



Effect of Obesity on Prognosis After Early Breast Cancer

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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

- Evaluate the influence of obesity on the risk of recurrence and death from breast cancer following adjuvant therapy.

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Consulting Agreements: Amgen Inc, AstraZeneca Pharmaceuticals LP, Lilly USA LLC, Novartis Pharmaceuticals Corporation, Sanofi-Aventis; Paid Research: Lilly USA LLC; Speakers Bureau: Abraxis BioScience, AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Novartis Pharmaceuticals Corporation.

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This program is supported by educational grants from AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc, Genentech BioOncology, Genomic Health Inc and GlaxoSmithKline.

Last review date: February 2010
Expiration date: February 2011

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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Effect of Obesity on Prognosis After Early Breast Cancer

Presentation discussed in this issue

Ewertz M et al. **Effect of obesity on prognosis after early breast cancer.** San Antonio Breast Cancer Symposium 2009;**Abstract 18**.

Slides from a presentation at SABCS 2009 and transcribed comments from a recent interview with Rowan T Chlebowski, MD, PhD (1/15/10)

Effect of Obesity on Prognosis after Early Breast Cancer

Ewertz M et al.
SABCS 2009;Abstract 18

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Introduction

- Obesity, measured by body mass index (BMI, kg/m²), is associated with an increase in the risk of death from breast cancer (*NEJM* 2003;348:1625)
- **Current study objectives:**
 - Examine the influence of obesity on the risk of recurrence or death from breast cancer (BC) or other cause in relation to adjuvant treatment.
 - Determine whether obesity is an independent prognostic factor for recurrence or death from BC.
 - Investigate whether obesity is associated with poorer response to adjuvant treatment.

Ewertz M et al. SABCS 2009;Abstract 18.

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Methods

- Study group identified from the Danish Breast Cancer Cooperative Group (DBCG) database:
 - Study period: 1977 - 2006
 - Patients with complete data on 10-year follow-up: 53,816
 - Patients with data on height and weight: 18,967
- DBCG treatment protocols:
 - CMF, FEC or taxanes
 - Tamoxifen or aromatase inhibitors
 - Trastuzumab
- Statistical methods:
 - χ^2 for association between BMI (<25 versus ≥ 25 ; <30 versus ≥ 30) and other prognostic factors
 - Univariate/multivariate analysis for cause-specific survival and invasive disease-free survival

Ewertz M et al. SABCS 2009;Abstract 18.

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Association of BMI with Other Prognostic Factors and Risk of Recurrence or Death

- Patients with BMI ≥ 25 were associated with the following prognostic factors compared to patients in the reference group with BMI < 25 ($p < 0.0001$ for all):
 - older age
 - postmenopausal status
 - larger tumors
 - more positive lymph nodes
 - invasion into deep fascia
 - Grade III tumors
- Univariate analyses showed:
 - Risk of locoregional recurrence was not related to BMI
 - \uparrow risk of distant recurrence is associated with \uparrow BMI after 3 years of follow-up
 - \uparrow risk of death from breast cancer is associated with high BMI throughout 30 years of follow-up

Ewertz M et al. SABCS 2009;Abstract 18.

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Effect of Obesity on Risk of Distant Metastases

		Adjusted HR*	95% CI	p-value	Test for heterogeneity
BMI 25-30	0-5 yrs	1.01	0.92-1.10	0.85	0.002
	>5 yrs	1.42	1.17-1.73	0.0005	
BMI 30+	0-5 yrs	1.08	0.96-1.21	0.21	0.046
	>5 yrs	1.46	1.11-1.92	0.007	

*Hazard ratio (HR) adjusted for age, tumor size, fascial invasion, nodal status, histology, grade and ER status; Reference group BMI < 25 .

Ewertz M et al. SABCS 2009;Abstract 18.

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Effect of Obesity on Risk of Death from Breast Cancer

		Adjusted HR*	95% CI	p-value	Test for heterogeneity
BMI 25-30	0-10 yrs	1.02	0.96-1.09	0.50	0.01
	>10 yrs	1.26	1.09-1.46	0.002	
BMI 30+	0-10 yrs	1.11	1.02-1.21	0.02	0.06
	>10 yrs	1.38	1.11-1.71	0.003	

*Adjusted for age, tumor size, fascial invasion, nodal status, histology, grade and ER status; Reference group BMI < 25.

Ewertz M et al. SABCS 2009;Abstract 18.

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Conclusions

- Patients with BMI ≥ 25 were older and diagnosed at a more advanced stage of disease compared to patients with a BMI < 25.
- Obesity is an independent prognostic factor for distant metastasis and death from BC.
 - In patients with BC, BMI > 25 is associated with:
 - 42-46% \uparrow risk of distant metastases within 10 years
 - 26-38% \uparrow risk of death from breast cancer ≥ 10 years after diagnosis
- Efficacy of adjuvant therapy appears to be less in patients with BMI > 30 (data not shown).
 - Overall survival adjusted HR (≥ 10 years after diagnosis)
 - HR chemotherapy: 1.77
 - HR endocrine therapy: 1.57

Ewertz M et al. SABCS 2009;Abstract 18.

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DR CHLEBOWSKI: This study was an interesting analysis. It was from a group in Denmark that examined body mass index in a large patient population. The comparison was between patients with body mass index values over 30 and those with values between 25 and 30. Essentially, they were examining obese versus overweight patients.

I believe the picture is emerging that HER2 is one major pathway driving the growth of a tumor. The ER pathway is another. Insulin and its signaling through insulin growth factor (IGF) may be another major driving pathway.

Last year, data from the WHI (Women's Health Initiative) study published in the *JNCI* reported that higher levels of fasting insulin were associated with a doubling in the incidence of breast cancer. The hypothesis would be to try to shut down or to slow down the insulin pathway and remove its potential driving effects. This may be done through drugs, such as metformin, or through lifestyle changes.

Compared to younger, leaner populations — BMI < 25 — those patients with body mass index values between 25 and 30 had a 42 percent increased risk of developing distant metastases within 10 years. Patients with a body mass index value over 30 had a 46 percent increased risk of developing distant metastases within 10 years. This goes along with our old WINS data, in which we demonstrated that a moderate weight loss was associated with 24 percent fewer recurrences.

It appears that there was an effect of obesity on the risk of dying from breast cancer. There was a 26 percent increased risk of death among patients whose body mass index values were from 25 to 30 compared to the reference group. Patients with a BMI value over 30 had a 38 percent increased risk of death.

The area of obesity and physical activity is a field with emerging data. The NCI recently held a conference in Seattle on nutrition and cancer. I believe that epidemiologists feel that the relationship between nutrition and cancer is established and should be discussed in medical practice. Clinicians would like to see a clinical trial. It would be nice to have a randomized trial so that people would fully engage this issue.

DR LOVE: Are any ongoing studies addressing this question?

DR CHLEBOWSKI: Our group will be capturing 500 tumor specimens from the Women's Health Initiative dietary modification trial that targeted dietary fat intake. We will be attempting to categorize ER, PR, HER2 and triple-negative cancer in that population.

Pam Goodwin's trial examining postmenopausal patients receiving adjuvant letrozole was launched. The patients are randomly assigned to a standardized intervention focusing on healthy living versus a lifestyle intervention targeting weight reduction and increased physical activity. However, accrual for that trial is currently on hold.

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