer approach to pharmaceutical and medical test marketing is disturbing, especially when the disease involved is one that is particularly feared or when the data provided are partial and misleading. When both these problems come together—as they do in this case—the situation constitutes a public health concern. In this commentary, we hope to help physicians understand the power of these advertisements for consumers and to provide information on the advertisement's interpretation and omissions of fact (**Table 1**).

"If you care about breast cancer. . . "

Women are very concerned about breast cancer. Considerable data support the claim that American women overestimate their risk for breast cancer, as well as that of the average woman, many fold.[2–5] Data also demonstrate that breast cancer is now seen by many as a risk for *young* women, rather than for middle-aged and elderly women.[6, 7] The ad is a graphic example of how anxiety about breast cancer is promulgated: A lovely young woman, a lacy bra, an average (perhaps even ideal) bra size. These are images that speak to the daily world of women. The headline abruptly shifts direction, suggesting that the woman who, at that moment, might have been thinking about the pleasurable, nurturing, and aesthetic value of her breasts was misguided and perhaps even risking her health. Breasts, it reinforces, are about *disease*.

In a 1995 article in *Vogue*, Oxenhandler[8] says that, for women today, breasts are no longer associated with nuturing, pleasure, or aesthetics; rather, "breasts now radiate anxiety." It is not hyperbole to say that many American women have been terrorized by lifetime breast cancer risk numbers, which have "moved" with lightning speed from 1 in 12 to 1 in 10 to, currently, 1 in 8. The constant recalculation of these numbers—revisions that are often made as a result of new assumptions about life expectancy—has given women the erroneous impression that breast cancer incidence is increasing at epidemic proportions. The ad speaks to these anxieties and sets up a logical train of commands: *Worry about breast cancer. Relate that worry to yourself. Do something*.

This paper is available at ecp.acponline.org.

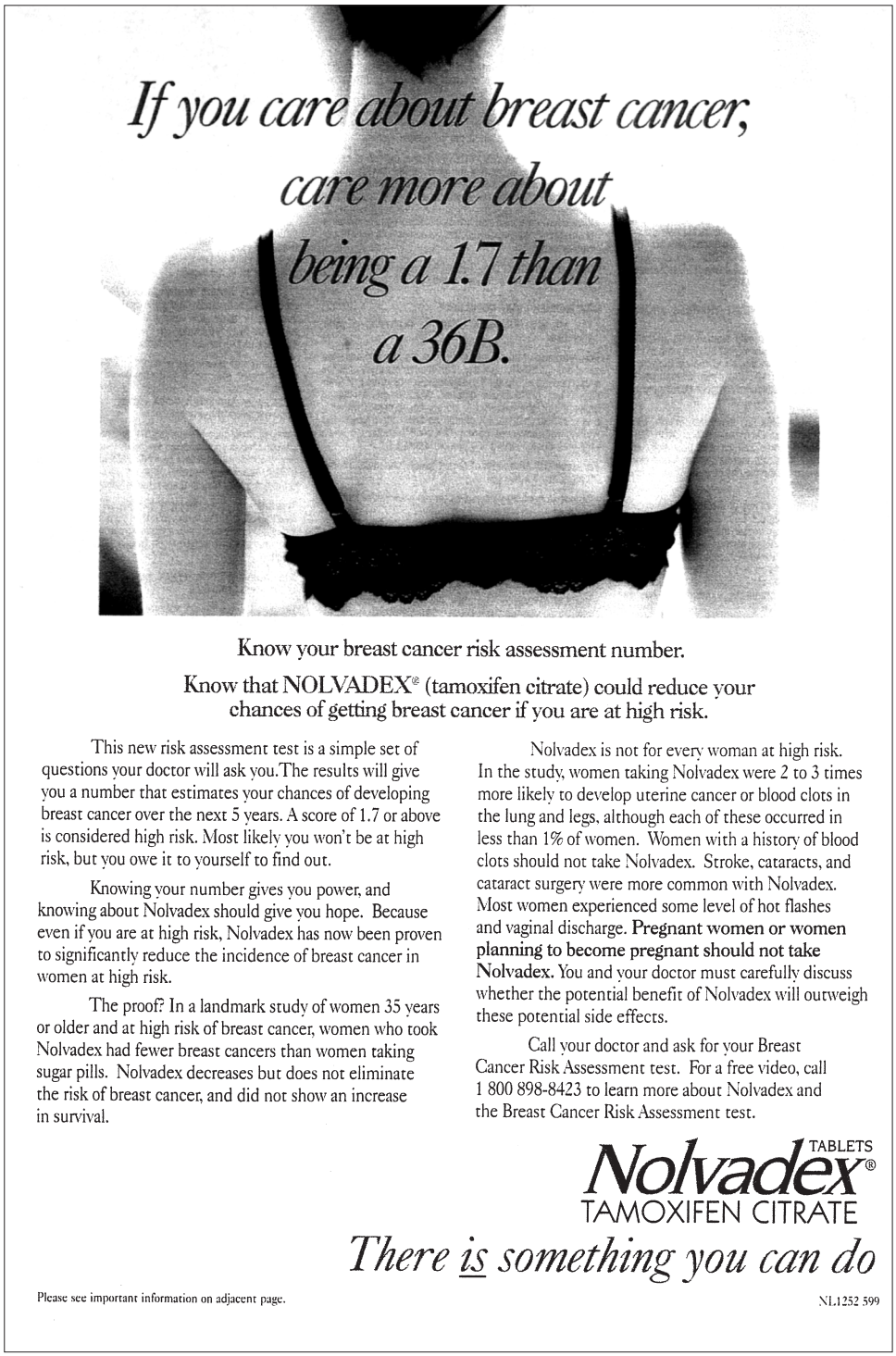

FIGURE 1. Direct-to-consumer advertisement for tamoxifen.

"...care more about being a 1.7 than a 36B"

Having succeeded in focusing the reader's attention on breast cancer, the ad then provides the way for a woman to relate that breast cancer worry directly to herself as a potential consumer of tamoxifen. It does this by introducing yet another new, and mysterious, risk number—1.7—and instructing the reader in a subheadline to "Know your breast cancer risk assessment number."

What Is 1.7?

The number 1.7 means a 1.7% chance of being diagnosed as having breast cancer in the next 5 years. Interestingly, even at face value, 1.7 means that a woman has a 98.3% chance of *not* developing breast cancer in the next 5 years. Ironically, it would seem that most women—of any risk category—would be enormously relieved to discover that their risk for developing breast

TABLE 1

Selected Statements and Relevant Information Not Addressed in the Tamoxifen Advertisement

STATEMENT	RELEVANT INFORMATION NOT ADDRESSED
"If you care about breast cancer, care more about being a 1.7 than a 36B."	1.7 means a 1.7% absolute risk for developing breast cancer in the next 5 years This predicted risk is generated by using the Gail model of breast cancer risk, which may be inaccurate for some women Specifically, the model overestimates risk in some younger women, fails to adequately differentiate family history (i.e., does not account for age of cancer diagnosis in first-degree relatives and does not count second-degree relatives), and is not validated in African-American or other minority populations
"A score of 1.7 or above is considered high risk."	A predicted risk of 1.7% or higher was the entry criteria for the U.S. trial; although this threshold was used as a criterion for study enrollment, it does not constitute a generally accepted measure of "high risk"
"Nolvadex [tamoxifen] has been proven to significantly reduce the incidence of breast cancer in women at high risk."	Although the U.S. trial found a 49% risk reduction, two European tamoxifen trials did not find a significant reduction in breast cancer incidence Breast cancer incidence was reduced in the U.S. trial; however, too few breast cancer deaths were observed to determine whether the reduction was significant Tamoxifen may delay, not prevent, breast cancer The duration of beneficial tamoxifen treatment is unknown
"...women taking Nolvadex were 2 to 3 times more likely to develop uterine cancer or blood clots in the lungs and legs, although each of these occurred in less than 1% of women."	Three women in the tamoxifen group died of pulmonary embolism There is a contrast between presentation of harms ("in less than 1% of women") and presentation of breast cancer risk (1.7 never presented as a percentage, could be discussed as occurring "in less than 2% of women")

cancer in the next 5 years was less than 2%. The 1.7 figure remains frightening—and thus motivating—only as long as it is not understood. But by insisting that women *"owe it to [themselves]. . ."* to know their risk number, the ad insidiously bolsters its credibility to consumers by appealing to the deeply held American belief that knowledge is power.

Where Does 1.7 Come from?

The power of this new number (for physicians as well as for consumers) depends in large part on the imprimatur of the National Cancer Institute (NCI) and the National Surgical Adjuvant Breast and Bowel Project Biostatistics Center,[9] which jointly produced the breast cancer risk-assessment tool. It is this tool that allows calculation of individual risk and that informs a woman whether she is "a 1.7." The central importance of the risk-assessment tool in the tamoxifen marketing campaign is evidenced in several ways: The advertisement includes a toll-free number through which any consumer in the United States can order a computer disk that contains the tool, doctors are provided the tool in the form of a hand-held instrument with the brand name for tamoxifen on it, and a video (also available by calling the toll-free number) shows women working through their risk numbers with the help of physicians. Yet, although the ad and its associated marketing materials convey the importance of this number as a measure of risk, they do not explain how the number is derived.

The calculation of risk used by the breast cancer risk-assessment tool is based on the Gail model, a population-based model of breast cancer risk.[10] An average American woman who is 60 years of age has a 5-year risk of 1.7%.[11] A young woman may have this 5-year risk if she has one or more of the breast cancer risk factors evaluated in the Gail model. These factors include early menarche; late menopause; late first birth or nulliparity; one or more first-degree relatives with breast

cancer; or a history of breast biopsies, particularly if one or more biopsies showed atypical hyperplasia.

The risk tool, however, does not accurately predict risk for all women. It tends to overestimate risk in women younger than 50 years who are not receiving regular mammography screening or who have had two or more breast biopsies, and to underestimate risk in older women.[12, 13] For family history, it uses information about affected first-degree relatives only and does not take into account the age at onset of cancer in affected relatives.[10] In other words, having a mother affected with breast cancer at an elderly age results in the same risk calculation as having a mother who developed breast cancer before 50 years of age, although actual risk is unlikely to be equal in these two situations.[14] In addition, although the risk-assessment tool has been modified to incorporate separate breast cancer incidence data for African-American women, it has not been validated in this population.

"A score of 1.7 or above is considered high risk."

Why is the 1.7% five-year risk level so important? This risk level was the main entry criterion for the U.S. tamoxifen prevention trial. Among the women enrolled in the trial, 30% were 60 years of age or older and thus qualified for participation on the basis of age alone (i.e., a 60-year-old woman's 5-year risk is 1.7%); the remaining 70% were younger women with additional breast cancer risk factors. The percentage 1.7% was chosen as a sufficiently elevated risk level to ensure that an adequate number of cases of breast cancer would occur among control participants to permit a protective effect to be measured in the treated group. Although 1.7% defined the entry criteria for this trial, it is not a generally accepted definition of "high risk."

Neither the ad nor the related marketing materials explain this reasoning. Women are simply advised to *know your number*. That locution fundamentally changes the connotations of "1.7": The number is now constructed as internal to each individual woman—*"your number,"* that is, your personal risk level. Rather than a cut-off point created by the statistical needs of power calculations in a randomized clinical trial, 1.7 represents a crucial break-point on a continuum of risk along which every woman can locate herself. That the ad encourages this sort of reading is supported by the text in the advertisement's second paragraph: *"Knowing your number gives you power, and knowing about Nolvadex should give you hope."* Thus, women are shown precisely how to relate breast cancer risk to themselves, and now, with personal anxiety raised, they are given hope because *"Nolvadex has now been proven to significantly reduce the incidence of breast cancer in woman at high risk."* But a review of the tamoxifen trial data suggests that even this conclusion is premature.

". . .proven to significantly reduce the incidence of breast cancer. . ."

As with the risk-assessment tool, this assertion gains powerful support from its cited source, the recently terminated U.S. tamoxifen trial. This randomized, clinical trial enrolled women who did not have breast cancer at the start of the trial. It provided evidence of a cumulative 49% decrease in breast cancer during a 69-month period of tamoxifen treatment.[15] Although the statement in the ad is not a false claim, the data are more complex and equivocal than it suggests.

First, interim results from two European tamoxifen trials have not shown the substantial reduction in risk seen in the American trial (**Table 2**).[16, 17] The European trials are smaller and include a higher proportion of younger women but nevertheless have sufficient power to observe a risk reduction of the magnitude seen in the U.S. trial.[18] The difference in results may be explained by differences in study design. For example, the European trials included some women receiving hormone-replacement therapy (HRT), whereas the U.S. trial did not; if HRT interferes with the preventive effect of tamoxifen, this could explain some of the difference in study results.

Finally, the study inclusion criteria for family history were more stringent in the U.K. than in the U.S. trial and may have led to a higher proportion of participants with an inherited risk for breast cancer. The lack of benefit observed in the U.K. trial could thus reflect a reduced benefit of tamoxifen for women from high-risk families. This hypothesis is made more plausible by recent data indicating that tumors caused by *BRCA1* gene mutations are more likely than sporadic tumors to be estrogen-receptor negative[19–21] and thus not preventable by tamoxifen.[15]

Finally, the current data do not rule out that tamoxifen therapy delays, rather than prevents, breast cancer.[22] As summarized in **Table 2**, fewer deaths attributable to breast cancer were seen among treated participants in the U.S. trial (although the difference was not statistically significant) but not in the European trials. However, the numbers are too small to draw firm conclusions from these results. In short, questions remain about the degree of risk reduction provided by tamoxifen and about which women are most likely to benefit from its use.

TABLE 2

Summary of Three Randomized Trials Evaluating the Efficacy of Tamoxifen in the Primary Prevention of Breast Cancer

VARIABLE	UNITED STATES[15]		ITALY[16]		UNITED KINGDOM[17]	
Entry criteria	60 years of age *or* 35–59 years of age with 1.66% five-year risk for invasive cancer diagnosis by Gail model *or* History of lobular carcinoma in situ		35–70 years of age *and* total hysterectomy for reasons other than neoplasia		30–70 years of age *and* 1 first-degree relative younger than 50 years of age with breast cancer *or* 2 affected relatives (1 first-degree and 1 first- or second-degree)	
Minority participants	3.5%		Not reported		Not reported	
Median duration of trial	4.6 years (55 months)		3.8 years (46 months)		5.8 years (70 months)	
	TREATED	CONTROLS	TREATED	CONTROLS	TREATED	CONTROLS
Participants, *n*	6788	6707	2700	2708	1250	1244
Cases of invasive breast cancer, *n**	89	175	19	22	30	32
Cumulative incidence of invasive breast cancer	2.6%		0.8%		2.6%	
Breast cancer deaths, *n*	3	6	0	0	4	1
Deaths from other causes, *n*	54	65	6	9	5	5

**The Italian trial may include noninvasive cases.*

Uncertainty about Potential Harms

Although the ad is scrupulous in its inclusion of the Food and Drug Administration–required caveats in regard to documented drug risks (e.g. *"...women taking Nolvadex were 2 to 3 times more likely to develop uterine cancer or blood clots in the lungs and legs, although each of these occurred in less than 1% of women"*), it fails to mention the life-threatening nature of pulmonary embolism. Three women receiving tamoxifen died of pulmonary embolism. Although the advertisement seeks to heighten concern about the risk for breast cancer, a risk of less than 2%, it minimizes potential harms by explicitly stating that they occur in less than 1% of women. Furthermore, the ad does not mention that the severity and frequency of side effects with long-term tamoxifen use are unknown (in part, because the trial was ended early when benefit was found).

Other data point to an additional potential harm. There is evidence that tamoxifen is teratogenic in mice,[23–26] which raises concerns about its use in women who have not completed childbearing. Although targeted to women as young as 35, the ad does not mention this risk (although detailed drug information provided in small print on a separate page indicates that the drug may cause fetal harm).

Finally, the implications of forgoing estrogen in favor of tamoxifen prophylaxis have not been evaluated. Conventional wisdom dictates against concurrent use of estrogen and tamoxifen, because estrogen may blunt the preventive effect of tamoxifen and potentiate its side effects. As a result, premenopausal women who want to avoid pregnancy would have to forgo oral contraceptives. Of even greater concern is that tamoxifen use precludes HRT in postmenopausal women, although most U.S. women will achieve a "score" of 1.7 by age 60. The NCI trial provides no guidance to clinicians trying to determine the relative risks and benefits of tamoxifen compared with HRT for such women.

The Dangers for Consumers; the Challenges for Providers

It could be argued that because tamoxifen must be prescribed by a physician, consumers are protected from misinterpretation and misuse of the information in this advertisement by their physicians' knowledge. However, the ad invites all women to consider whether they are candidates for tamoxifen prophylaxis and urges them to find out their "score." It therefore seems reasonable to expect that women will be motivated to seek the information themselves. The information generated by the breast cancer risk-assessment tool is readily available to consumers as a computer-based "risk disk" through the NCI Web site and a telephone number given at the end of the ad.

With the use of direct-to-consumer marketing, women are likely to come to physicians' offices with copies of the tamoxifen ad or questions about it. How many physicians will be comfortable trying to convince their patients of a lack of definitive evidence for prescribing tamoxifen, or feel adequately informed to address the question, in the face of this ad with its imprimatur of two powerful authorities, the NCI risk-assessment tool and the U.S. tamoxifen trial? Despite the American folk belief appealed to in this ad—that all information is knowledge and knowledge in itself brings power—an evidence-based medical approach is predicated on a view that information is worth seeking only when it leads to a net outcome benefit. As summarized in **Table 1**, many of the positions taken in the tamoxifen advertisement have inherent limitations that are apparent only with a detailed review of relevant data. Thus, it is unclear which women clearly stand to benefit from tamoxifen. In this case, the net outcome benefit seems clear only from the point of view of the company marketing Nolvadex.

References

1. Standard Periodical Directory. New York: Oxbridge Publishing; 1999.
2. Lavelle K, Charlton A. Women's perception of risk of cancer. BMJ. 1998;317:542.
3. Pilote L, Hlatky MA. Attitudes of women toward hormone therapy and prevention of heart disease. Am Heart J. 1995;129:1237-8.
4. Bunker JP, Houghton J, Baum M. Putting the risk of breast cancer in perspective. BMJ. 1998;317:1307-9.
5. McCaul KD, O'Donnell SM. Naive beliefs about breast cancer risk. Womens Health. 1998;4:93-101.
6. Press N. Survey conducted for the California State Breast Cancer Early Detection Partnership Program (BCEDP); 1995.
7. Fulton JP, Rakowski W, Jones AC. Determinants of breast cancer screening among inner-city Hispanic women in comparison with other inner-city women. Public Health Rep. 1995;110:476-82.
8. Oxenhandler N. Fruits of the body. Vogue. 1995:56-63.
9. The National Cancer Institute. Breast cancer risk assessment tool; 1998.
10. Gail MH, Benichou J. Validation studies on a model for breast cancer risk. J Natl Cancer Inst. 1994;86:573-5.
11. Feuer EJ, Wun LM, Boring CC, Flanders WD, Timmel MJ, Tong T. The lifetime risk of developing breast cancer. J Natl Cancer Inst. 1993;85:892-6.
12. Constantino 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;91:1541-8.
13. Spiegelman D, Colditz GA, Hunter D, Hertzmark E. Validation of the Gail et al. model for predicting individual breast cancer risk. J Natl Cancer Inst. 1994;86:600-7.
14. Claus EB, Risch N, Thompson WD. Genetic analysis of breast cancer in the cancer and steroid hormone study. Am J Hum Genet. 1991;48:232-42.
15. Fisher B, Constantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1999;90:1371-88.
16. Veronesi U, Maisonneuve P, Costa A, et al. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. Italian Tamoxifen Prevention Study. Lancet. 1998;352:93-7.
17. Powles T, Eeles R, Ashley S, et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. Lancet. 1998;352:98-101.
18. Pritchard KI. Is tamoxifen effective in prevention of breast cancer? Lancet. 1998;352:80-1.
19. Verhoog LC, Brekelmans CTM, Seynaeve C, et al. Survival and tumour characteristics of breast-cancer patients with germline mutations of BRCA1. Lancet. 1998;351:316-21.
20. Wagner TMU, Moslinger RA, Muhr D, et al. BRCA1-related breast cancer in Austrian breast and ovarian cancer families: specific BRCA1 mutations and pathological characteristics. Int J Cancer. 1998;77:354-60.
21. Ostrander EA, Malone KE, Porter PL, et al. BRCA1/BRCA2 mutations in relation to tumor characteristics and prognosis. Am J Hum Genet. 1999;65(Suppl):A65.
22. Carbone PP. Case commentary on Preventing Breast Cancer with Tamoxifen. Hospital Practice. 1998;33:72-8.
23. Tucker MJ, Adam HK, Patterson JS. Tamoxifen. In: Laurence DR, McLean AEM, Wetherall M, eds. Safety testing of new drugs: laboratory predictions and clinical performance. London: Academic Pr; 1984:125-61.
24. Chamness GC, Bannayan LA, Landry JR, et al. Abnormal reproductive development in rats after neonatally administered antiestrogen (tamoxifen). Biol Reprod. 1979;21:1087-90.
25. Iguchi T, Hirokawa M, Takasugi M. Occurrence of genital tract abnormalities and bladder hernia in female mice exposed neonatally to tamoxifen. Toxicology. 1986;42:1-11.
26. Cunha GR, Taguchi O, Namikawa R, Nishizuka Y, Robboy SJ. Teratogenic effects of clomiphene, tamoxifen and diethylstilbestrol on the developing human female genital tract. Hum Pathol. 1987;18:1132-43.

Correspondence

Nancy Press, PhD, Department of Public Health and Preventive Medicine, Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, CB-669, Portland, OR 97201; telephone: 503-494-2535; fax: 503-494-4981; e-mail: pressn@OHSU.edu.