Breast Cancer Advisor

BY DR. SILVANA MARTINO

August/September 2015

Dear Readers,

With this issue, the Breast Cancer Advisor begins its fifth year of publication. I wish to express my gratitude to all of our faithful readers for their questions, comments and interest during the past four years.

Beginning with this issue, you will notice certain changes. The Angeles Clinic and Research Institute (the original corporate sponsor of The Angeles Clinic Foundation) will be our new sponsor. Subsequent issues will be published every other month. All prior issues will remain available on both The Angeles Clinic Foundation and The Angeles Clinic and Research Institute websites.

BIOGRAPHY

Dr. Silvana Martino

Dr. Martino is board certified in internal medicine and medical oncology. She has specialized in the treatment and research of breast cancer for over three decades. Dr. Martino is a nationally recognized leader and educator 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

TELOMERES AND CANCER

I do not recall when I first heard the idea or who was giving the lecture; it was many years ago. "Normal cells have a set number of times that they can divide, but cancer cells can continue to divide forever; they are immortal." I was struck both by the terror of this statement but also by its potential. Cancer cells knew something that normal cells either did not know or had forgotten. Though my job was to find ways to destroy cancer cells, was there not something that we could learn from these cells? Immortality struck me as an impressive attribute. Nature, at least in the form of a cancer cell, knew how to accomplish this feat.

The accuracy of the assertion that normal cells are only capable of a set number of divisions and that cancer cells have no limit is now less certain and may turn out to be only an approximation. Both the concepts of stem cells and of cell differentiation (cells

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BIOLOGY BASICS continued

committed to a specific function) have suggested that it is a more complex biological issue than first believed. The identification of structures called telomeres located at the ends of chromosomes have demonstrated a potential mechanism that controls the number of cell divisions that are possible for each cell.

As a reminder, the process of cell division, which is the basis for growth and repair, involves the process of each cell dividing into two identical daughter cells. In preparation for this process, each cell must duplicate its genetic material (DNA) so that at division, half will go to each new daughter cell. This process is complex and subject to error and to loss of genetic material. The ends of each chromosome are particularly vulnerable. Telomeres are special pieces of DNA positioned at the end of each chromosome and function to protect the chromosomes from losing bits from their ends. They also stop chromosomes from sticking to each other at their ends. A common way to pictures chromosomes with telomeres at their ends is to visualize a chromosome as a shoelace. The plastic portion at the end represents the telomere. With each cell division, a portion of telomere is lost and the telomere becomes shorter. When a critical length is reached, it appears that the cell can no longer divide and prepares to die. In this manner, telomeres control longevity and cell death.

Initially it was believed that telomere length was predetermined. However, it is now known that telomere length can be altered, resulting in both reducing or increasing the length. The enzyme telomerase has been identified as a mechanism by which the length of telomeres can be increased. Most adult human cells (somatic cells) have very little telomerase. It is found in fetal tissues, adult germ cells and cancer cells. Telomerase has been found to be 10-20 times more active in cancer cells than normal cells. If telomerase activity were turned off in cancer cells, they would also undergo shortening of the telomere and cell division would be limited. Learning how to manipulate both the telomere and telomerase systems are presently an active area of research.

In addition to the telomere length being influenced by the telomerase enzyme, it also appears that external stimuli can influence its length. In this respect, both increased stress level and behaviors that reduce stress level have been found capable of affecting the length of telomeres.

The idea of cellular immortality holds particular interest for other fields of medicine besides oncology. The fields of longevity and regenerative medicine have become a popular and lucrative business. Can the aging process be slowed down? Can we look younger? Can we delay the onset of disease? Can we live longer? Though at present much of these fields of medicine (both traditional and alternative) are hype, I suspect that in time some real biological understanding will come from them which may have wide applications.

WHAT'S NEW

IMMUNOTHERAPY DEMONSTRATES ACTIVITY IN TRIPLE-NEGATIVE BREAST CANCER

Triple-negative breast cancer (estrogen/progesterone hormone negative and HER2-negative) is an aggressive variant of breast cancer for which there is no available targeted therapy. Its treatment is primarily with chemotherapy. Some countries other than the U.S. have also approved Avastin for its use. However, these approaches are not particularly effective. Triple-negative disease does appear to be more immunogenic than

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WHAT'S NEW continued

other versions of breast cancer. It contains higher levels of programmed death-ligand 1 (PD-L1) expression and contains more tumor infiltrating lymphocytes. For these reasons, there is great interest in investigating immunotherapies for the treatment of triple-negative breast cancer.

At the recent annual meeting of the American Association of Cancer Research (AACR), Dr. Leisha A. Emens from Johns Hopkins Kimmel Cancer Center in Baltimore, presented preliminary results from a phase I study of the investigational agent MPDL3280A, an engineered anti-PD-L1 antibody that interferes with the binding of PD-L1 to PD-1 and B7, believed to restore antitumor T-cell activity and improve T-cell priming. This therapeutic agent has been developed by Genentech. The study included 54 patients with metastatic, triple-negative disease. Eighty-five percent had received at least four previous therapies, most participants were of good performance status and 69% had PD-L1 positive disease. They were treated with various doses of MPDL3280A.

Dr. Emens presented preliminary results involving 21 patients with PD-L1 positive disease who were evaluable for both efficacy and side effect analysis. Within this group, two patients achieved a complete response and two others experienced a partial response. Three of the four patients were still responding at the time of her report, so she was unable to provide the final length of time of tumor control.

Sixty-three percent of patients experience at least one drug-related side effect. The most common side effects reported were fever, fatigue, nausea and loss of appetite. Most side effects were mild. One patient experienced a severe inflammation of the lungs. Two patients died. Their cause of death is still being investigated to determine if it was due to the experimental therapy. Overall, these preliminary results are felt to be promising.

A global, randomized, phase III study has been planned where MPDL3280A will be combined with Taxol as front line therapy in patients with metastatic, triple-negative breast cancer.

In general, breast cancer has been viewed as a tumor that is not particularly immunogenic, so the expectations of success with immunological agents has been modest. However, it now appears that breast cancers are not all the same in this respect. The demonstration of activity with immunological drugs is very encouraging.

HORMONAL BASIS FOR MALE BREAST CANCER

Breast cancer in men is uncommon. It represents one percent of all breast cancer cases. Because of its rarity, its biology and treatment have been difficult to study. Genetic risk factors such as family history of breast cancer in both female or male relatives and a relationship to BRCA gene mutations have been established. Other risk factors are less well identified. Some studies have suggested a relationship with obesity, lack of physical activity, hormone use and diabetes. Other studies have reported a higher risk association with gynecomastia (enlargement of the male breast) as well as with Klinefelter syndrome; both circumstances where excess estrogen relative to androgens (male hormones) are found.

Much of what is known about breast cancer has been derived from observations and research done in women with breast cancer. It is from this large body of work that the relationship of estrogen as a key component of breast cancer development was determined. Whether breast cancer in men is also influenced by estrogen levels, whether it is under the influence of male hormones or whether a ratio of these two is the key factor remains uncertain.

To obtain more information on various biological and clinical aspects of male breast cancer, an international consortium

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PREVIOUS ISSUES

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WHAT'S NEW continued

called the Male Breast Cancer Pooling Project was established. A recent report from this group published in the June 20, 2015 issue of the Journal of Clinical Oncology has shed some light on the possible hormonal underpinning of breast cancer in men.

Dr. Louise A. Brinton from the National Cancer Institute in Bethesda, on behalf of global collaborators, identified 101 men with breast cancer who years prior to their breast cancer diagnosis had blood samples taken and stored. In addition, they identified 217 matched controls (men without breast cancer who were otherwise similar clinically to the men with breast cancer), who also had blood samples stored. The blood samples were used to measure levels of both male and female hormones.

The average age of blood draw for the 101 men who later developed breast cancer was 51.6 years and was 50.9 years for the 217 matched controls. The mean age at the time of diagnosis for those who developed breast cancer was 66.9 years. The analyses of data obtained from these participants demonstrated that a family history of breast cancer was more common in the men with breast cancer versus the control group. They did not find a significant difference in body-mass-index (BMI) or in history of diabetes between the two groups. Interestingly, the men with breast cancer were less likely to be smokers but more likely to report alcohol use.

Measurement of hormonal levels demonstrated the following: (1) In general, androgens-male hormones, were not related to breast cancer risk, although there was a slight increase in risk associated specifically with elevation of testosterone levels. (2) Breast cancer risk was most associated with elevated levels of estradiol-a female hormone. (3) Breast cancer risk was not associated with the female hormone estrone. (4) Various ratios of estrogens and androgens did not predict further breast cancer risk. (5) The findings were the same whether the diagnosis of breast cancer occurred within or after ten years from the procurement of the blood sample.

The primary limit of these data are the fact that these conclusions are based on only 101 men with breast cancer. However, we need to recognize that identifying such a group of men for whom blood samples existed from years before their diagnosis is a difficult task. The proposed influence of estrogen on male breast cancer is biologically plausible and of a magnitude similar to the effects of estrogen on post-menopausal women. From these data, it appears that androgen levels are less influential relative to risk of breast cancer. Another limit of these data is the lack of details about the type of breast cancer seen in these men, though most would be expected to have hormone positive, HER2-negative disease. Whether the role of estrogens is similar in all of the breast cancer variants cannot be determined from this study.

ALTERNATIVE MEDICINE RESOURCE

I am often asked questions about vitamins and various supplements that are sold for cancer prevention and/or treatment. Though there is much salesmanship, there is only limited scientific data involving these products. A branch of oncology named INTEGRATIVE ONCOLOGY has developed with the purpose of doing research and providing knowledge with a scientific basis regarding these products. Most oncologists, myself included, have limited training in this field, and patients often have to seek other sources of information about these product.

Barrie R. Cassileth, MS, PhD, is Chief of the Integrative Medicine Service and Laurance S. Rockefeller Chair in Integrative Medicine at Memorial Sloan Kettering Cancer Center, in New York. The Memorial Sloan Kettering Cancer Center has developed a free website—www.mskcc.org/aboutherbs—that contains information regarding herbs, vitamins, minerals, and other dietary supplements as well as unproven anticancer treatments. This website may be useful to both medical professionals and patients. It is regularly updated with new information. A mobile application is also available.

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DISCLOSURE

QUESTIONS AND ANSWERS

(Q) Dr. Martino, my mother is 78 years old and believes that she is too old to need mammograms. Is that true?

(A) First of all, I am assuming that your question refers to mammograms done on a routine basis in the absence of symptoms (screening mammograms), rather than a mammogram done because the person has symptoms suspicious of breast cancer (diagnostic mammograms).

I do not agree with your mother that her age alone is a reason to not have a screening mammogram. However, recent debates about this issue have confused many women. For many years in the U.S., recommendations for screening mammography did not include an upper age limit above which mammograms were not advised. More recently, as the entire premise of screening mammography has come under review and pressure, some authorities have suggested that in "older" women, mammography should not be done yearly on a routine basis, but should be individualized. What does that mean? It is meant to convey the concept that each woman should have a discussion with her doctor about her risk of developing breast cancer and based on that, a decision should be made about when and how frequently to do mammography. Inherent in this is a decision as to whether the woman's overall health is such that if she needed therapy for breast cancer, she is well enough to tolerate it and that she would want to be treated. In essence, it is an educated calculation of her life expectancy.

My advice is that you encourage your mother to have a discussion with her own doctor and that together they reach a decision as to whether she falls in a category where a screening mammogram is no longer of benefit.

(Q) Dr. Martino, I come from a family where many women have had breast cancer. I have been tested myself and carry the BRCA 2 gene. I have chosen to have bilateral mastectomy and will soon have my ovaries and tubes removed. I want to test my two daughters who are ages 14 and 12 to find out if they have the gene as well. My husband feels that they are too young and that we should wait until they are older. I do not feel comfortable waiting. When they are older they may decide not to do it in time and then I will have missed the opportunity.

(A) Though I can appreciate your deep concern for your daughters, I agree with your husband. Though there have been reports of girls under 18 developing breast cancer, it is very uncommon. The question is whether, even if you knew that your daughters had inherited the BRCA gene, there is something that you and they would do about it right now? They are considered too young to undergo any of the known preventive maneuvers such as hormonal therapy, or bilateral mastectomy or oophorectomy. They are also considered too young to perform screening mammography or MRI. You have to decide what value the knowledge would have for them right now. Also, keep in mind that with time and as your daughters get older, the testing will continue to improve and they may be better served in the future. Finally, consider whether the decision of what to do for them should they carry a high risk gene is one that you want to make for them, rather than allow them to make their own decisions on this matter.

You do not state whether you have any sons, but I would like to remind you that if you do, they are equally as likely as your daughters to inherit the BRCA genes.

GUEST WRITER

There are many times in a physician's life when patients become your teachers. The article that follows is exactly such an occasion. From what I had been told by the patient, I suspected that her enlarged lymph nodes were likely to contain recurrent cancer. However, one cannot guess at a diagnosis based on history, physical findings and scans alone. A biopsy was necessary to

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GUEST WRITER continued

confirm the suspected diagnosis. The pathology report was a surprise and an experience that I had not dealt with before. Please enjoy the experience as described by the patient herself.

WHO KNEW THE POWER OF A TATTOO?

By Dawn Younani

As a 12-year, stage 2B breast cancer survivor (3 out of 8 positive nodes), I thought I knew just about everything there was to know about breast cancer. Following bilateral mastectomies and reconstruction, I was treated with six rounds of Adriamycin and Taxotere, before undergoing seven weeks of radiation. Until a few weeks ago, I would proudly show off, raising both my arms above my head, never once having felt the effect of the mastectomies except for, of course, that never-ending feeling of trying to take off that tight bra after a hard day's work – you know, the one you can't take off?

Last year for the holidays, my children asked what they could get me as a gift. I suggested a tattoo; I had always wanted one on my shoulder. I do have one on my foot and one on my breast that I had done for my 10-year anniversary as a survivor. This time I decided on a beautiful hummingbird that was awash with water colors in blues, greens, yellows, and reds would be just perfect.

Several weeks ago I was called in by my oncologist, who told me that my CEA count was elevated and although he waited and ran it again, the level was up even higher. He suggested that I have a PET/CAT scan, which I did immediately. To my surprise, I received a call a few days later telling me that I had a 2.3 cm node in my left axilla and that the radiologist's impression was that it was a malignancy. Because of the size of the "tumor/node," it was suggested that I have it removed immediately. After being told over and over again how it only takes one cell to travel away from home (to spread or metastasize), I made the decision to have the surgery right away.

I am a trooper, a writer, an actor, and a daydreamer, but most of all I am a fighter and so I decided to continue on this journey with the same optimistic outlook I had the first time around. Don't get me wrong, I don't think there is anything funny about cancer, but I have travelled this far with laughter and grace and I was prepared to be no different the second time around. The day following surgery my doctor called to make sure I was taking my pain medication and said that she was sorry that she had "beat me up" in the operating room. I remember thinking to myself that although I was surprised that I couldn't raise my arm, that things would fall into place and I would once again be on the mend. My surgeon asked me to see a doctor who specialized in treating lymphedema, and I quickly made an appointment.

As I undressed in the doctor's office, I couldn't imagine what she would say upon examining me and I was "gob-smacked" when she said to me, "this isn't a malignant tumor, it's from the tattoo on your shoulder!" She said she was 100% positive and gave me a course of treatment, which, to my chagrin, included wearing a compression sleeve. All the way home I questioned her findings. How could it be from the tattoo on my shoulder, when I tattooed my entire breast just two years earlier as a celebration? Sure enough, she was right. The pathology report came back and the tumor was benign. It was as though the lymph node recognized the ink as a toxin and, doing what a lymph node is supposed to do, it gathered everything up. In fact the tumor was, what I have been told, a beautiful color of lavender.

While I always seek my own doctor's advice and everyone, in my opinion should do the same, if you've recently had a tattoo, are planning on getting one, or know someone who might, give them a "heads up" to speak with their personal physician prior to doing so. What started off as a $150 tattoo for me is now about the most expensive tattoo around town ~ I can't lie though, it's beautiful!