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Running title: Breast cancer chemoprevention

Use of Tamoxifen and Raloxifene for Breast Cancer Chemoprevention in 2010

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Key words: Chemoprevention, tamoxifen, raloxifene, breast cancer, side effect

Abstract

PURPOSE: Two selective estrogen receptor modulators (SERMs), tamoxifen and raloxifene, have been shown in randomized clinical trials to reduce the risk of developing primary invasive breast cancer (IBC) in high-risk women. In 1998, the U.S. Food and Drug Administration (FDA) used these studies as a basis for approving tamoxifen for primary breast chemoprevention in both premenopausal and postmenopausal women at high risk. In 2007, the FDA approved raloxifene for primary breast cancer chemoprevention for postmenopausal women.

METHODS: Data from the year 2010 National Health Interview Survey (NHIS) were analyzed to estimate the prevalence of tamoxifen and raloxifene use for chemoprevention of primary breast cancers among U.S. women.

RESULTS: Prevalence of use of chemopreventive agents for primary tumors was 20,598 (95% CI, 518-114,864) for U.S. women aged 35 to 79 for tamoxifen. Prevalence was 96,890 (95% CI, 41,277-192,391) for U.S. women aged 50 to 79 for raloxifene.

CONCLUSION: Use of tamoxifen and raloxifene for prevention of primary breast cancers continues to be low. In 2010, women reporting medication use for breast cancer chemoprevention were primarily using the more recently FDA-approved drug raloxifene. Multiple possible explanations for the low use exist, including lack of awareness and/or concern about side effects among primary care physicians and patients.

Background

Several chemoprevention trials have examined whether selective estrogen receptor modulators (SERMs) can prevent breast cancer in high-risk women [1-4]. In 1998, the Breast Cancer Prevention Trial (BCPT) demonstrated that tamoxifen reduced the risk of invasive breast cancer (IBC) by 49% in U.S. women at elevated risk [2]. However, it also increased the risk of several serious side effects, including endometrial cancer, stroke, pulmonary embolism, and deep-vein thrombosis. After close examination of the risks and benefits of treatment, the U.S. Food and Drug Administration (FDA) approved tamoxifen for breast cancer chemoprevention among women aged 35 years or older with a 5-year breast cancer risk of 1.67% or higher.

Trials that tested a SERM called raloxifene for the treatment of osteoporosis [5, 6], cardiovascular events, and breast cancer [7] also reported substantial reductions in IBC risk among postmenopausal women. The National Surgical Adjuvant Breast and Bowel Project (NSABP) Study of Tamoxifen and Raloxifene (STAR) demonstrated that raloxifene was as effective as tamoxifen in reducing risk of IBC [8]. Importantly, raloxifene also resulted in lower risk of endometrial cancer, thrombotic events, and cataracts, but a non-statistically significant higher risk of non-invasive 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 (but not premenopausal) women at high risk of IBC [9]. A recent benefit/risk analysis of these two chemopreventive agents indicated that raloxifene displayed a better benefit-to-risk profile than tamoxifen for postmenopausal women with a uterus. For women without a uterus, the benefit/risk profile for raloxifene was similar to that of tamoxifen [10].

In a complex series of analyses, Freedman and colleagues used nationally representative

data from the year 2000 NHIS to estimate that more than 10 million women in the US would be eligible for use of tamoxifen for breast cancer chemoprevention, and the benefits would outweigh the risks for more than 2 million women [11]. Because raloxifene was not approved for breast cancer chemoprevention until 2007, equivalent data about the number of women who would be eligible (and/or for whom the benefits would outweigh the risks) for using raloxifene during that same timeframe are unavailable. Our previous analyses of nationally representative data from the years 2000 and 2005 showed that tamoxifen use for primary prevention of breast cancer was very low [12]. Less than one percent of women aged 40 to 79 years were taking tamoxifen for breast cancer chemoprevention. In the current study, we use data from the 2010 iteration of the National Health Interview Survey (NHIS) to update our previous analyses and to examine the prevalence of both tamoxifen and raloxifene for chemoprevention. To our knowledge, this is the first study to report national prevalence data of raloxifene use for breast cancer chemoprevention since it was approved for that purpose by the FDA in 2007.

Methods

NHIS is a population-based, nationally-representative survey that is the primary source of information about the health of the noninstitutionalized civilian population of the United States. Survey data are collected by approximately 750 interviewers hired and trained in computer-assisted personal interviewing (CAPI) by the U.S. Census Bureau. The sampling design is complex. In brief, it uses a multi-stage sampling methodology, engages state-level stratification with 428 primary sampling units (PSUs) drawn from approximately 1,900 geographically-defined PSUs, and oversamples Black, Hispanic, and Asian populations. More detailed methodological information can be located online [13, 14].

We used NHIS 2010 data to estimate the number of women taking tamoxifen and

raloxifene for: 1) chemoprevention of a primary breast tumor (i.e., self-reported medication use specifically for breast cancer risk reduction, and no prior breast cancer diagnosis); and 2) chemoprevention of a secondary tumor or a recurrence (i.e., self-reported medication use for breast cancer treatment or risk reduction, and prior breast cancer diagnosis). We also estimated the prevalence of raloxifene use to treat osteoporosis (i.e., self-reported medication use for osteoporosis treatment, no prior breast cancer diagnosis).

The denominators for the calculations varied by treatment modality. Although the eligibility criteria for tamoxifen and raloxifene use are the same (i.e., a risk of 1.67% over five years), they are approved for use for different ages. This distinction is due to differences in the design of the clinical trials that the FDA referred to during the approval process and because raloxifene has a more favorable risk-benefit profile than tamoxifen among women with a uterus. Consequently, for tamoxifen, the denominator included all women aged 35 to 79 ($N_{\text{sample}}=9906$; $N_{\text{population}}=76,889,399$). For raloxifene, the denominator included all women aged 50 to 79 ($N_{\text{sample}}=5959$; $N_{\text{population}}=45,226,315$).

Prevalence estimates, totals, and percentages were weighted by the NHIS sample weights to the total U.S. population. Standard errors used in computing the 95% confidence intervals (CIs) were estimated to take into account the complex multistage probability sampling design of the NHIS [15]. We calculated CIs for small percentages using a modified binomial CI [16].

Results

Prevalence was very low for breast cancer chemoprevention (see Table 1). Among women who did not report a prior breast cancer diagnosis and who reported using the medication specifically for breast cancer risk reduction, only 0.03% (95% CI, 0.001-0.15) or 20,598 (95% CI, 518-114,864) of U.S. women aged 35 to 79 reported taking tamoxifen for primary

chemoprevention. Only 0.21% (95% CI, 0.09-0.43) or 96,890 (95% CI, 41,277-192,391) of U.S. women aged 50 to 79 reported using raloxifene for that purpose.

A somewhat larger (yet still small) proportion of U.S. women reported that they were breast cancer survivors taking tamoxifen to reduce their risk of developing a secondary tumor or of experiencing a recurrence. Among women who reported having a prior breast cancer diagnosis and who reported using the medication for breast cancer treatment or risk reduction, we estimate that 0.36% (95% CI, 0.22-0.56) or 277,621 (95% CI, 168,988-429,690) of U.S. women were taking tamoxifen.

An additional 0.63% (95% CI 0.40-0.96) or 287,100 (95% CI, 180,417-433,391) of U.S. women without a history of breast cancer used raloxifene to treat osteoporosis. However, a small percentage of U.S. women, 0.03% (95% CI, 0.004-0.12) or 14,854 (95% CI, 1,738-54,292) women with a history of breast cancer reported taking raloxifene to reduce their risk of developing a new or recurrent breast cancer.

Discussion

More than ten years after the FDA approved tamoxifen for the chemoprevention of breast cancer, and three years after it approved raloxifene for the same purpose in postmenopausal women, the prevalence of tamoxifen and raloxifene use by U.S. women for primary breast cancer chemoprevention remains very low. In 2010, we estimated that 120,737 (95% CI, 75,416-183,219) and 51,575 (95% CI, 19,595-109,936) women were taking tamoxifen for breast cancer chemoprevention in the years 2000 and 2005, respectively [12]. Our current analysis of data from NHIS 2010 estimates that 20,598 (95% CI, 518-114,864) U.S. women were taking tamoxifen for primary chemoprevention, and 96,890 (95% CI, 41,277-192,391) U.S. women were taking raloxifene for that purpose.

These prevalence estimates do not suggest an increase in chemoprevention use from 2000 through 2010. Rather, with the 2007 FDA approval of raloxifene for primary chemoprevention of breast cancer, there appears to be a slight shift away from tamoxifen and towards raloxifene, with no overall increase in chemoprevention use. There also appears to be a small number of women taking raloxifene for prevention of a secondary tumor or recurrence. This represents off-label use of raloxifene, because the FDA has not approved it for prevention of secondary breast tumors or recurrent disease.

The results of our studies examining 10 years of primary chemoprevention utilization in the U.S. population are consistent with a decade of clinical research describing low utilization of tamoxifen among women at high risk of developing breast cancer [17]. Several possible explanations have been suggested for the low uptake of tamoxifen, and in the intervening years there have been widespread attempts to increase awareness of using tamoxifen (and, after its approval by the FDA, raloxifene) for primary chemoprevention.

First, many physicians, particularly non-oncologists, may be reluctant to prescribe tamoxifen due to concerns about side effects and/or because they feel that they lack sufficient information about risk reduction options and counseling [18-20]. Efforts to ameliorate this problem were most often represented by letters or articles published in clinical journals [21-25]. There have also been recent calls for developing support tools to help physicians learn about chemoprevention [26].

Patients are also reluctant to take tamoxifen, even when they are at high risk of developing breast cancer, due to certain risk factors [17, 18]. Patients' reluctance has been attributed to not recognizing or believing that the risks may outweigh the benefits [12], but knowing that the numerical benefits outweigh the numerical risks is not sufficient to explain

reluctance to accept chemopreventive therapy [27-29]. Recent research even suggests that women who know more about the risks and benefits of tamoxifen may be less willing to take it [30]. Paradoxically, interventions designed to educate and support patients in their decisions have resulted in *lower* uptake of tamoxifen [31]. This occurs even when great care is taken to communicate the risks and benefits of treatment in a way that is understood by the public and when women can accurately describe the magnitude of the risks and benefits of treatment [32]. This suggests that more informed patients may view the benefits of tamoxifen (i.e., reduced breast cancer risk reduction) as less desirable than its potential risks (e.g., increases risk of stroke).

It could be that merely suggesting that a treatment has a side effect is highly aversive [33, 34]. This idea is partially supported by research demonstrating that some women perceive the risks of side effects as more probable and as more dangerous than the risks of breast cancer [35, 36]. These reasons may explain why there appears to be a shift away from tamoxifen to raloxifene for chemoprevention. However, overall chemoprevention use may remain low because raloxifene is still associated with serious side effects, despite its more advantageous side effect profile compared with tamoxifen [8, 28]. This assertion is supported by research suggesting that women may be reluctant to “add” new risks to their health when tamoxifen will not eliminate their risk of breast cancer completely [37]. Women may also perceive that the score conferred by the Gail model is too small to be of concern. This is consistent with the risk communication and decision-making literatures, which discourage communicating risks using a 1-100 scale [38].

Aromatase inhibitors (AIs) may become an additional prevention treatment option in the near future [39-42]. However, AIs are effective only in postmenopausal women, and treatment

with these agents increases the potential for osteoporosis (bone mineral loss and increased fracture rates in the absence of bone-sparing therapy), musculoskeletal complaints (joint pain and stiffness), and adverse lipid effects. Therefore, a direct evaluation of AIs as chemopreventive agents as well as a head-to-head comparison with tamoxifen and/or raloxifene as chemopreventive strategy is necessary. There are several ongoing randomized clinical trials that address this issue. The NCIC Clinical Trials Group Mammary Prevention.3 trial (NCIC CTG MAP.3) reported that AI use decreased the incidence of invasive breast cancer by 65% (HR 0.35 (95% CI, 0.18-0.70) [43]. However, until other studies show similar results, particularly over the long-term, available recommendations do not support the use of these agents for breast cancer chemoprevention outside of clinical trials [39].

Limitations and Future Research

The number of women in the NHIS sample who reported taking either tamoxifen or raloxifene was extremely small. This led to wide confidence intervals in the prevalence estimates. It also precluded stratifying prevalence of use by sociodemographic factors or risk status. Clinic-based research should examine the risk status characteristics (e.g., Gail score, breast cancer history, etc.) of women who are taking tamoxifen or raloxifene for any purpose.

The second limitation is that the data are self-reported. Women might be reluctant to report their medication use, be unaware of the purpose of taking tamoxifen or raloxifene (i.e. joint indication for osteoporosis and breast cancer risk reduction), or be unaware of the name of the medication. They may also simply forget they are taking it. All of these factors would result in an underestimation of the prevalence of tamoxifen and raloxifene use. Nevertheless, based on the upper limit of the confidence intervals, it is reasonable to conclude that prevalence of tamoxifen or raloxifene use for chemoprevention in the United States is well below 1%.

It is also possible that raloxifene is prescribed preferentially for women at high risk of breast cancer who also happen to have high (rather than low) risk of osteoporosis. Thus, the slight shift away from tamoxifen to raloxifene use may be due to factors related to osteoporosis rather than breast cancer. Unfortunately, the relevant bone mass density data needed to test such a hypothesis are unavailable in NHIS. Future research should examine the issue in more detail.

Implications

We found that the prevalence of tamoxifen use for primary chemoprevention was low in 2010, as it was in 2000 and 2005. The prevalence of raloxifene for primary chemoprevention was also low, although there was the suggestion of a shift away from tamoxifen and towards raloxifene for this purpose. Considering the number of women who might benefit from chemopreventive therapy for breast cancer [11], it appears that few eligible women are taking these drugs. Despite the ability to calculate the likelihood of benefiting from chemopreventive agents, they are not appropriate for all eligible high-risk women. For each woman, the benefits and risks of chemoprevention must be weighed carefully against each other. Researchers and clinicians should also recognize that, for many women, a calculated risk score is one of countless factors that comprise their experience of being at risk for breast cancer [37] and, perhaps more importantly, that comprise their everyday lives and concerns. Consequently, the decision-making process should also incorporate the unique medical, psychosocial, and personal factors [28, 44] that are most relevant to each patient.

Conflict of Interest Disclosures

None.

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Table 1. Prevalence estimates and stated reasons for use of tamoxifen and raloxifene, NHIS 2010.				
	Tamoxifen ¹		Raloxifene ²	
Reason for Use	Number using Tamoxifen	Percentage	Number using Raloxifene	Percentage
Prevention of a primary tumor	20,598 (95% CI 518-114,864)	0.03 (95% CI 0.001-0.15)	96,890 (95% CI 41,277-192,391)	0.21 (95% CI 0.09-0.43)
Prevention of a recurrence or secondary tumor	277,621 (95% CI 168,988-429,690)	0.36 (95% CI 0.22-0.56)	14,854 (95% CI 1,738-54,292)	0.03 (95% CI 0.004-0.12)
Osteoporosis treatment	N/A	N/A	287,100 (95% CI 180,417-433,391)	0.63 (95% CI 0.40-0.96)

¹ Weighted estimate from a sample of 32 women aged 35-79 who report using tamoxifen out of a total sample size of 9,906.

² Weighted estimate from a sample of 46 women aged 50-79 who report using raloxifene out of a total sample size of 5,959.

