



**Oral Bisphosphonates and Breast
Cancer — Prospective Results from
the Women’s Health Initiative (WHI)**

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual San Antonio Breast Cancer Symposium (SABCS) is unmatched in its significance with regard to the advancement of breast cancer treatment. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year where published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in breast cancer. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest SABCS meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for breast cancer.

LEARNING OBJECTIVE

- Identify the association between the use of oral bisphosphonates and the incidence of breast cancer in postmenopausal women.

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IN THIS ISSUE:

- **Obesity** associated with increased risk of breast cancer recurrence and death
- **Bisphosphonates** associated with lower risk of developing primary breast cancer
- **Vitamin D** replacement for AI-induced musculoskeletal pain and bone loss

A lot of people remember the historic 2005 ASCO Annual Meeting in steamy Orlando for the last-minute “Breast Cancer Education Session” chaired by George Sledge, featuring the first reports of adjuvant trastuzumab in three major Phase III trials, and the initial positive study of bevacizumab in metastatic disease. However, during that same meeting Rowan Chlebowski reported, with decidedly less fanfare, the initial and some might say stunning results of a randomized trial — the WINS study — demonstrating that “adjuvant” dietary counseling to reduce fat intake significantly lowered the risk of breast cancer recurrence. Five years later, we have two huge ongoing second-generation adjuvant trials in HER2-positive disease and a slew of studies evaluating bev in a number of settings, but the impact of diet and exercise on breast cancer progression has been pretty much ignored despite very similar compelling data in colon cancer.

It is interesting to consider the semi-hysteria that greeted Joyce O’Shaughnessy’s 2009 ASCO plenary talk on the use of the PARP1 inhibitor, BSI-201, in metastatic triple-negative breast cancer when WINS demonstrated a relative reduction of 56 percent in recurrences and 64 percent in deaths in patients with ER/PR-negative tumors, and although we don’t have HER2 assays in this older study, one can assume most were HER2-negative, thus triple-negative.

There are a number of potential explanations for why WINS and other similar data sets are not being followed up in spite of the dearth of current adjuvant trials in HER2-negative breast cancer and colon cancer. Top of the list is lack of industry interest in this type of research, which in my mind sort of means it won’t get done because nowadays the somnolent NCI and maybe misdirected mammography-oriented advocacy groups don’t seem to be executing a whole lot of practice-changing oncology research.

This issue is admittedly complicated, and there is justifiable pessimism about people altering their lifestyles along with the feeling that diet has as much to do with heart disease and other pathologies as neoplasia, thus “not our thing.” However, translational

research can be done to begin to understand how changes to the human internal milieu and the ever-commented-on tumor microenvironment are correlated with nutritional intake and level of activity, and perhaps this will lead us to new or even existing targeted interventions, like insulin growth factor inhibitors, to get the job done.

Fans of our audio work may know how much this gripes me and I am constantly editing out large chunks of recorded conversations with my rants and raves about this issue, but the truth is that the public sector needs to get off its collective rear end and do something about it. In the interim, oncologists on the front lines owe it to their patients with breast cancer to let them know that in addition to surgery, radiation, chemo and biologics there may be something else they can do to further reduce the risk of recurrence.

Next up on the final issue of our 2009 San Antonio 5MJC, an eye-opening analysis from the historic MA17 trial demonstrating a profound reduction in risk of recurrence when an AI is used after five years of tamoxifen in patients who initially were premenopausal.

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Oral Bisphosphonates and Breast Cancer – Prospective Results from the Women’s Health Initiative (WHI)

Presentation discussed in this issue

Chlebowski RT et al. **Oral bisphosphonate and breast cancer: Prospective results from the Women’s Health Initiative (WHI)**. San Antonio Breast Cancer Symposium 2009; **Abstract 21**.

Slides from a presentation at SABCS 2009 and transcribed comments from a recent interview with Rowan T Chlebowski, MD, PhD (12/30/09)

Oral Bisphosphonate and Breast Cancer: Prospective Results from the Women’s Health Initiative (WHI)

Chlebowski RT et al.
SABCS 2009; Abstract 21.

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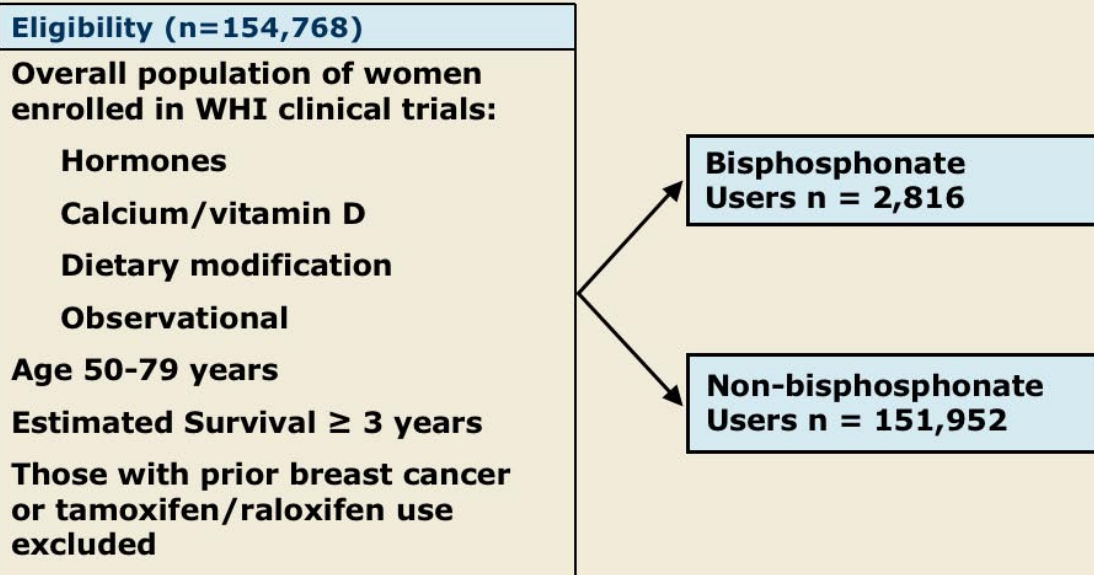
Introduction

- Bisphosphonate administration in metastatic breast cancer has been shown to reduce skeletal related complications (*JCO* 1998;16;2038).
- Results from phase III trials ABCSG-12 and ZO-FAST suggest that bisphosphonate use in the adjuvant setting in breast cancer may lower loco-regional disease recurrence (*NEJM* 2009;360:679, *Oncologist* 2008;13:503).
- Evidence suggests that women with low bone mineral density (BMD) are at a lower breast cancer risk (*Cancer* 2008;113:907).
- **Current study objective:**
 - Assess the relationship between oral bisphosphonate use and breast cancer incidence while controlling for differences in BMD, using hip fracture risk score.

Chlebowski RT et al. SABCS 2009;Abstract 21.

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Bisphosphonates and Breast Cancer: Women's Health Initiative (WHI) Clinical Trials Cohort



Chlebowski RT et al. SABCS 2009;Abstract 21.

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Methods

- Medication use details were collected at baseline and at 3 years for all patients.
- Medical histories were updated annually (observational study) or semi-annually (clinical trials).
- BMD determined by DXA bone densitometry in ancillary study at three WHI clinical centers (n=10,693).
- Five-year risk of hip fracture calculated using algorithm developed in the WHI cohort (*JAMA* 2007;298:2389).
- Hip fracture risk score used to adjust for potential BMD differences between bisphosphonate users and non-users.

Chlebowski RT et al. SABCS 2009;Abstract 21.

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Baseline Characteristics

	Bisphosphonate Users		Non-Bisphosphonate Users	
	N	%	N	%
5 year breast cancer risk (Gail) > 1.7%	1,633	58%	57,581	37.9%
Family history of breast cancer	586	22.1%	26,123	18.2%
Benign breast disease	760	27.3%	30,592	21.3%

All differences, $p < 0.01$.

Types of Bisphosphonate Use:

- **Alendronate = 89.7% (n = 2,527)**
- **Etidronate = 10.1% (n = 285)**

Chlebowski RT et al. SABCS 2009;Abstract 21.

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Breast Cancer Incidence by Bisphosphonate Use

Breast Cancer Type	Bisphosphonate Use		Multivariate	
	Yes (rate/1,000 person-years)	No (rate/1,000 person-years)	HR*	P value
Invasive Breast Cancer	3.29	4.38	0.68	< 0.01
ER-positive	2.56	3.28	0.70	0.02
ER-negative	0.41	0.61	0.66	0.27
Carcinoma In Situ [†]	1.53	0.92	1.59	0.002

* HR = hazard ratio adjusted for age, ethnicity, smoking, alcohol use, physical activity, BMI, mammograms, prior hormone use, calcium, vitamin D, hip fracture risk, Gail risk and stratified on WHI trial randomization arm

[†] Lobular carcinoma in situ tumors excluded

Chlebowski RT et al. SABCS 2009;Abstract 21.

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Conclusions

- Oral bisphosphonate use is associated with a lower incidence of invasive breast cancer in postmenopausal women after adjustment for potential BMD differences.
- The hazard ratios for ER-positive and ER-negative invasive breast cancers among bisphosphonate users versus non-users were similar, although statistical significance was not seen with the ER-negative breast cancers.
- Carcinoma in situ (DCIS) incidence is higher among bisphosphonate users.

Chlebowski RT et al. SABCS 2009;Abstract 21.

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DR CHLEBOWSKI: The impetus for this study was the data from the ABCSG-12 trial, where it was shown that patients who received zoledronic acid had 36 percent fewer breast cancer recurrences than those who did not receive the bisphosphonate.

I thought that I could examine the recurrence risk in the WHI where we have a cohort of about 154,000 women. This study was not a clinical trial. We just tracked patients who took bisphosphonates or not.

In general, low bone mineral density (BMD) is the indication for bisphosphonate use. Women with low BMD have a lower breast cancer risk, and this is probably related to their duration of endogenous estrogen exposure. We controlled for this in our study because we had around 10,000 women who had BMD determinations in substudies. We also had a hip fracture risk score that was validated and published by WHI, which predicted a five-year hip fracture risk without the inclusion of BMD as a factor. The validation of the hip fracture risk score allowed us to feel confident about using it to adjust for potential BMD differences.

When we used the hip fracture risk score to adjust for potential BMD differences, we found that bisphosphonate users had 32 percent fewer invasive breast cancers than those individuals who did not use bisphosphonates. The incidence rate by bisphosphonate use was almost the same for ER-positive and ER-negative cancers. The result was statistically significant for ER-positive breast cancers. It wasn't significant for ER-negative cancers, but the hazard ratio was similar.

An Israeli group conducted a case control study with similar results, which is helpful. They did not control for bone mineral density differences, however.

The use of bisphosphonates in the United States has been increasing and that may provide an explanation for the little shoulder of decrease in breast cancer that was seen beginning in 2001, before a big drop was reported in 2003.

DR LOVE: Where do you stand in terms of using bisphosphonates with adjuvant therapy?

DR CHLEBOWSKI: I believe that the data are pretty good. Charlie Shapiro showed that zoledronic acid prevents chemotherapy-induced bone loss. The Z-FAST study is being conducted in postmenopausal patients and Trevor Powles's data are both in pre- and postmenopausal women. It looks like probably everybody could benefit.

What we are really waiting for are the results of the NSABP clodronate trial and the AZURE trial in which zoledronic acid is the sole treatment variable, in order to see if perhaps contralateral breast cancers will be reduced.

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