

Dear Readers,

Some of you have asked if the Breast Cancer Advisor can be added or linked to your own website so that you can make it available to your own patients or service groups. The answer is yes. Please let us know if we can assist you in this process. Our goal is to make the Breast Cancer Advisor available to anyone who has an interest in the treatment of breast cancer.

Best Regards,  
Dr. Silvana Martino



# Breast Cancer Advisor

BY DR. SILVANA MARTINO • July 2012

## BIOLOGY BASICS

Thus far in this section, I have primarily dealt with topics pertaining to patients with early breast cancer. During the next several months, I will shift my focus to issues that pertain to metastatic disease. Metastatic disease refers to disease that is apparent in areas other than the breast and the lymph nodes in the nearby axilla (under the arm pit).

In the March 2012 issue, I discussed how your doctors will watch you once your adjuvant therapy is completed. Again, the reason for watching you is for the purpose of looking for evidence of tumor recurrence or metastasis. A recurrence can occur in any part of the body, but certain areas are more typical for breast cancer. These are: (1) the same breast if you have had breast sparing surgery; (2) lymph nodes; (3) skin; (4) bones and the bone marrow; (5) lungs; (6) liver; (7) the brain and its surrounding structures; (8) the covering of internal organs causing fluid surrounding the lungs or obstruction of the urinary system or the intestines; (9) the ovaries or uterus; (10) the eyes; (11) the stomach and (12) anywhere else. Please note that I have not included the opposite breast in this list. It is extremely uncommon for breast cancer to spread to the opposite breast. I have seen this happen on a few occasion as part

*continued next page*

### WHAT'S INSIDE

BIOLOGY BASICS . . . . . 1

### WHAT'S NEW

POSSIBLE CAUSE OF DRUG FAILURE . 2

CARPAL TUNNEL SYNDROME IN  
POSTMENOPAUSAL WOMEN TREATED  
WITH EXEMESTANE (AROMASIN) . . . . 3

QUESTIONS & ANSWERS . . . . . 4

### NEW RESEARCH

BRCA1 AND BRCA2 METASTATIC  
BREAST CANCER . . . . . 5

### MEMORIES OF A

GREAT TEACHER . . . . . 6

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## Biology Basics continued

of a more wide spread process. Cancer in the opposite breast is much more likely to be a second independent event.

Our present understanding is that for a recurrence to be noted, some portion of the original cancer must have remained in the body at the time of original diagnosis and treatment. This does not necessarily mean that it was left in the breast. It is more likely that the remnant had relocated itself prior to the diagnosis and was simply residing somewhere else. The bone marrow is suspected to be a favorite place for this process. It is believed that these cancer cells can lie dormant for many years, presumably waiting for some signal to trigger them to begin to regrow. We do not know what these triggers are. As these cells begin to divide and multiply, their size increases to a point where they cause a problem and become apparent on x-rays.

In the next issue, I will discuss how to proceed once a recurrence is suspected.

# WHAT'S NEW

## 1. Possible Cause of Drug Failure

Thus far the antiangiogenesis drugs such as bevacizumab (Avastin) and sunitinib (Sutent) have not been demonstrated to be of great value in metastatic breast cancer. Though there does appear to be some tumor shrinkage at first; subsequently, the tumor appears to behave in a more aggressive manner. These observations have led researchers to try and figure out why this is so.

Dr. Max Wicha from the University of Michigan Comprehensive Cancer Center and his colleagues have provided a possible explanation. Using mice with breast cancer, they observed that in animals treated with these drugs, the tumors developed large areas where the cells were not getting enough oxygen (hypoxia). They did not see these large areas in tumors from mice

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*“When you get into a tight place and everything goes against you, till it seems as though you could not hang on a minute longer, never give up then, for that is just the place and time that the tide will turn.”*

*— Harriet Beecher Stowe*

## 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

## What's New continued

when these drugs were not given. They also observed that in these areas of low oxygen, the cells activated a particular biological pathway (the wint pathway), which is believed to stimulate cancer stem cells. Stem cells are the cells within a tumor that are believed to be most aggressive. These cells then result in subsequent tumor growth that is even more aggressive than before the antiangiogenesis drugs were administered.

Please keep in mind that though this explanation is logical, it is an observation in animals. Whether it also applies to breast cancers in humans is not yet known.

Reference: Max Wicha, et al. Proceedings of the National Academy of Sciences (DOI:10.1073/pnas.1018866109).

## 2. Carpal Tunnel Syndrome in Postmenopausal Women Treated with Exemestane (Aromasin)

In postmenopausal women with early hormone receptor positive breast cancer, treatment with the aromatase inhibitors (Arimidex, Femara and Aromasin) has become standard therapy. Each of these drugs has been shown to give better results when compared to tamoxifen. There are also less blood clots and gynecological side effects with this class of hormones. However, each of these drugs has been shown to increase joint and muscle aches which for some are severe and result in discontinuation of treatment. An uncommon side

effect that has also been noted with these agents is the development of carpal tunnel syndrome. Carpal tunnel syndrome results from compression of one of the nerves that controls the function of the hand. It results in pain and weakness of the hand and fingers. Surgery may be required to correct it.

The occurrence of this syndrome was evaluated in a large study comparing Aromasin and tamoxifen. A total of 4657 postmenopausal women with early breast cancer who had received 2-3 years of tamoxifen and who had not experienced a recurrence were treated with either continuing tamoxifen to complete a total of 5 years or were switched to Aromasin for an additional time period to achieve a total of 5 years of treatment. The entire group was observed for many events including breast cancer recurrence over time, survival, and side effects. Carpal tunnel syndrome was reported in 73 women, 66 on Aromasin and 7 on tamoxifen. Though the overall number of events is relatively small, the difference between the two groups is obvious. Similar findings have also been reported with the other two commonly used aromatase inhibitors Arimidex and Femara. The specific mechanism by which this and other musculoskeletal symptoms occur with these drugs is not clear, but we presume it must

be related to the decreased estrogen levels that occur in the body when these drugs are used. It is not clear at this time whether this problem corrects once these treatments are discontinued.

There has been some suggestion that the degree of side effects experienced with hormonal therapy may have a correlation with how well the drug is working and with how much anticancer effect a person can expect. This idea has been suggested for both tamoxifen and the aromatase inhibitors. Various studies have tried to make this connection but the results have been inconsistent. It is not certain that in fact, the more side effects you experience the less likely you are to have a recurrence.

This study reinforces the connection between carpal tunnel syndrome and treatment with the aromatase inhibitors. Be aware of this, and bring any symptoms to the attention of your oncologist.

Reference: Mieog, JSD, Morden JP, Bliss JM, Coombes RC, van de Velde CJH. Carpal tunnel syndrome and musculoskeletal symptoms in postmenopausal women with early breast cancer treated with exemestane or tamoxifen after 2-3 years of tamoxifen: a retrospective analysis of the Intergroup Exemestane Study. *Lancet Oncology* 2012; 13: 420-32.

***Carpal tunnel syndrome results from compression of one of the nerves that controls the function of the hand. It results in pain and weakness of the hand and fingers.***

# QUESTIONS & ANSWERS

**Q** Dr. Martino, my doctor recently changed my chemotherapy. It includes the drug Cytoxan which I am to take as a tablet. I was told to take it early in the morning but I find that I tend to forget it. Should I not take it at all if it isn't morning?

**A** The reason why it is best to take Cytoxan tablets in the morning is that the drug is broken down in the body and then removed with your urine. If it sits in your bladder for a long time, and especially if you have not taken a lot of fluids to increase your urine volume, it can irritate your bladder and cause it to bleed. This can usually be prevented by avoiding taking the drug late in the day when its products are more likely to remain in your bladder overnight. So the idea is to avoid taking it late in the day.

If you find that you truly do forget taking it on a frequent basis, then please tell your doctor. The drug cannot help you if you don't take it. Cytoxan is available intravenously, and this may be the more reliable way for you to take it.



**Q** Dr. Martino, do you believe in alternative medicine? My doctor wants me to stay away from alternatives and insists that they are all a waste of money. I have friends who take a lot of supplements and have told me that they feel better.

**A** Your question is so general that I am not sure how to answer you. Alternative medicine is a large category of treatments. I think it is fair to say that those of us trained in traditional Western medicine have minimal to no training on the many alternatives that are now available. All of us, whether we practice standard medicine or an alternative version assume that the brand of medicine we chose to learn and practice is the best. We also tend to fear and hold suspect what we do not understand. Part of our limits is based on what modern medicine considers the scientific method of research and investigation. Within Western medicine, we have a set way that a new therapy has to be studied for it to be accepted and approved by the FDA and the medical community. Alternative medicine is not held to this same principle, primarily because most such therapies do not require FDA approval. Consequently, they simply can be sold to you and me with minimal evidence that they are effective in humans. For many physicians, this lack of rigor makes all alternatives suspect. Personally, I would favor that the same rules be applied to any therapy or supplement that is used for medicinal or preventive purposes. I do suspect that there are alternatives that are valuable. I also believe that there are many that are simply well advertised and are of little benefit. Until the

same standard of research and proof are applied to both categories, we will all be guessing.

Let me add that both standard and alternative medicine are "big business." In my experience, alternative medicine is not inexpensive as many would like to imply. I think that companies that produce alternative therapies should be held to equal standards of proof of benefit. It is their responsibility to demonstrate benefit of their brands and compare them to other therapies.

**Q** Dr. Martino, I have recently heard that the drug Neurontin can help with hot flashes and helps you feel better. Should I be taking it?

**A** Neurontin (gabapentin) is an anti-seizure medication. It has several other uses including reduction of hot flashes. This effect has been known for some time. It can be sedating, so it can also help you sleep. For this reason, many of us prescribe it to be taken at night. A recent study demonstrated that a low dose of 300mg per day improved "physical well-being" at 4 and 8 weeks of use. A larger dose of 900mg per day was found to reduce hot flashes but had little effect on well-being. There are other alternatives for the treatment of hot flashes, so you should discuss this with your own doctor to choose what is best for you.

E-mail your questions to:  
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# NEW RESEARCH

## Highlights of a New Study for BRCA1 and BRCA2 Metastatic Breast Cancer

With the development of gene expression array technology, the variability of breast cancer has become increasingly apparent. The clear recognition that breast cancer is not one disease but rather a group of diseases has resulted in the ability to identify specific mutations. These mutations can become specific targets for therapy. One such target is the inherited mutations in the BRCA1 and BRCA2 genes that are estimated to be responsible for about 5% of breast cancers seen in both men and women. Tumors with these mutations have specific inabilities to repair DNA damage caused

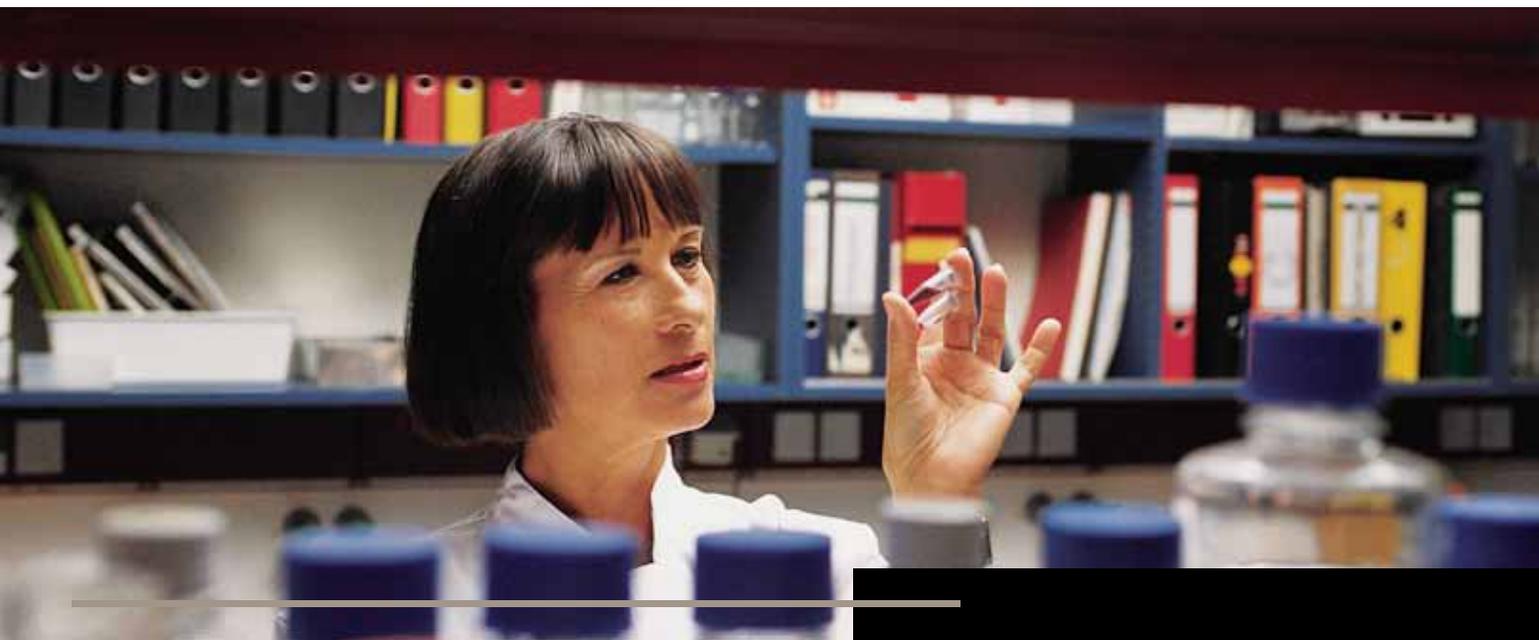
by certain chemotherapy drugs. These cancers rely more on the PARP (poly ADP-ribose-polymerase) system to repair damage that has been done to them. Drugs known as PARP inhibitors interfere with this repair mechanism resulting in cancer cells being more vulnerable to chemotherapy and a better outcome for patients.

Because patients with these mutations are relatively uncommon, studies in those with BRCA1 and BRCA2 mutations require considerable effort and coordination. To find enough of these patients, one needs to go beyond the U.S. and perform international trials. Such a study sponsored by Abbott Laboratories is just getting underway.

*To find enough of these patients, one needs to go beyond the U.S. and perform international trials. Such a study, sponsored by Abbott Laboratories, is just getting underway.*

The study is for both men and women who are BRCA1 or 2 positive and have metastatic breast cancer. It will be carried out in approximately 80 centers around the world including the U.S. It will study the PARP inhibitor Veliparib in combination with two chemotherapy programs, temozolomide or carboplatin and paclitaxel. A third group will receive carboplatin and paclitaxel, but will be given a placebo rather than the PARP inhibitor. This third group serves as the control group receiving what is now a standard therapy. The third group is critical as it is by comparison to this group that we can figure out if the Veliparib adds any real value or only adds toxicity.

Since patients with these mutations are relatively uncommon, it is important that everyone is aware of studies like this so we don't miss the opportunity to figure out what treatments might be best for them. Any of you who are in this category or know of others who are, I would encourage you to ask your oncologist about referring you to a center conducting this and other similar studies.



# MEMORIES OF A GREAT TEACHER

During my medical school training, I was particularly impressed by the medical oncologists who taught me. They struck me as being the most knowledgeable, thorough, committed and the most kind of all who taught me. I was often assigned to their service and came to admire them greatly. One in particular stands out in my mind. He was particularly gentle and loving with his patients. To me, he was the ideal doctor. He was what I hoped to become.

About 10 years after my training, while at the airport, I ran into one of his partners who informed me that my teacher had given up the practice of oncology and was now teaching at one of the medical schools. I was shocked by this news. How could the man I idolized so much have given up the care of patients at such a young age? He was the last person I would have expected to do such a thing.

His partner, who had also been my teacher, realized that I was too young to understand. He looked at me and said, "Silvana, it is those who are most dedicated and who give the most that burnout the first. It is because he was so giving to his patients that he needed to get out." I pondered his words for some time, as I felt that he was trying to impart wisdom to me. As I have grown older and with experience at being an oncologist, I have come to completely understand what was not clear to me then.

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