

# Breast Cancer Advisor

BY DR. SILVANA MARTINO

January 2015



Dear Readers,

As we begin 2015, it is time for each of us to renew our commitment to actively participate in maintaining our health and that of our families. Proper diet, regular exercise, weight control, adequate sleep, reduction in alcohol consumption, and cessation of tobacco use are our own responsibility. The new year is a good time to commit ourselves to achieving these goals.

Best regards,  
Dr. Silvana Martino

## BIOGRAPHY

### Dr. Silvana Martino

is the Director of Breast Cancer Research and Education at The Angeles Clinic Foundation in Santa Monica, California. She is board certified in internal medicine and medical oncology. Dr. Martino has specialized in the treatment and research of breast cancer for over three decades. She is a nationally recognized leader in the field of breast cancer. Her body of work has included research in breast cancer prevention, treatments for early breast cancer and metastatic disease. Dr. Martino has conducted and coordinated large national and international studies which have resulted in changing the standard of care worldwide.

DR. MARTINO'S  
CURRICULUM VITAE

## CONTENTS

BIOLOGY BASICS	1
WHAT'S NEW	
GEPARSEPTO; GBG 69 TRIAL	2
THE TNT TRIAL	3
TEN YEAR UPDATE OF STUDY E1199	3
THE ICE STUDY	4
PREVENTION TRIAL IBIS 1	4
THE WINS TRIAL	5
QUESTIONS AND ANSWERS	6

## BIOLOGY BASICS

### WEIGHT CONTROL

The American Society of Clinical Oncology (ASCO) recently published a "position statement" on OBESITY and CANCER. In its first policy statement on this issue, ASCO warned that obesity could soon become the leading cause of cancer in the United States. Further, it stated that it is estimated that by the year 2030, up to half a million cancers in the U.S. will be related to obesity. Considerable research now demonstrates that being obese or overweight is related to (1) developing cancer, (2) increasing the risk of cancer recurrence and (3) reducing survival in cancer patients.

Perhaps the biggest impact that this position statement will make is to elevate this topic from a peripheral, pseudo-scientific issue to the level of "BASIC BIOLOGY." In the past, both the medical profession and the public have understood the influence of weight and diet on blood pressure, lipid (cholesterol) levels

*continued next page*

# The Angeles Clinic FOUNDATION

*The Angeles Clinic Foundation is a nonprofit organization whose purpose is to sponsor and support programs, services, education, advocacy, and research related to cancer. Our goal is to make a difference in all aspects of the lives of people touched by cancer. Your support is important in the fight against cancer and the journey towards a cure.*

**BIOLOGY BASICS continued**

and diabetes. We have not fully appreciated or acknowledged the deep biological effect that diet and weight have on cancer. Nearly three in four Americans are obese or overweight, making this a major health challenge.

The ASCO report cites a recent meta-analysis of 82 studies that collectively included more than 200,000 breast cancer patients. The results demonstrate a 75% increase in mortality among premenopausal women and a 34% increase in mortality among postmenopausal women who were obese at the time of their diagnosis, compared with those who were of normal weight. These results cannot be ignored.

The manner by which obesity leads to both increased incidence and increased mortality from cancer is not fully understood, but several mechanisms are already apparent: (1) obesity increases inflammation, (2) obesity has an influence on hormonal levels such as estrogen, (3) obesity interferes with wound healing, (4) obesity interferes with drug dosing and drug distribution throughout the body, (5) obesity increases post-operative infections, (6) obesity increases the risk of developing lymphedema, and (7) obesity increases the risk of co-morbid conditions such as diabetes and cardiovascular disease. The last point needs to be further stressed as over 50% of non-cancer related deaths in cancer survivors are from cardiovascular disease and diabetes.

The ASCO paper points out that in spite of what is already known about diet and health, cancer survivors are not more likely to be consuming a healthy diet, exercising, or maintaining a healthy weight than are people without a history of cancer. There is a tendency to consider these issues when patients are first diagnosed, but behavioral changes are short lived and patients quickly return to their pre-diagnosis patterns.

The position paper points out that oncologists have traditionally “not taken an active role in weight management for patients and many feel they lack the training or skills necessary to help a patient initiate behavior changes.” I believe this to be correct. Few physicians have any training in the field of nutrition, exercise, or how to inspire and affect behavior changes in their patients. Even physicians who already recognize the value of these aspects of medical care, rarely have personal skills, or routinely recommend other professionals with such skills to their patients. These health aspects have simply not been viewed as part of our responsibility. Yet, we know that patients are more likely to change behavior if it is strongly encouraged by their physician.

The ASCO position paper specifies four critical priorities for addressing the problem of obesity and weight control: (1) increasing education and awareness, (2) developing new physician tools and resources dedicated to the link between obesity and cancer, (3) coordinating and intensifying research efforts, and (4) policy changes to increase access to obesity screening, diagnosis and treatment.

For information on this and other topics on cancer and its management, ASCO has created a patient-centered website—[www.cancer.net](http://www.cancer.net)— that readers will find useful.

**WHAT'S NEW****ADDITIONAL UPDATES FROM THE SAN ANTONIO BREAST CANCER SYMPOSIUM, DECEMBER 2014  
GEPARSEPTO; GBG 69 TRIAL**

This was a phase III, randomized, neo-adjuvant trial comparing weekly nanoparticle-based paclitaxel (Abraxane) with weekly solvent-based paclitaxel (Taxol), each followed by Adriamycin/

*continued next page*

**YOUR SUPPORT**

The **Breast Cancer Advisor** newsletter is funded by donors like you.

Help us keep the content pure, with no outside influence, by donating to The Angeles Clinic Foundation.

Make a donation directly online by clicking

[Donate Now](#)

or mail to: The Angeles Clinic Foundation, 2001 Santa Monica Blvd., #560W, Santa Monica CA, 90404

Your gift to The Angeles Clinic Foundation is fully tax deductible.

**WHAT'S NEW continued**

Cytosan. The primary objective was to measure the rate of pathologic complete response or pCR (no remaining invasive cancer found in the breast and lymph nodes at time of surgery) and to compare toxicity. The patients continue to be followed for disease-free and overall survival data which will be presented at a later date. At the San Antonio meeting, the authors reported a statistically significantly higher rate of pCR with Abraxane versus Taxol (38% versus 29%). A difference was noted in all subgroups of breast cancer, especially triple-negative breast cancer. More toxicity, especially neuropathy was noted with Abraxane.

Other studies in neo-adjuvant and metastatic disease have suggested the possibility that Abraxane is a more effective version of paclitaxel. There has not been a well conducted trial comparing these two agents in the adjuvant setting. The FDA has refused to accept the argument that Abraxane is simply a version of paclitaxel and, therefore, should be accepted in place of Taxol without a direct comparison in the adjuvant setting. Consequently, the use of Abraxane in breast cancer has remained limited.

The present study adds to the body of information on this issue, but again raises the question of how much difference in pCR must be demonstrated between two therapies to expect an improvement in disease-free or overall survival, which are the more meaningful endpoints. Longer follow-up is needed for this particular trial to provide these more clinically meaningful answers.

**THE TNT TRIAL**

This study is a randomized phase III trial of carboplatin compared with docetaxel (Taxotere) in patients with metastatic or recurrent, locally advanced, triple-negative or BRCA 1/2 positive breast cancer. The role of platinum drugs in breast cancer has been debated for several decades. Most have concluded that these agents have little effect in breast cancer. It is in triple-negative and BRCA 1/2 positive patients where, in recent years, there

has been a resurgence of interest in the use of platinum therapy. This clinical trial from the United Kingdom enrolled 376 patients who either had triple-negative disease or were known to be BRCA 1 or BRCA 2 positive. They were randomized to carboplatin or docetaxel. If their disease progressed, they were allowed treatment with the alternate drug. Thirty-five percent of patients had received prior taxane therapy in the adjuvant setting. Forty-three patients were BRCA 1/2 positive. Median time of observation for the group was eleven months.

The results demonstrated that when the entire group was compared, both the response rate and survival were the same between the two therapies. Equal results were seen when comparing the patients who were not BRCA 1/2 positive. However, in the small subgroup of patients who were BRCA 1/2 positive, a significant difference in response rate was observed in favor of carboplatin therapy. A larger study looking at this subgroup alone is warranted to either confirm or refute this observation.

**TEN YEAR UPDATE OF STUDY E1199**

This large, phase III, adjuvant trial conducted by the U.S. Breast Cancer Intergroup was designed to compare the two taxane drugs Taxol and Taxotere when given either every three weeks or once per week. Patients included had either node positive disease or node negative, high risk breast cancer. All patients were initially treated with four cycles of Adriamycin/Cytosan, followed by (1) Taxol every three weeks for four doses, which was standard therapy at the time, (2) Taxol given weekly for 12 doses, (3) Taxotere given every three weeks for four doses, or (4) Taxotere given weekly for 12 doses. The initial results were published at five years of follow-up, and demonstrated that the two best treatments were weekly Taxol and every-three-week Taxotere. Since these two therapies were best, but every-three-week Taxotere was clearly more toxic, and a reasonable number of patients could not tolerate the full program

*continued next page*

**PREVIOUS ISSUES**

You can review all previous issues of the Breast Cancer Advisor on our website at:

[www.theangelesclinicfoundation.org](http://www.theangelesclinicfoundation.org)

click on the NEWSLETTER tab

**WHAT'S NEW continued**

of Taxotere, weekly Taxol was essentially declared the winning therapy and widely adopted for both adjuvant and metastatic disease. The other two therapies, weekly Taxotere and every-three-week Taxol were essentially abandoned.

The patients in this study have been followed long term, with many now being beyond the ten year point. Dr. Joseph Sparano updated the results on behalf of a large group of researchers, myself included. At the 10 year time point, both weekly Taxol and every-three-week Taxotere continue to demonstrate a statistically improved disease free survival. However, overall survival is improved but no longer to a statistically significant level. The weekly Taxol therapy remains statistically significantly better in both disease free survival and overall survival for patients with triple negative breast cancer. Somewhat surprisingly, at this longer time point, none of the four therapies remain significantly better for patients with hormone positive/HER 2 negative breast cancer.

As has been noted in other trials with long term follow-up, these data show that patients with triple negative disease are more likely to relapse during the first five years following a diagnosis. In contrast, those with hormone positive/HER 2 negative disease, are relatively less likely to relapse during the first five years, but demonstrate a more prolonged pattern of recurrence beyond the five year point. These differences are important in providing comprehensive treatment programs for hormone positive patients where management includes long term hormonal therapy.

Additional conclusions based on long term follow-up of patients from E1199 are that women who were obese at the time of diagnosis and African-American women did less well than those of normal weight and non-African American women. Full details of these data will be published in an upcoming manuscript.

**THE ICE STUDY**

This is a study specifically designed for the elderly; a designation

identifying those age 65 and older. In general, the benefit from adjuvant chemotherapy has been demonstrated to be less for an older population than a younger population of patients. Further, older patients are known to experience more toxicity and more side effects. For these reasons, there is a general tendency to treat them less aggressively. This German trial included 1,358 patients age 65 or older with high risk node negative or node positive breast cancer. They were randomized into two groups: one treated with either oral or intravenous Ibandronate (a bisphosphonate) or Ibandronate plus six cycles or capecitabine (Xeloda). The median age of the group was 71 years, with 25% over age 75. Eighty percent had hormone positive disease and most were also treated with hormonal therapy, mostly consisting of an aromatase inhibitor.

At a median follow-up period of five years, the disease free survival and overall survival were the same for both groups. Twenty-five percent of both groups had bone related events such as bone recurrence and benign fractures in spite of receiving a bisphosphonate. The authors concluded that, in general, both groups did well. Further, they saw no role for Xeloda alone as adjuvant chemotherapy even in an elderly population. If patients in this age group are deemed to be at sufficient high risk for tumor recurrence and fit enough to receive chemotherapy, the authors advised that these elderly patients should be treated with more standard chemotherapy regimens.

**BREAST CANCER PREVENTION TRIAL IBIS 1**

Breast cancer prevention remains an important goal both in the U.S. and internationally. During the past 20 years, several studies have been done using hormonal therapies in women at an increased risk of developing breast cancer such as those with strong family histories. The IBIS 1 study is an international trial in high risk women randomized to either five years of tamoxifen or five years of placebo. The initial results of this trial, combined with other similar trials, resulted in the FDA approval of tamoxifen

*continued next page*

**DISCLOSURE**

The information contained in this newsletter is for educational purposes only. It is not designed to diagnose or provide treatment recommendations. Please consult your own physicians for all decisions about your care.

**WHAT'S NEW continued**

as the first drug designated for breast cancer prevention.

Dr. Cuzick presented the results of the long term follow-up of this study. A total of 7,154 high risk women were enrolled. Tamoxifen or placebo were taken daily for five years. Approximately one-half of the women were premenopausal when they entered the trial. One unusual feature of this trial is that the women were allowed to use estrogen replacement therapy along with the study drug. Dr. Cuzick reported that 40 to 50% of participants did use estrogen replacement.

The present results, at a median follow-up of 20 years, continue to demonstrate that the group of women given tamoxifen have a lower incidence of breast cancer. The rates are 7.8% for the tamoxifen group versus 12.3% for the placebo group. The difference is more striking in the second decade relative to the first decade; suggesting, that the effect of five years of tamoxifen persist long term. However, very little benefit has been seen in the group of women who also used estrogen replacement. The benefit appears confined to those who did not.

There continues to be a slight imbalance of endometrial cancers, with more seen in those randomized to tamoxifen. Most of this imbalance occurred during the five years of treatment. There has also emerged an increase in non-melanoma skin cancers in the tamoxifen group. A slight increase in hormone negative breast cancers has been noted in the second decade. No difference in either cardiovascular disease or strokes has been noted.

In spite of a lower incidence of breast cancer in the tamoxifen group, there has not emerged a reduction in deaths from breast cancer in the tamoxifen group. Rather, a numerically higher but statistically insignificantly higher death rate from breast cancer and endometrial cancer has been observed in the tamoxifen group versus those given placebo. This small imbalance needs to be watched closely.

The women in the IBIS 1 trial will continue to be followed for additional long term findings. We applaud the researchers who have conducted this trial specifically because of the fact that long term follow-up continues. Prevention studies by their very nature are difficult and costly to conduct. It is easier for both participants and researchers to move on to other things. Yet, the critical question of long term benefit, survival, and side effects can only be answered with long periods of follow-up.

**THE WINS TRIAL**

The Women's Intervention Nutrition Study was begun in the early 1990s when it was strongly believed by many that dietary fat intake was a probable cause of disease and death around the world. A comparison of fat consumption in Japan versus the U.S. and the U.K. demonstrated that Japan had a much lower intake of fat and a much lower incidence of breast cancer. Based on these observations, a study was designed to test the hypotheses of whether severe fat restriction in postmenopausal women with early breast cancer would reduce breast cancer recurrence.

The WINS study enrolled 2,437 mostly postmenopausal women between 1994 and 2001. Treatment of their breast cancer was selected by their own treating physician and not dictated by the study. The women were then randomized to either remain on their own usual diet or assigned to a dietary intervention group and instructed to reduce fat intake to 15% of their caloric intake for a period of five years. This value was based on the fat intake of the typical Japanese diet. To achieve this low level of fat intake required considerable instruction by dieticians.

The initial results of this study when first presented, demonstrated several interesting observations. Even though weight loss had not been a goal of the study, the group on the low fat diet lost an average of 5.6 pounds. As anticipated, less breast cancer recurrence was noted in the group on the low fat diet. Unexpectedly, this effect was most noticeable in patients who had hormone negative breast

*continued next page*

**HOW TO RECEIVE FUTURE ISSUES**

You may request future issues of this newsletter by e-mailing your request to:

[smartino@theangelesclinicfoundation.org](mailto:smartino@theangelesclinicfoundation.org)

**WHAT'S NEW continued**

cancer. It had been anticipated that perhaps the participants with hormone positive breast cancer would benefit most based on the known relationship of body fat and estrogen production. Other studies looking at fat intake and breast cancer recurrence have failed to demonstrate much benefit. That, coupled with the complexity of reducing fat intake to such a low level, a level not quite achieved by most study participants, discouraged most oncologists from pursuing such a dietary intervention in their patients.

This study lost funding after its initial years and it then became difficult to follow these patients further. The update recently presented by Dr. Rowan Chlebowski is based on death registry statistics and not the entire population of participants. At about 20 years from the start of the study, fewer breast cancer deaths have been observed in the low fat group versus the regular diet group (13.6% versus 17%). However, this difference is not statistically or significantly different.

Again the authors have subdivided the patients based on hormonal status of their tumors. In doing so, among the 748 women with estrogen receptor negative disease, there was a clear reduction in mortality for those on the low fat diet. Median survival was improved by about two years. The difference was even greater for women who had disease that was both estrogen and progesterone receptor negative. No difference was seen for those with hormone positive disease.

Several lessons can be learned from this study: (1) dietary intervention studies are feasible even in a large group of women, (2) reduction in dietary fat content alone may not be optimal for most breast cancer patients, and (3) physical activity and weight loss may be more important life style changes.

**QUESTIONS AND ANSWERS**

(Q) Dr. Martino, can you explain the meaning of “disease free

survival.” Is it always used to mean the same thing?

(A) The term “disease free survival” is an expression used to represent the time between when a person starts on adjuvant therapy for early breast cancer and when some other specified event occurs to that same individual. For example, the person may develop a recurrence of their tumor, they may develop a second breast cancer of the opposite breast, they may die from any cause, they may develop a different type of cancer such as colon cancer, they may voluntarily stop participating in a study, or they may change doctors and provide no further information to those conducting the study. Note that many things can happen and be used as the second time point. Different studies will define which of these events they will include in their definition of disease free survival. Based on their choices, considerable variation can be introduced. This is one of the reasons why different studies will reach different conclusions even when the two studies look the same.

Disease free survival can also be expressed numerically in different ways. For example, it can be expressed as the number of months elapsed between the two time points (start of therapy date and date when the first recurrence was noted). It can also be expressed as the ratio of participants in a study who have remained disease free at a time point such as five years later.

Most adjuvant trials use a definition of disease free survival as a way to calculate how much difference a new therapy must demonstrate over an older standard therapy to declare the new therapy a winner. This difference is also useful in calculating how many participants a study must include for the conclusions to reach a certain level of mathematical statistical significance.

Finally, note that in patients with metastatic or advanced disease, where there is a recognized tumor in their body, the expression disease free survival is not appropriate, as by definition, they are not disease free.

VISIT OUR WEBSITE AT

[www.theangelesclinicfoundation.org](http://www.theangelesclinicfoundation.org)

or call us at (310) 582-7909