

# Breast Cancer Advisor

BY DR. SILVANA MARTINO

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Dear Readers,

In the January issue, I discussed the biological importance of weight control and the fact that many aspects of our health are our own responsibility. I hope you understood that I was very earnest about that idea. However, ideas by themselves are of minimal value unless they lead to personal action. So, what are you doing about it?

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

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## BIOLOGY BASICS

### LYMPHEDEMA

Lymphedema is a swelling that occurs in a part of the body secondary to accumulation of lymphatic fluid or lymph. Lymphatic fluid is a liquid substance produced by cells, which contains multiple substances including various proteins and waste products from the body's metabolic processes. It travels through the body through a system of vessels that parallel blood vessels. Lymph nodes are part of the lymphatic system and function to filter the lymphatic fluid and remove waste. Following this cleansing process, the lymphatic fluid enters the bloodstream. It is a dynamic and circular system that, like blood, covers the entire body. If the lymph nodes or lymph vessels are blocked, fluid accumulates in the surrounding tissues causing a feeling of pressure, heaviness and swelling. It can become painful.

There are rare disorders where the lymphatic system does

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**BIOLOGY BASICS** continued

not develop properly that can result in lymphedema. More commonly, the causes of lymphedema are infection, traumatic injury, tumor, surgical procedures and radiation therapy. Each of these secondary causes can occur in patients with breast cancer. Surgery and radiation are the two more common causes. They each cause lymphedema by causing scarring and obstruction of the lymph nodes and lymphatic channels.

Evaluation of axillary lymph nodes is an inherent part of the management of early breast cancer. Some lymph nodes are surgically removed as part of a lymph node dissection. This procedure has been the major cause of lymphedema of the arm. The more nodes that are removed, the more likely it is that one will develop lymphedema. The development of the sentinel lymph node dissection technique which removes only a few lymph nodes was motivated as a way to decrease the probability of lymphedema. This technique has resulted in a much lower incidence of lymphedema. Patients treated with both surgery and radiation have a higher risk of lymphedema than those treated with only one modality. The amount of surgery and the amount and extent of radiation correlate with the probability of experiencing this complication.

Tumor can directly invade structures and also cause compression. In doing so, it can cause lymphedema. Chemotherapy does not directly cause lymphedema, but the incidence is higher in patients who have received it as part of their therapy program. Hormonal therapy and anti-HER2 directed drugs have not been shown to correlate with risk of lymphedema; although, overweight and obese patients have been noted to be at higher risk.

Lymphedema of the arm in patients with breast cancer can occur at any time. It can be seen during therapy and can also

first appear many years later. In my experience, it is most often the patients themselves who note the problem rather than their doctor. At times the arm is frankly swollen and the diagnosis is obvious. Most often what is noted by the patient are subtle signs such as an ache, or a feeling of heaviness, or simply noting that one's jewelry does not fit as comfortably as it did before. At times, the hand and finger are the only area affected. Patients often fail to recognize this early pattern, and tend to suspect other causes such as arthritis. It is best for all patients to be educated by their doctor and medical team about the various subtle presentations of lymphedema so that the diagnosis is suspected early. The sooner the problem is identified and treated, the more correctable it is. If it becomes chronic, it may no longer be correctable though it can generally be improved.

When lymphedema is first noted or when the degree of lymphedema suddenly becomes worse, one must consider and rule out both infection and tumor as the cause. This is not always easy. Infection can cause not only a swollen arm, but also a red, hot and painful appearance of the arm and chest wall area. The patient may have a fever and have systemic signs of infection. Tumor can also present in this manner, but more commonly simply causes swelling. A physical exam, including measurements and comparison of the circumference of both arms can often diagnose lymphedema. If the diagnosis remains uncertain, scans, ultrasound, MRI or Pet scans may be added to clarify the diagnosis and the possible underlying cause. Lymphatic scintigraphy, a test using a radioactive dye to identify the area of obstruction is available but rarely necessary. Treatment must be appropriate to the underlying cause.

When diagnosed and treated promptly, lymphedema can be managed well. If it is neglected and becomes a chronic issue, it

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**BIOLOGY BASICS continued**

can lead to: (1) extreme swelling where long sleeves cannot be worn as they do not accommodate the arm, (2) pain, (3) severe heaviness of the arm, (4) restricted use of the arm, hand and shoulder, and (5) chronic infections of the arm.

Rarely, patients with lymphedema may develop a malignancy called lymphangiosarcoma.

In the next issue, we will discuss what can be done to prevent lymphedema and treatment options should it occur.

**WHAT'S NEW****STUDY SWOG S0221: COMPARING CHEMOTHERAPY SCHEDULES**

In addition to testing new drugs for the treatment of early breast cancer (adjuvant therapy), some studies have focused on the schedule by which drugs are given. Research has shown that not all schedules of a drug are equally as effective or result in the same side effects. This study, conducted by the Southwest Oncology Group, was designed to test two different schedules of the commonly used drugs Adriamycin/Cytosin/Taxol.

The study was a phase III randomized trial of patients with node positive or high risk node negative breast cancer. Patients were first given either Adriamycin/Cytosin on an every two week schedule for six doses, or they were given a "continuous" schedule of Adriamycin once per week, with Cytosin taken orally daily for 15 weeks. Once this portion of therapy was completed, the participants then received either Taxol once every two weeks for six doses, or Taxol once per week for twelve doses. Each group also received growth factors to maintain an elevated white count. The weekly schedule required a daily injection of growth factors, except on the day of intravenous chemotherapy administration. The two week schedule was

accompanied with one growth factor injection the day after each chemotherapy injection.

The study was overseen by a data monitoring committee who after a period of observation concluded that the two ways of giving Adriamycin/Cytosin gave the same results and advised that all subsequent study participants receive the two drugs at the two week schedule but only for the previously established standard of four doses and not six.

A total of 3,294 patients were entered in the trial. Of these, 2,716 were randomized to both portions of the study. The others received four cycles of Adriamycin/Cytosin every two weeks and were randomized only to the Taxol portions of the study. Results at a mean follow-up of six years have now been published. A trend toward an improved disease free survival and a significant difference in overall survival has emerged favoring the patients who received all therapy at a two week interval. This difference was primarily seen in patients with triple negative breast cancer and not in those with hormone positive disease.

I believe that this was an interesting and needed study to clarify whether the more continuous use of Adriamycin/Cytosin with its more labor intensive growth factor schedule was a better therapeutic option. It turned out that it was not better. It appears that the two week schedule remains the best way to administer these two drugs when used in the adjuvant setting. There is no clear advantage to giving Taxol on a weekly basis in the adjuvant setting. Toxicities were similar but not identical. Decreased white blood count was more common in the weekly Taxol schedule. Allergic reaction, musculoskeletal pain and neurologic toxicity were more pronounced in the two week Taxol schedule. Perhaps for patients who begin to experience these issues, the weekly schedule may offer some advantage.

In summary, I believe that this study confirms that the way we

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**WHAT'S NEW continued**

have been giving Adriamycin/Cytosan—Taxol, specifically on a two week schedule (dose dense) remains standard therapy. This is particularly so for those with triple negative breast cancer.

Reference: Budd GT, Barlow WE, Moore HCF: SWOG S0221: A phase III trial comparing chemotherapy schedules in high-risk early-stage breast cancer. *Journal of Clinical Oncology* 33:58-64, 2015

**PATTERNS OF BREAST CANCER RECURRENCE**

It was recognized many decades ago that breast cancer behaved differently in different patients. Some were cured, others were not. Some had rapidly progressive disease while others had slow indolent disease. Some recurred shortly after surgery while others would recur many years later. Some tumors responded to hormonal therapy while others did not. These observations led to an understanding that the disease was complex. To a reasonable degree, these patterns were clarified when estrogen receptors were identified. It was recognized that, in general, hormone positive disease had a less aggressive behavior pattern than estrogen receptor negative breast cancer. The subsequent identification of the HER2 receptor in more recent times has further clarified breast cancer behavior patterns.

In the 1990s, an important article was published by Saphner and colleagues which captured the long term patterns of recurrence of hormone positive and hormone negative tumors. This publication demonstrated and confirmed several facts: (1) recurrence patterns were clearly different between hormone positive and hormone negative breast cancers, (2) both tumor types had a peak recurrence during the first few years following diagnosis, (3) more hormone negative patients recurred during this initial peak, (4) following this initial peak, both tumor types experienced a decrease in the risk of recurrence during the subsequent years, (5) the subsequent decrease in recurrence rate was most striking for hormone negative tumors and less so for hormone positive tumors, (6) hormone positive tumors continued to relapse at a relatively constant rate for many years,

and surprisingly, (7) after the first five years, it was the hormone positive patients who were more likely to recur rather than those with hormone negative breast cancer.

Saphner's publication was very influential. It was instrumental in helping us understand that for hormone receptor negative patients, the greatest risk was early in their diagnosis but that it was the hormone positive patients who needed to be observed many years for a possible recurrence. These data were influential in the design of subsequent clinical trials. For example, in hormonal positive patients we had to re-consider whether five years of therapy was adequate.

Another critical observation has been made by many researchers in more recent times. In general, patients often do better than expected. This is a welcomed finding, but it has presented a challenge in adjuvant trial design where new therapies are compared to standard therapy. In designing such studies, one first "presumes" based on historical data what the outcome of patients treated with standard therapy will be. Then, one calculates how much better the new therapy must perform to be considered an improvement over standard. In essence, one calculates the minimal difference required. If it is accurate that in general, patients are now doing better, then is it time to update our expectations so that we can more accurately design clinical trials that compare therapies.

These two ideas led Dr. Rachel Cossetti and colleagues from the Vancouver Cancer Center to look at the recurrence patterns and outcomes of breast cancer patients treated in Canada from 1986 to 1992 and from 2004 to 2008, and compare recurrence patterns during these two different time points to see if changes had occurred. They identified 12,336 patients who had stage I, II or III breast cancer where data was available on tumor size, nodes, hormone receptor status (ER) and HER2 status. They then identified 3,589 patients from the first time period

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**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**

and 3,589 patients from the second time period who could be matched based on various parameters including stage, tumor grade, ER and HER2 status. These two groups served as the bases for their comparison.

Median follow-up times were 15.5 years for the first group and 6.1 years for the more recent group. The treatments received by these two groups was different. More patients received chemotherapy in the second group versus the first group. The second group received hormonal therapy for a longer period of time. HER2 directed therapy was used in the second time period but was not available during the first time period.

The primary observation made by these researchers was that when comparing the first seven years of each time period, there were about half the recurrences in the more recent time period than the earlier time period. Meaning, that for all breast cancer types combined, in the more modern era, there has been a decrease in relapses of about 50%. This improvement in the number of relapses was most pronounced for the more aggressive forms of breast cancer; namely, the HER2 positive and the triple negative subtypes. The peak time of relapse for these two subtypes in the more recent group is about one year following diagnosis. Thereafter, the rate of recurrence drops with each subsequent year until year four, with few recurrences thereafter.

Hormone positive patients have a different pattern of relapse. There is a slight peak observable during years 4-5 from diagnosis, but the initial peak of recurrence that was previously experienced by this group has almost disappeared. The pattern of relapse that has emerged for ER positive patients is one of a fairly uniform rate of relapse that persists over time. In fact, beyond five years, the hormone positive patients have a relapse rate that is higher than patients with hormone negative breast cancer.

This article provides important information not only for patients and their doctors; it also provides important data for researchers. It confirms that the outcome of patients with breast cancer has clearly improved over time. Collectively, our therapies have had considerable success. The groups of patients who have had the most benefit are those with the more aggressive forms of breast cancer; HER2 positive patients and even those with triple negative disease. These data confirm that the pattern of recurrence is different for different tumor subtypes. The thrust of our efforts for those with more aggressive forms of breast cancer (ER negative), must be a concentration on the high relapse rate seen early in the course of their disease. If patients get through this period, their probability of relapse thereafter is low and their prognosis is good. For patients with more indolent hormone positive disease, the relapse pattern suggests that they remain at risk of relapse for a long time though at a modest rate. With this group, long term therapy may be much more important. Perhaps, they need lifelong therapy.

The improvement in outcome from studies such as this one, should become the basis for designing subsequent adjuvant trials and these more current data should serve as the basis for establishing statistical expectations for new therapies.

The overall observations made by Cossetti and colleagues remind us that we are moving forward in both our understanding and treatment of early breast cancer. This progress is confirmed by national and international data that demonstrates an improvement in survival both in the U.S. and internationally.

**References:**

1. Saphner T, Tormey DC, Gray R: Annual hazard rates of recurrence for breast cancer after primary therapy. *Journal of Clinical Oncology* 14:2738-2746, 1996
2. Cossetti RJD, Tyldesley SK, Speers CH: Comparison of breast cancer recurrence and outcome patterns between patients treated from 1986 to 1992 and from 2004 to 2008. *Journal of Clinical Oncology* 33:65-72, 2015

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**WHAT'S NEW** continued**IBRANCE APPROVED FOR METASTATIC DISEASE**

The U.S. Food and Drug Administration (FDA) has given “accelerated” approval to the drug palbociclib marketed under the name of IBRANCE in combination with the hormonal drug letrozole (FEMARA) for women with metastatic or locally advanced breast cancer. This indication is restricted to women who are postmenopausal and have hormone receptor positive and HER2-neu negative breast cancer.

Approval was based on a multicenter trial involving 165 patients randomly assigned to either letrozole or the combination of letrozole and palbociclib. The primary goal of the study was to demonstrate an improved progression-free survival between the two treatments. The combination therapy was demonstrated to be statistically and clinically superior to therapy with letrozole alone. A longer period of observation is necessary to see if this difference will translate into a better overall survival for those treated with both drugs.

Palbociclib is given daily for 21 days with a seven day rest period each month. It is a new type of drug classified as a “cyclin-dependent kinase inhibitor.” It functions to block the cell cycle which is the underlying mechanism by which cells replicate themselves and divide.

It is clear that we have expanded our understanding of the biology of hormone dependent breast cancer. At a time when we were fearful that we had no new hormonal agents to discover, we have realized that the hormonal systems of the body function in a manner that is dependent on many other systems. These other systems can be exploited and used to our benefit as well. The already approved drug everolimus (AFINITOR) is another such example.

**QUESTIONS AND ANSWERS**

(Q) Dr. Martino, My grandmother has metastatic breast cancer. I have been accompanying her to a support group near her home. I have heard from many other patients who also attend the support group that very little research is being done for metastatic breast cancer. Why is that?

(A) I agree that research has not resulted in a major level of improvement in the survival of patients with metastatic disease. Whether this is the result of “not enough” research versus the fact that, by the time a tumor is metastatic, its nature is aggressive and resistant to available therapies is the question. It is because of the inherent aggressive nature of cancer as it becomes more advanced and a desire to prevent metastatic disease that so much attention has been focused on finding effective therapy for early disease. In that setting, we have been more successful.

New drugs are first studied in patients with metastatic disease. Those that prove most effective in this setting are then studied in early disease (the adjuvant setting). When therapies are studied in the early setting, the intent is to increase cure rate. When studies are done in metastatic disease, the intent is different: it is to slow the disease, prevent symptoms and prolong survival.

Because metastatic disease has proven to be so difficult to cure, a decision was made several years ago that the goal should be to turn metastatic cancer into a chronic disease. That is, a state where one would continue to use some type of drug therapy to keep the disease under control as is done for high blood pressure or diabetes. I do not completely agree with this decision. I believe that “cure” should remain the major goal even in metastatic breast cancer.

I don't know if I have answered the question to your satisfaction. I do agree that we have not done enough and that a new emphasis needs to be brought to bear on this issue.

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