Dear Readers,

As summer comes to an end and the weather cools down, I encourage each of you to spend more time outdoors. Throughout most of the U.S., the trees are already beginning to change the color of their foliage; a reminder of the beauty that nature provides. Take advantage of it.

Best regards,
Dr. Silvana Martino

BIOLOGY BASICS

SCREENING MAMMOGRAPHY—HOW OFTEN?

Mammography is performed for one of two reasons: either as a screen for a woman who has no symptoms or, as a diagnostic procedure for either a woman or a man with symptoms. The ordering physician must specify one or the other of these two choices when they order a mammogram. Performing diagnostic mammography is generally not a procedure that is argued since it is a symptom such as a palpable mass that prompts the performance of the exam. The rules for doing a screening mammogram on the other hand, are a moving target. Whenever we think we have answered this question, some new information comes along to make us rethink our answer. This leads to considerable uncertainty on the part of the ordering physician and even more uncertainty on the part of women. Why is there so much confusion?

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Though we screen one person at a time, the concept of screening for a disease like breast cancer really has to do with the effect of the screening process on a large population. The real question that is addressed is whether the group as a whole does better, not necessarily whether an individual does better. The primary outcome that is generally measured is the group’s survival.

It is commonly assumed that screening, by potentially finding disease at an earlier time point, will automatically lead to a better survival for the group. This is not always true. It would be true if all breast cancers were the same, and if all breast cancers grew and spread in an orderly pattern such that they would grow at a constant rate and spread only when they achieved a certain size. This is not the way the process works, however. A slow, somewhat more predictable growth rate and pattern may be typical of some hormone positive, HER2-negative breast cancers. It is probably not true of HER2-positive and triple negative disease. The biology of breast cancer is diverse and generally not easily predicted. It is believed that many if not all breast cancers spread early in their course, so finding them in the breast when they are relatively small does not mean that they have not already started to spread.

It was once thought that tumors spread first to the neighboring lymph nodes in the area of the armpit before they spread to other parts of the body. This is no longer believed to be the case. Tumors can spread to various parts of the body simultaneously; or, first to distant locations and then the nodes. For all of these reasons, finding a tumor when it appears to be small in size in the breast does not always correlate to preventing death from the disease; and therefore, improving the survival of either the individual or the group.

For many years in the U.S., screening mammography was strongly urged as a yearly exam for all women starting at age 40. This was never a universal rule. Many other countries followed different recommendations. Some countries began at age 50. Others did mammography at two year intervals. Still others, stopped mammography at an upper age such as 70. These variations exist primarily because not all studies of screening mammography have demonstrated a clear improvement in survival. Particularly when different age groups have been evaluated, many studies have suggested that not all obtain a clear improvement. This has been particularly true for both younger and older women.

Yearly mammography for the general population of women starting at age 40 and continuing without a clear upper age limit was the recommendation in the U.S. until 2009. That year, the U.S. Preventive Services Task Force proposed that women from age 50 to 74 perform mammography every two years. Younger and older women were advised to discuss mammography schedule with their physicians. These recommendations caused considerable controversy and have yet to be accepted by all experts.

More recently, another idea has been brought into this discussion. This idea was first recognized by the late Dr. John Wolfe, a radiologist from Detroit, Michigan, who noted that some women had dense breasts on mammography. This observation led to a recognition that not only did density make mammographic readings more difficult as tumors could hide more easily in dense breasts; but he recognized that women with increased breast density developed more breast cancers.

Dr. Wolfe’s observations were ignored for many years. During the past decade however, this concept has gained considerable scientific support. Presently, half of the states in the U.S. have legislation that requires an assessment of breast density on...
mammography. Further, this information must be included in the written report with advice that the ordering physician discuss this finding with the patient. The specific purpose is to recognize the increased breast cancer risk and decide if further imaging is necessary.

Though this is a step forward, studies have shown that the language used in most mammography reports is often not at a level that many women will understand. The language describing mammographic density is not yet standardized and there is considerable variation across the country.

A study supported by the National Cancer Institute and recently published in the Annals of Internal Medicine describes the creation of a new tool that includes mammographic density in predicting a woman’s breast cancer risk. Based on this new predictive model, the authors were able to divide women into different risk groups. From this exercise, they then suggested the frequency of screening mammography that was most appropriate. Specifically, women over the age of 50 with dense breast tissue who have higher than normal risk of breast cancer based on this new model (less than 1% of the population), should have annual mammograms. For most women who are at average risk and have low breast density, the model suggests that death rate from breast cancer would be the same whether they had mammography every two years as has been already recommended, or even every three years. The every-three year schedule resulted in less follow-up procedures, including less benign biopsies.

The practice of performing screening mammograms based on risk assessment is in use in several European countries. Observations from these countries appear to demonstrate that this reduces over-diagnosis and identifies more missed cancers. Whether the U.S. is ready to move in this same direction seems likely.

WHAT’S NEW?

NEW STUDY IN BLACK WOMEN WITH BREast CANCER

African-American women are not more prone to developing breast cancer, but once they do, their outcome is worse. This is particularly so in younger women. Why black women have a worse prognosis has been debated for several decades. Some have argued that the reasons are probably social and economic suggesting that African-Americans are less trusting of the medical profession, more prone to the use of “home remedies,” less likely to adhere to recommended mammography schedules, less likely to see a doctor when they first note a symptom, less likely to accept therapy, and less able to afford expensive medical care. Though it is likely that some of these assumptions are correct, it is unclear whether they explain everything.

It was recognized over 20 years ago that African-American women with breast cancer had a higher proportion of hormone negative tumors. Following the discovery of the HER2-positive breast cancer subtype, it became apparent that the more aggressive triple negative variant of breast cancer was more frequent in black women. Some studies have shown that even when treated with the same protocol, African-American women do less well.

A recent study from Massachusetts General Hospital Cancer Center using data from women with early breast cancer (stage 1 to 3) collected between 1988 and 2013 as well as tumors submitted to The Cancer Genome Atlas Project from 2010 to 2014, demonstrated that tumor samples from black women differed in several respects from tumors obtained from white women. A greater number of black women had tumors that harbored TP53 mutations. Black women had tumors that demonstrated more genetic heterogeneity (variability). Also, among the subgroup with triple-negative tumors, more black women had basal-like and mesenchymal stem-like tumors than found in white women.

PREVIOUS ISSUES

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These and other observations have led to the conclusion that for some reason(s), as a group, black women in the U.S. have a less favorable prognosis once they are diagnosed with breast cancer. The National Cancer Institute has launched a new breast cancer study called The Breast Cancer Genetic Study in African-Ancestry Populations. This will be a large cooperative study including many institutions and research groups throughout the country. Data from 20,000 black women with breast cancer will be studied. The initial emphasis will be on genetic and other biological aspects of breast cancer with a comparison to black women without breast cancer. Subsequent comparisons will be with tumors from women of European ancestry. In addition to biological parameters, social and environmental factors will also be studied.

This should be a fruitful line of research; and hopefully will shed considerable light on our understanding of breast cancer in the African-American population who have not fully shared in the improvements in breast cancer outcomes that have occurred during the past few decades.

EXPECTATIONS AND SIDE EFFECTS

An interesting study has been reported by researchers from the Breast Cancer Centre at the University of Marburg, Germany. A group of 111 women treated for early breast cancer who were scheduled to start adjuvant hormonal therapy with either tamoxifen or an aromatase inhibitor were questioned about their expectations of side effects that might be caused by the recommended hormone. They were questioned at three time points; before starting therapy, at three months, and at two years. At the start of the trial, 8% said they expected no side effects, 63% expected mild side effects, and 29% stated that they expected moderate to severe side effects.

The researchers reported that at the end of two years, their data demonstrated that adherence to the hormonal therapy was associated with both an expectation of side effects at the beginning of the study, and was also associated with a report of side effects at the three month time point. Of patients with an initial low expectation of side effects, 87% were still taking their hormonal therapy at two years. In contrast, of those who prior to the start of therapy expected more side effects, only 69% were still taking the drug.

The side effects reported by the women were typical of side effects known to be caused by these hormonal drugs and included: joint pain (71%), weight gain (53%), and hot flashes (47%). However, the women also reported symptoms that are not generally attributed to their medications including, back pain (31%), breathing problems (28%), and dizziness (26%).

The authors concluded that one’s expectations influence the side effects that are experienced. This has an effect on the likelihood that one will discontinue taking the medication. This in turn, has an effect on the probability of disease control and tumor recurrence. They are now conducting further studies to identify how these expectations might be modified so as to encourage patients to complete their planned therapy schedule.

My own clinical experience is in keeping with the observations reported in this study. I have often felt that to a reasonable degree, I could predict which of my patients would have a difficult time with almost any therapy that I prescribed, and which would be less likely to report side effects. Expectations do seem to matter. This is probably further proof of the “placebo effect.” It is also my opinion that the manner used in presenting possible side effects to a patient probably also matters. At present in the U.S., a physician must make each patient aware of the likely and unlikely side effects that may occur. It is encouraged that this be done not only verbally but also in a written form. “Full disclosure” is the goal. Often, a patient is required to sign acknowledging that they have been made aware of and understand all of the potential side

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

effects. It has not always been so. In the past, both the physician and often the family considered which possible side effects to convey to the patient. This was based on what they believed the patient could handle. It is not entirely clear which of these two approaches serve the patient best.

NIPPLE-SPARING MASTECTOMY

Nipple-sparing mastectomy procedures are becoming increasingly popular due to the superior cosmetic results obtained. The reconstruction looks more “normal” and women have more of a feeling that they look as they did prior to their surgery. The concern with this procedure has been the fear that one is leaving more breast tissue behind, and that cancer recurrence or a new breast cancer is more likely to occur than with a traditional mastectomy. There has been particular concern with this issue when the mastectomy is done as a preventive measure (prophylactically) in a woman with a BRCA1 or BRCA2 mutation. In this setting, the intent is to remove essentially all of the breast tissue. There is concern that some remaining breast tissue is left under the skin of the breast and particularly under the nipple and areolar complex.

It has become increasingly apparent that many surgeons are technically capable of removing the necessary breast tissue. It requires an understanding of cancer biology, skilled hands and experience. In my personal clinical experience, not all surgeons are equally as capable of doing this procedure. However, there are an increasing number of surgeons who meet these criteria. In spite of this fact, there remains considerable concern regarding the safety of this procedure in those at high risk of developing breast cancer due to a genetic predisposition.

Dr. James Jakub, a breast surgeon at the Mayo Clinic, Rochester, Minnesota, reported their experience with this procedure at the 2016 American Society of Breast Surgeons Annual Meeting. He stated that the use of nipple-sparing mastectomy at the Mayo Clinic has increased considerably in the past years. In 2009, only 8% of mastectomies performed spared the nipple and areolar complex. By 2014, this number had risen to 30%.

Dr. Jakub reported on 204 women who carried the BRCA1 and 144 women who had the BRCA2 mutation. This group underwent 551 prophylactic nipple-sparing mastectomies at nine institutions from 1968 to 2013. All the mastectomies were prophylactic; however, 145 women had a single breast removed prophylactically following a diagnosis of either a new or previous cancer in the opposite breast. The remaining 203 women had bilateral prophylactic mastectomies.

At a median follow-up of 34 months, none of the women who had bilateral nipple-sparing mastectomy had developed breast cancer. There were seven deaths from breast cancer, but all were in women who had a concurrent or previous cancer in the opposite breast at the time of their prophylactic surgery. Five other deaths occurred in the group, but were described as being unrelated to breast cancer.

This report joins other similar reports describing small samples of women who have had prophylactic mastectomies for a variety of reasons. The follow-up approaching three years is short, and longer follow-up is required to provide a greater level of comfort. Nevertheless, I believe that there is a growing body of evidence that nipple-sparing mastectomy, when performed in well-chosen patients and by experienced surgeons, may be a reasonable option even for those at high risk.

THE SWISH TRIAL for STOMATITIS

An unpleasant side effect of the drug everolimus (Afinitor), commonly used in conjunction with the hormone exemestane (Aromasin), is stomatitis. The mouth pain experienced can be minimal, but for some it is severe and interferes with eating.
drinking and swallowing. It can extend beyond the mouth and into the throat and esophagus. For some, it means reducing the dose of Afinitor or discontinuing the drug altogether. At a recent meeting on palliative care held in Adelaide, Australia, Dr. Hope Rugo from the University of California San Francisco, presented the results of the SWISH study on behalf of her colleagues. The motivation for the present study was the high degree of stomatitis reported with this combination therapy in a prior study known as Bolero-2.

The SWISH study included 92 postmenopausal women with metastatic, hormone receptor-positive, HER2-positive breast cancer, who were treated with the combination of everolimus at 10 mg and exemestane at 25 mg daily.

The primary goal of the SWISH study was to test the effectiveness of a steroid containing oral solution (a mouthwash) in preventing the symptoms of stomatitis. All participants in the study were given 10 mL of alcohol-free dexamethasone (0.5 mg/5 mL solution) by mouth starting on day one. Patients were instructed to swish with the mouthwash for two minutes and then spit out the solution, four times per day for a period of eight weeks. They were further instructed to refrain from eating for one hour after using the mouthwash. Dr. Rugo explained that this was not a randomized study since they already knew from the Bolero-2 study of the high incidence of stomatitis experienced, and they did not feel that it was justified to withhold a probable preventive measure from any of the participants. The time of measurement was designated to occur at eight weeks from the start of therapy.

At eight weeks of treatment, the incidence of grade 2 (symptomatic) or higher stomatitis in the SWISH study was 2.4% compared to 33% reported in the BOLERO-2 trial. The incidence of any degree of stomatitis at eight weeks was 21.2% in this trial, compared with 67% in the BOLERO-2 trial. In the SWISH study, 88% of patients were tolerating a normal diet at eight weeks and 90% experienced no or few dietary restrictions throughout the study. Dr. Rugo cautioned that some patients developed an elevated glucose level (sugar) similar to what was noted in the BOLERO-2 trial.

The results of this study provide welcomed information for patients and clinicians. It is likely that the use of this dexamethasone mouthwash will become a common clinical practice.

QUESTIONS AND ANSWERS

(Q) Dr. Martino, I was diagnosed and treated for breast cancer six years ago. I now have a tumor in my liver. My doctor who has been seeing me for all of these years has informed me that I need to have a biopsy of my liver to prove that this is again cancer. Is this necessary? Can’t they tell from my scan that my tumor has come back and I need to be treated as soon as possible? Why do I have to wait for more tests to be done?

(A) Dear Reader, There are several important reasons for doing a biopsy of your liver lesion. I assume that the abnormality in question was seen on a scan. Though your doctor may be suspicious that this is a manifestation of your previous breast cancer, he or she cannot be certain without doing a biopsy. The lesion could be benign, could be another type of cancer or could in fact be a recurrence of your prior breast cancer. The treatment would depend on the answer to this question. Even if it is breast cancer, it may now have characteristics that are different from your prior breast cancer. A biopsy will allow your doctors to figure this out and to better tailor your therapy. Cancers change over time and can also change as a result of prior therapy that may have been used.

I agree that the steps necessary to start your therapy if needed, should proceed with minimal delay. However, making the best decision based on information obtained from a new biopsy is important.