

# Breast Cancer Advisor

BY DR. SILVANA MARTINO

May 2015



Dear Readers,

The annual meeting of the American Society of Clinical Oncology (ASCO) will take place in Chicago from May 29 to June 2, 2015. I will be attending the meeting and will discuss important findings from

that event in the June issue of The Breast Cancer Advisor. You may also want to be attentive to the public media during those dates as they also will cover selected ASCO presentations.

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

### WHAT CAUSES CANCER?

Do we know what causes cancer? Not really! We do know that certain factors are related to the probability of developing certain cancers. For example, we know that there is a relationship between family history, certain genetically inherited factors, smoking, alcohol use, certain viruses, diet, obesity and the risk of developing cancer in one's lifetime; but, this has never explained everything. So, what else is there?

A possible answer may have been recently provided by work performed by Cristian Tomasetti, PhD, and Bert Vogelstein, MD, from Johns Hopkins University and published in the journal *Science* (2015;347:78-81). To understand their work, one must realize that a basic concept of how cancer occurs has changed in recent years. For decades, it was believed that each of the cells in the body could become cancerous. Once that event

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*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

took place, that first cancer cell would divide and become two identical cancer cells. They, in turn, would also divide and create two essentially identical cancer cells. By this continuous and persistent process, eventually enough cells would grow to create a mass, with each cell having the capacity for further growth and division.

Though this concept has not been totally discredited, a different idea has greatly replaced it. The prevailing belief is that within each population of cancer cells, there is a small group of cells making up only a few percent of the total that have the ability to divide and create the cancer process. These special cells have been named “cancer stem cells.” It is believed that perhaps the reason why many cancer therapies fail is because though they may kill many cancer cells, they are not always successful at killing off the entire stem cell population. It is this failure that leads to regrowth even following what appears to be successful therapy.

The recent paper by Doctors Tomasetti and Vogelstein has proposed an origin for the cancer stem cells. Like cancers, normal organs such as the lungs, liver and others, have normal stem cells that are always present. The purpose of these normal stem cells is for organ growth and for repair. They are a normal and necessary part of the life process. Some organs have a higher proportion of stem cells than other organs. In addition to the actual number of stem cells that an organ has, the rate of division of the stem cells is different among different organs. For example, the large intestine (the colon) has stem cells that divide more frequently than does the brain.

These two researchers examined 31 normal human organs and enumerated the number of stem cells in each as well as the rate at which the stem cells divided in each organ. This information

was correlated with the average life span of the U.S. population, to then calculate the number of stem cell divisions that would occur in each organ during an average life span. They then correlated this with the known incidence of cancers of these 31 organs in the U. S. population. Their results demonstrated that there is a close correlation between the stem cell number and divisions in an organ and the incidence of cancer in that organ. The explanation to this relationship is that as a normal stem cell divides, it is subject to errors or mutations (an average of three mutations per cell division). These mutations are passed on to the new stem cells. Some of these mutations may be trivial and of no consequence, but some may be vital and turn the normal stem cell into an abnormal cancer stem cell. The more divisions that occur within an organ, the more likely it is that critical mutations will occur and/or accumulate leading to this conversion.

What is the significance of this work? It suggests important possibilities; most importantly, it suggests that the process of cancer is inherent in our organs. Their data suggest that about 65% of cancer risk is at this level. This has been coined the “bad luck” factor by the public press, as it suggests that there is nothing that you and I can do about it. It is a risk of cancer inherent in all people simply as part of the process of living.

Some may favor this fatalistic interpretation. Does this research imply that prevention strategies are of no use against such odds? The authors acknowledge that this may be a logical conclusion. However, at least one third of cancer risk is not explained by their analysis. Perhaps this is the portion that can be influenced by changes in behavior such as diet, exercise, alcohol consumption, tobacco use, etc. The authors acknowledge this, and advise that stronger efforts should be directed towards early diagnosis for most cancers and for the general population rather than only for

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**BIOLOGY BASICS continued**

those viewed as being at “high risk.”

The results from this work did not include risk estimates of either breast cancer or prostate cancer. Apparently, the authors were unable to quantify the information on stem cells for these two tissues.

My personal interpretation of this work is that it may be correct and it may provide a new model for how cancers begin. However, as with all new ideas in science, it needs to be replicated and confirmed by others. If that is accomplished, it may serve to focus our attention on the nature of the mutations that naturally occur and understand which are meaningless versus those that can lead to the development of cancer stem cells from normal tissue stem cells. We may then figure out how to alter these steps in ways that we cannot even imagine now.

**WHAT'S NEW****NO BENEFIT FROM AVASTIN IN HORMONE TREATED PATIENTS**

Most breast cancers are hormone positive (estrogen or progesterone receptor positive), and various hormonal therapies are used for their management. Resistance to hormonal therapy is common and, therefore, ways to prevent or reduce hormonal resistance is an important area of clinical research. A type of therapy proposed for this purpose has been the use of antiangiogenesis drugs such as bevacizumab (Avastin). These agents work primarily by interfering with the blood supply to cancers. There is considerable preclinical data suggesting a close relationship and a dependence between this mechanism and hormonal properties of cells. Therefore, a combination of these two types of therapies in patients with hormone positive breast cancer seemed reasonable.

Dr. Miguel Martin and colleagues from both Spain and Germany reported the results of a clinical trial using this combination in the March 2015 issue of the Journal of Clinical Oncology (33, No 9, March 20, 2015, 1045-1052). The study was a multicenter, open-label, randomized, phase III study, comparing the hormone letrozole (Femara) at its standard dose of 2.5 mg per day, versus the combination of letrozole plus Avastin at 15 mg /kg of body weight every three weeks until either disease progression or the occurrence of some unacceptable toxicity. The primary objective of the study was to compare the interval from the date of randomization to the two treatments to the date of disease progression. Overall survival between the two groups was also measured. The study was conducted between the years 2007 and 2011. A total of 380 patients with hormone positive, metastatic breast cancer who were receiving their first hormonal therapy for advanced disease were enrolled. Six patients did not receive treatment and were excluded from analysis. Thirty-seven patients, 21 in the hormone alone group versus 16 in the combination group were treated with the hormone fulvestrant (Faslodex) rather than Femara.

After about two years of observation of these patients, the researchers calculated that the difference in outcome between the two treatment groups was not significantly better to endorse the combination of the hormonal therapy plus Avastin rather than the hormonal therapy alone. Further, there were considerably more serious side effects with the combination. This included eight patients treated with the combination who died either during therapy or shortly thereafter, and in whom it was judged that the therapy was the probable cause of death. No toxicity related deaths were observed in the hormonal treatment alone group.

As our readers know from other data that have been reported in prior issues of The Breast Cancer Advisor, the drug Avastin

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**WHAT'S NEW continued**

and similar drugs whose underlying mechanism is based on the principle of interfering with blood supply to tumors have provided primarily negative results in the treatment of breast cancer. Though initial results when Avastin was combined with chemotherapy were very promising, many subsequent studies have failed to demonstrate an advantage to this family of drugs. Though this has been a serious disappointment, it serves to remind us that premature data can at times be misleading. It is important to repeat small studies and to allow drugs to be well investigated before we reach conclusions.

**INTERVAL CANCERS**

The intent of screening mammography is to identify cancers prior to their becoming clinically apparent. To achieve this, women without symptoms have been advised to obtain routine mammography starting at ages 40 to 50. In some countries the mammograms are performed yearly and in others at two year intervals. Breast cancers found on screening mammograms are called screen detected cancers. Some breast cancers, however, are found between screening visits and have been termed "interval cancers." Within this category, there are cancers that were simply missed on the last screening mammogram and also cancers that even on review, were not apparent on the prior films. Over the years, several researchers have observed that cancers that fall into the category of interval cancers are more aggressive. The general opinion has been that these cancers are probably faster growing than cancers identified on routine screening.

Dr. Johanna Holm and colleagues reported on a group of interval cancers identified from 2001 to 2008 from a cancer registry in Stockholm, Sweden. The results were published in the *Journal of Clinical Oncology* (33, (9), March 20, 2015, 1030-1037). Screening mammography was performed at 18 month intervals in women ages 40 to 50, and at two year intervals for

women between the ages of 50 to 69. Their study population included 4,091 women diagnosed with invasive breast cancer. Of these cancers, 2,844 (70%) were diagnosed on a screening visit and 1,247 (30%) were diagnosed in the time period between screening mammograms and were considered interval cancers. Of the interval cancers, 791 (63%) were diagnosed in the second year after mammographic screening.

They then obtained pathological information about all of the cancers including factors such as: tumor size, nodal involvement, hormonal status, HER2 status and tumor grade. Additionally, they graded the patient's mammograms by the degree of breast density seen on the mammogram films. Following these analyses, their data demonstrated that family history of breast cancer, increased breast density, low BMI and current use of hormonal replacement therapy (HRT) were more common in women with interval breast cancers.

When comparing features of biological aggression of the breast cancers, their data demonstrated that it was primarily in women who did not have dense breasts on mammograms that a clear difference between screen detected and interval detected cancers was found. The interval cancers were more aggressive with larger size, higher grade, more nodal involvement, more likely to be HER2 positive and more were triple negative cancers. However, in women who had dense breasts on mammography, the biological features of the interval breast cancers were quite similar to the biological features of screen detected cancers, with the exception of tumor size and estrogen receptor status. They also reported that when comparing interval cancers based on time since the last screening mammogram, interval cancers detected within a year of the last screening mammogram were not more aggressive than those detected after 13 to 24 months. What can we conclude from this information? This report confirms that there are clinical features such as family history

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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 use of hormonal replacement therapy that increase the probability of having an interval cancer. It also confirms that in general, interval cancers have a different biology than cancers found on screening mammography. They are likely to be cancers that are larger, grow faster and have a worse prognosis. Whether more intense screening such as more frequent mammography, the addition of ultrasound, or MRI might diagnose them at an earlier stage is unclear. It is likely that they inherently have more aggressive features irrespective of when they are diagnosed. That this more aggressive biology of interval cancers is more apparent in breasts of low mammographic density is a bit surprising. It is known that increased mammographic density is a marker of increased breast cancer risk and also that it decreases detection rate. Perhaps within the population with more dense breasts there are simply a higher percent of missed cancers that are not truly interval cancers and retain a more typical biology.

I anticipate that others will look at this aspect of breast density and interval cancers and either support or refute these observations.

**A NEW WAY TO RECEIVE NEULASTA**

A common side effect of most chemotherapy drugs is to decrease the white blood cell count. The result of this, is an increased risk of fevers and infections. To help reduce the probability of these complications, the drugs Neupogen and Neulasta are often administered along with chemotherapy. These products are generally injected under the skin the day after chemotherapy. There are many years of experience with these products. They have proven to be quite effective.

A new way to administer Neulasta has been recently developed by Amgen. It is marketed as the "On-Body Injector for Neulasta." This formulation delivers the standard dose of Neulasta through a small cannula via a small box that adheres to the skin. Its

primary advantage is that it can be applied by a nurse in the doctor's office on the same day that chemotherapy is given. In this manner, it avoids a second visit to the clinic the day after chemotherapy administration specifically to receive Neulasta. The applicator containing Neulasta can be placed either on the back of the arm or on the abdomen. Twenty-seven hours after it is applied, it will then administer the dose of Neulasta over a period of 45 minutes. The patient can observe the applicator to see that the injection has been completed and then simply peel the applicator off of their body. Because the adhesive is made of an acrylic material, those with an allergy to acrylic or latex will not be able to use this system.

I anticipate that this will be a useful product. For many patients, it will reduce the number of visits to the clinic. It does require some involvement and judgement on the patient's part. The system communicates its status with beeps and color messages that a patient must understand. There is a risk that the drug may leak around the injection site and not all of the Neulasta will be administered to the patient. Some patients may not welcome the necessary involvement from them. One must also learn to not have electronic devices such as a cell phone near the delivery system. Nevertheless, for many patients it will prove to be a welcomed option.

You may wish to discuss this option with your doctor. You will also find a lot of information about this product online and from Amgen, who at present is the only company that has this delivery system for Neulasta.

**QUESTIONS AND ANSWERS**

(Q) Dr. Martino, My mother was recently diagnosed with early breast cancer and is receiving chemotherapy. She gets chemo every two weeks. Her doctor told her she would need four treatments. She is tolerating the therapy pretty well. The problem is that she only sees the nurse when we go to the office where

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**QUESTIONS & ANSWERS continued**

she is being treated but not the doctor. She was told that he would see her at the end of her therapy, but not until then. Is this unusual? My mother and our whole family feel that the doctor should see her each time she gets a treatment. How can he know it's working if he does not see her? Are we asking too much?

(A) I do not believe that you are asking too much. I suspect that your mother is probably receiving a standardized chemotherapy program where the entire program is planned by her doctor at the beginning. However, many of us like to see our patients at the time of each treatment as there are often adjustments that need to be made to deal with issues of tolerance and side effects experienced by each patient. It may be that your mother's doctor knows his nursing staff well and feels that they have enough experience to be able to handle most issues that might arise and notify him of any issues that require his level of expertise. Many patients develop strong bonds with the nursing staff and do not feel a need to see the doctor each time they receive their chemotherapy. However, some patients only feel comfortable when their questions and issues are handled by their doctor. If your mother and your family fall in this category, I would advise that you make the doctor aware of it.

(Q) Dr. Martino, I have been diagnosed with stage IV breast cancer and I have received my first cycle of chemotherapy. I am scheduled to receive the second cycle in a few days. I was told that I would lose my hair, but so far very little has come off. Does this mean that the chemo is not working?

(A) No, it does not mean that your chemotherapy is not working. Since you do not specify which chemotherapy drugs you are receiving, what doses and the schedule of administration, I cannot be certain of how likely it is that you will lose your hair. Chemotherapy drugs are not all the same in the likelihood of causing this side effect. Some programs cause only a gradual

thinning of hair, while others are more likely to cause total loss. The larger the dose given, the more likely it is that hair loss will occur. Even with programs that are prone to causing severe hair loss, the amount and timing of hair loss is not the same for all people. Often, one will experience most of the hair loss with the first dose, but for some, most of the hair loss will occur after cycle two. There is a reasonable degree of variability with all side effects. The key point that I want to make, however, is that there is no direct correlation between amount of hair loss and effectiveness of chemotherapy.

(Q) Dr. Martino, I am on chemotherapy and I also get Neulasta injections after each dose of chemotherapy. I develop a lot of bone pain from the Neulasta. My oncologist has had me try pain medications, anti-inflammatory drugs and even anti-allergy medications, but nothing has really helped me. Should I just stop the Neulasta? I can't tolerate much more of this.

(A) As you know, Neulasta and similar products work by stimulating the bone marrow to produce white blood cells. Many patients experience varying degrees of bone pain. For most it is mild. For some it can be severe and at times debilitating. It sounds like you and your doctor have already tried the usual remedies, but with little benefit. A few other things that you can try are to reduce the dose of Neulasta. This must be monitored by your blood counts to see that the dose is still adequate, however. You can also try using Neupogen which can be given daily. This is a lower concentration and may be easier for you. It also gives your doctor the option to monitor your counts and only give you the number of daily injections necessary to achieve control of your white cell count. Ultimately, you and your oncologist may need to change your chemotherapy program or the dose and schedule at which your present therapy is given so that perhaps you can avoid the use of these products all together. I suspect that your oncologist is aware of all of these options and can discuss them with you.

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