CORRESPONDENCE


Mariotto et al. (1) presented unique information on trends in use of adjuvant chemotherapy and tamoxifen for breast cancer in the United States from 1975 through 1999, using data from eight registries of the SEER (1). In their study, information on adjuvant chemotherapy from the Patterns of Care studies was also used to correct the SEER bias due to underreporting (1). We used national population-based Medicare claims data from 1991 through 1996 to study temporal changes in adjuvant chemotherapy administration for breast cancer in women aged 65 years or older who were identified by the 11 SEER registries as having been diagnosed with stage I–IIIA breast cancer during this period (2). The internal validity of Medicare claims information on chemotherapy for breast cancer is good (2,3), and a recent external validation study comparing Medicare claims with medical chart and physician reviews showed a 98% agreement and a kappa of 0.82 (4). In our recent multivariable logistic regression re-analysis that was performed for 30,644 women with stage I–IIIA breast cancer from the 11 SEER registries and adjusted for age (65–69, 70–74, 75–79, or 80 or more years), ethnicity, marital status, cancer stage, tumor size, lymph node status, estrogen receptor status, comorbidity score, and SEER area, women diagnosed in 1996 were statistically significantly more likely to receive adjuvant chemotherapy than women diagnosed in 1991 (odds ratio = 1.28, 95% confidence interval = 1.09 to 1.51). Statistically significant interactions were observed among age, tumor stage, and year of diagnosis. After adjustment for the above variables, the increase in the likelihood of receiving adjuvant chemotherapy was statistically significant in all four age groups for women with stage II breast cancer, whereas for women with stage IIIA breast cancer, the increase was statistically significant only for women who were aged 65–69 or 70–74 years. Mariotto et al. (1) made a similar observation. However, in contrast to Mariotto et al., we found no statistically significant increase over time in use of adjuvant chemotherapy from 1991 to 1996 among older women with stage I breast cancer in any of the four age groups (2).

Age is a strong factor in determining adjuvant chemotherapy use for patients with breast cancer (1–3,5,6), even after controlling for comorbidity and patient and tumor characteristics (2,3). The influence of age was seen even in younger women 20–64 years of age with high-risk breast cancer (e.g., lymph node-positive tumors or lymph node-negative tumors larger than 1.0 cm that are hormone receptor-negative), for whom adjuvant chemotherapy is generally recommended (6). Although randomized trials have shown efficacy of adjuvant chemotherapy in women younger than 70 years, adjuvant chemotherapy has not been found to have an effect on recurrence and mortality in women aged 70 years or older (7).

Despite the lack of evidence about the benefit of adjuvant chemotherapy in women aged 70 years or older, both Mariotto et al. (1) and our group (2) have found an increase over time in use of chemotherapy in these women. One reason for this increase may be that the well-established benefit of adjuvant chemotherapy in women aged 69 years or younger with operable breast cancer may have influenced some oncologists to recommend chemotherapy in older women. Further studies will be needed to determine the benefits of adjuvant chemotherapy in women aged 70 years or older with operable breast cancer.

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1. Editor’s note: SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local non-profit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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The finding of Mariotto et al. (1)—a decline in the use of adjuvant tamoxifen in lymph node-positive postmenopausal women since 1991—is of great interest. The authors suggest that the decline resulted from the recognition of an association between tamoxifen and endometrial cancer in this group of women. However, we suggest that the explanation is more complex. Tamoxifen is associated with only a modest increase in the incidence of endometrial cancer (two to three cases per thousand). We believe that there was much unwarranted publicity about this association, possibly because of two published research findings that came at a time when the evaluation of tamoxifen as the first chemopreventive in breast cancer was being intensely scrutinized. One finding (2) suggested that the endometrial cancer was likely to be of high grade. The other (3) was a laboratory finding that tamoxifen was a complete carcinogen in rat liver.

In the early 1990s, tamoxifen had been used successfully around the world for the treatment of breast cancer for...
nearly two decades. Tamoxifen was known to prevent both mammary carcinogenesis in rodents and contralateral breast cancer in patients (a surrogate for chemoprevention), so the idea that tamoxifen could reduce the incidence of breast cancer in high-risk women was a natural extension of laboratory and clinical observations. The often acrimonious debate about the wisdom of using tamoxifen in well women spilled over into the treatment population, causing some breast cancer patients (and their physicians) to question the safety and efficacy of tamoxifen as a therapeutic agent. Tamoxifen was subsequently listed as a carcinogen, first in California and then by the U.S. federal government. Scientists from pharmaceutical companies competing with AstraZeneca, the manufacturer of tamoxifen, saw opportunities to strongly support new, supposedly less toxic substitutes (that, incidentally, had not gone through extensive clinical testing) for tamoxifen, which further confused women with breast cancer who needed treatment.

Despite the intense media attention to the “bad” rather than the “good” aspects of clinical research on tamoxifen (Fig. 1), tamoxifen-induced rat liver carcinogenesis is now believed to be ratspecific (4). The low risk of both an endometrial carcinoma diagnosis and death in tamoxifen-treated women has been confirmed, and there is evidence that preselection can eliminate susceptible women (5). Moreover, the Oxford Overview Analysis and randomized clinical trials have shown repeatedly (6) that tamoxifen is the most effective single therapy for the treatment of estrogen receptor (ER)-positive breast cancer. The survival advantages obtained from tamoxifen in ER-positive women are superior to those seen with chemotherapy. Indeed, after women complete the recommended 5-year course of treatment, they are protected from recurrence and from contralateral breast cancer for an additional 10 years (6).

These data have important national consequences. In the United Kingdom, where little attention was paid to the negative side effects of tamoxifen and the inexpensive drug was prescribed ubiquitously through the national health service as standard of care, the death rate for women with breast cancer has fallen dramatically (7). By contrast, decreases in the death rate in the United States (which admittedly was initially far lower than that in the United Kingdom) were less dramatic throughout the 1990s (7). How many American lives were lost by breast cancer patients too frightened to use tamoxifen during the “Tamoxifen Wars”? There is now increasing recognition that endocrine therapy, not chemotherapy, provides the major survival advantage for ER-positive patients. The success of tamoxifen, the pioneering endocrine treatment, has spawned a new generation of potentially even safer and more effective endocrine agents for the treatment and prevention of breast cancer.

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RESPONSE

We appreciate the findings and comments of Du, who used a different source of information—Medicare claims linked to the SEER database—to estimate temporal changes in the use of adjuvant chemotherapy for breast cancer and obtained findings that are very similar to ours. He observes that both Mariotto et al. (1) and Du and Goodwin (2) estimate an increase in the use of adjuvant chemotherapy for women diagnosed with breast cancer.

Fig. 1. A time line of the “Good” and “Bad” aspects of the clinical evaluation of tamoxifen that unequivocally demonstrated survival advantages with the use of 5 years of adjuvant therapy. The concerns about an increased risk of low-incidence, high-grade endometrial cancer and the possibility that liver carcinogenesis observed exclusively in rats would result in liver cancer in humans enhanced patient fears that tamoxifen treatment should be stopped.
stages II and IIIA from 1991 to 1996. However, he may have overinterpreted our figures when he says that, in contrast to his results, we showed an increase over time in the use of adjuvant chemotherapy from 1991 to 1996 among older women with stage I breast cancer. Using our model, we estimated that, from 1991 through 1996, the use of adjuvant chemotherapy among women diagnosed with stage I breast cancer at ages 50–69 years and ages 70 years or older increased slightly, from 9% to 11% and from 0.2% to 0.3%, respectively. However, we do not know if these small increases are statistically significant, especially because the number of older women with stage I breast cancer receiving adjuvant chemotherapy is still quite small.

As mentioned by Du, Medicare claims have proven to be an important resource for estimating chemotherapy use (3). Patterns of care (POC) data, which are based on medical record review, contain more accurate information than claims data on first-line therapy from hospitals and treating physicians from a sample of SEER patients. The drawbacks of POC data are that the sample size is small, especially for older patients, and that these data are not available for all years. The SEER-Medicare linked database thus provides a useful complement to the POC data.

In regard to the comments by Jordan and Morrow, we thank them for a plausible and more detailed explanation for the decline in tamoxifen usage observed in our data during the 1990s. Although we do not have data to support their explanation, the timing of the decline does coincide with the debate over tamoxifen endometrial toxicity reports, and we agree that this debate was exacerbated because of a misunderstanding of the role of tamoxifen in prevention and treatment. Better education of physicians and the public has likely led to a reversal of these trends, but we must await evidence from newer SEER studies before we can confirm this. However, it is also noteworthy that tamoxifen is now used only in women with ER-positive breast cancer, which undoubtedly also played a role in its decreased overall usage (4, 5).

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