BreastCancerAdvisor

BY DR. SILVANA MARTINO

Spring 2016

Dear Readers,

I want to encourage you to spend some time outdoors. For many of us, our lives are spent inside our homes, in our automobiles, in our place of work and in various stores. We have become in-door people. This increases our sense of separation from nature and gives us a feeling of isolation. It is spring time. Make it a time of renewal and new beginnings.

Best regards,
Dr. Silvana Martino

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

CONTENTS

BIOLOGY BASICS

ATYPICAL HYPERPLASIA OF THE BREAST

When a questionable area is found either on palpation of a breast or on a mammogram, a breast biopsy is commonly advised to establish its true nature and render a diagnosis. Most breast biopsies are benign, with an estimate of more than one million benign breast biopsies performed in the United States each year.

Some lesions however, though classified as benign, contain clues that cellular changes are taking place that predict for a higher risk of future breast cancer. These changes are apparent to a pathologist when viewing breast tissue under a microscope and described in detail in the pathology report.

Our present understanding is that most cancers found in the breast have their origin in the milk-making ductal system of

continued next page

The Angeles Clinic
AND RESEARCH INSTITUTE
A CEDARS-SINAI AFFILIATE

Santa Monica
2001 Santa Monica Blvd., Suite 560W
Santa Monica, CA 90404
(310) 582-7900

West Los Angeles
11818 Wilshire Blvd.
Los Angeles, CA 90025
(310) 231-2121

Cloverfield
2428 Santa Monica Blvd., Suite 103
Santa Monica, CA 90404
(310) 828-0061

BIOLOGY BASICS continued

the breast. These ducts resemble a bunch of grapes. Milk is produced in the grape-like structures and is then passed down the stems or tube-like portions of the system. The stems then carry milk down to the nipple where, through a small opening, milk leaves the body. It is in this grape-like system where the first visible changes suggesting that the cells are not entirely normal can first be appreciated.

Inherent in our present understanding is the assumption that going from a normal cell to a cancer cell is not a one-step event, but rather a series of steps that move cells in a cancerous direction. It was originally assumed that this process started with a single cell rather than a group of cells, but this is no longer as certain.

As this pre-cancerous process evolves, a point is reached when a milk-making duct starts to look a bit odd. More cells are seen in the ductal structure than what is considered normal (hyperplasia). The cells are not yet abnormal in appearance, there are simply more cells than usual. The next step that can be distinguished under a microscope is when the cells actually begin to look a bit odd. This is when the term atypia is used by the pathologist to describe them. Still, these cells are not cancer; but, enough changes have occurred to recognize that a person with such a biopsy is at a higher lifetime risk of developing breast cancer.

Hyperplasia can occur in both the grape-like structures of the milk-making system (the lobules) and the tube-like structures (the ducts). The terms atypical lobular and atypical ductal hyperplasia are used to identify the specific location. Both predict for an increased risk of breast cancer. Studies with long term follow-up have demonstrated that this risk continues for many years, with a cumulative incidence of breast cancer at 25 years of follow-up of about 30%.

As more changes occur to the cells of the milk-making system, the process becomes more irregular and more obvious. This leads to a diagnosis of lobular carcinoma in situ and ductal carcinoma in situ. At this point the patient is more easily recognized as having an abnormal process and further therapy is generally advised.

The importance of understanding atypical hyperplasia of the breast is that this finding on a biopsy is not often made clear to the patient. They are correctly informed that their biopsy is benign. They are happy that they do not have cancer and rarely ask questions beyond that issue. Yet, they are at a higher risk for developing breast cancer in the future and this needs to be made clear. Plans for more attentive follow up should be encouraged. Therapy for breast cancer prevention should be discussed.

Each breast biopsy results in a written pathology report. This report is available to each patient. The report should be read in detail and if not clear, questions should be asked of your doctor. Though the final summary of the report may read “benign breast biopsy,” details may be contained in the report that may have considerable biological meaning.

WHAT’S NEW

ARIMIDEX AS A CAUSE OF CARPAL TUNNEL SYNDROME

A frequent side effect of many hormonal therapy drugs such as tamoxifen and the aromatase inhibitors (Arimidex, Femara and Aromasin) is the development of musculoskeletal discomforts

continued next page

YOUR SUPPORT

The Angeles Clinic and Research Institute and **The Angeles Clinic Foundation** are dedicated to providing patient care, cancer research, and community education. Your donations help make our work possible.

Make a donation directly online by clicking Donate Now

or mail to: The Angeles Clinic Foundation, 2001 Santa Monica Blvd., #560W, Santa Monica CA, 90404

Your gift to The Angeles Clinic Foundation is fully tax deductible.

WHAT'S NEW continued

experienced as aches and pains in joints and or muscles. This is also a common experience when women go through the menopause. It is an experience that makes many of us feel like we are becoming an "old lady". It is believed that the underlying basis to this phenomenon is the reduction in estrogen level that occurs in the body. New evidence suggests that carpal tunnel syndrome is also a part of this biology.

Carpal tunnel syndrome occurs when the median nerve that controls the function of a portion of the hand is compressed as it courses from the arm into the hand and fingers. The point of compression is in the wrist area, where there is a band of tissue that is wrapped around the structures of the wrist. There are many causes of this syndrome, including, repetitive use of the hand as occurs with computer work. Its clinical features are a feeling of pins and needles, a burning sensation, tingling, heaviness of the hand and a feeling of electricity in the hand. Pain can occur not only in the hand but also can extend up the arm towards the elbow and shoulder area. Weakness of the hand can also be experienced. The problem can occur in one hand or both.

Women are more prone to developing carpal tunnel syndrome, especially around the time of menopause. There is also an association with pregnancy, removal of the ovaries and the use of birth control pills. The use of hormone replacement therapy at the time of menopause can improve the symptoms. These observations support the assumption that, at least to some degree, there is a hormonal basis to the development of carpal tunnel syndrome. As anti-estrogen type hormones have been administered to women as treatment for breast cancer, it was observed that women were experiencing carpal tunnel syndrome more frequently. Several studies comparing tamoxifen with the various aromatase inhibitors have suggested that this was more typical of the aromatase inhibitors, which in post-menopausal women lower estrogen levels more than does treatment with tamoxifen. A new study reported in the Journal of Clinical Oncology has added further information on this side effect.

The report comes from the International Breast Cancer Intervention Study II (IBIS-II), a randomized double-blind clinical trial in which 3,864 post-menopausal women at high risk for developing breast cancer were given either five years of daily Arimidex or placebo. The median age of the group was 59.5 years. At a median follow-up of 6.4 years, a total of 96 women were reported to have carpal tunnel syndrome; 65 (3.4%) in the Arimidex treated group and 31 (1.6%) in the placebo group. Women with other musculoskeletal discomforts were more likely to develop carpal tunnel syndrome as were women with a higher body-mass-index (BMI). This problem tended to occur during the first two years of therapy rather than later. For most participants who developed this symptom, it was mild, with few having severe symptoms and needing surgery. For many, the symptoms resolved over a period of one to two years.

The primary value of this study is a confirmation of several other studies, mostly in women treated for breast cancers, that have suggested an association between aromatase inhibitor therapy and carpal tunnel syndrome. Since this study was done in women without breast cancer, there are less other potentially confounding causes for carpal tunnel syndrome such as prior surgery to the affected arm, lymphedema, or repeated intravenous injections. Thus, it is more convincing that it is a syndrome caused by this drug.

Reference: Francesco Spagnolo et al, Anastrozole-Induced Carpal Tunnel Syndrome: Results From the International Breast Cancer Intervention Study II Prevention Trial, Journal of Clinical Oncology, Vol 34 (2), January 10, 2016, pg139-143.

continued next page

PREVIOUS ISSUES

You can review all previous issues of the Breast Cancer Advisor on our websites:

www.theangelesclinicfoundation.org
click on the NEWSLETTER tab

www.theangelesclinic.org
click on The Angeles Clinic Breast Cancer Advisor

WHAT'S NEW continued

FASTING TO PREVENT RECURRENCE?

The harmful effects of being overweight have provoked considerable interest in medicine, especially in the past decade. Calorie restriction has been shown to prolong life in many animal experiments. Along with these observations, there has also developed a body of work suggesting that prolonged periods of fasting are also of benefit. Much of this work has been done in animals, but some human data also exists. Some have suggested fasting a few days each week routinely as a life-long habit.

An interesting observation was reported at the 2015 San Antonio Breast Cancer Symposium by Catherine Marinac, a PhD candidate at the University of California at San Diego Cancer Center. These observations were based on a review of dietary records from 2,413 women that are part of the Women's Healthy Eating and Living Study, a phase III study designed to evaluate the role of a high fiber, high vegetable, low-fat diet versus a regular diet in women treated for early breast cancer. The study participants filled out multiple 24-hour dietary recalls collected over a 72 month period. They have been followed to ascertain further breast cancer events and to obtain data on death rate whether due specifically to breast cancer or to other causes.

At 7.3 years of follow-up, an interesting finding emerged from this analysis. Women with a prior history of breast cancer who reported eating their meals such that an interval of 13 hours occurred between the last meal of the day and the first meal of the next day (a period of fasting), were found to have a statistically lower risk of breast cancer recurrence than women whose meals were closer in time. Death rate either from breast cancer or from any other cause was also reduced in those who had a longer period of fasting between these two meals, though the difference, was not enough to be statistically significant.

The authors suggested that this beneficial effect of overnight fasting may involve regulation of the sleep cycles and regulation of glucose metabolism. In mice, this type of an eating pattern has improved control of glucose levels, reduced inflammation and generally improved circadian rhythm patterns.

Another connection to fasting and cancer has been offered by Valter D. Longo, PhD, from the University of Southern California and his colleagues. They have been interested in the observation that fasting prior to and after receiving chemotherapy may improve cancer outcome and reduce side effects from chemotherapy. Their group has studied various schedules of fasting surrounding the administration of chemotherapy. The principle is a few days of fasting prior to and after each dose. Though their work is preliminary, they have demonstrated that for most patients, a few days of fasting can be accomplished. Their work also suggests that side effects from chemotherapy are less than when the same therapy is given without fasting.

At this point I think that this type of work is interesting but not ready for common use. I do find it intriguing. At minimum, it points to the fact that what we eat, how much we eat, and probably when we eat are not minor health issues. Solutions for better heath may be more basic that we realize. They may not always come from more use of drugs.

Reference: Ed Susman, Those "Early Bird" Dinners Might Help Prevent Breast Cancer Recurrence, Oncology Times, Volume 38(4), February 25, 2016, pg30.

GUEST WRITER

Radiation therapy is a critical and dynamic modality that has many uses in the treatment of breast cancer. Its use has probably had the biggest impact in early breast cancer where, as an additive to lumpectomy, it provides an alternative to mastectomy. In that setting, radiation is generally given over a period of 5-7 weeks. An important question has been whether this time period could be shortened, yet maintaining

continued next page

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.

GUEST WRITER continued

the same effectiveness. Several studies have demonstrated that it can be done. The following is a review of this topic by a group of radiation oncologists from the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai Medical Center in Los Angeles.

HYPOFRACTIONATED BREAST RADIATION

HISTORICAL PERSPECTIVE

The role of radiation therapy in the treatment of early stage breast cancer has continued to evolve since completion more than 30 years ago of a pivotal study conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) that demonstrated the comparability of breast conservation (lumpectomy plus radiation) with mastectomy. A 20-year update from that study reported equivalent survivals for patients treated with breast conservation versus a modified radical mastectomy. This trial also validated the specific contribution of radiation, demonstrating a statistically significant decrease by more than half in the rate of tumor recurrence in the breast for those treated with lumpectomy plus radiation versus lumpectomy alone. More recently, in 2011, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported results of an analysis that included 17 randomized trials that involved over 1000 patients, and also found a distinct survival advantage conferred by post-lumpectomy radiation over lumpectomy alone.

Despite these reported benefits of post-lumpectomy radiation, approximately 15-20% of eligible patients never receive radiation, likely due to limited technical resources and/or personal hardship in completing a "standard" 6.5 weeks of adjuvant radiation. Because of this, decreasing the overall radiation time became a goal. This would likely improve patient compliance and result in better resource utilization. However, any change in a specific radiation parameter such as overall time course, dose per fraction or total dose needed testing, as a change in one variable might significantly impact long term outcomes of tumor control and/or side effects.

TRIALS OF HYPOFRACTIONATION

In general, the "standard fractionation" radiation schedule that has been in use for many years refers to the delivery of a dose of 1.8-2.0 Gy. per fraction given on a schedule of one treatment per day, five consecutive days per week over approximately 6.5 weeks. The newer approach called "hypofractionation" refers to a daily single fraction of greater than 2 Gy. over a relatively abbreviated 3-4 week time course.

Over the last 20 years, there have been four trials that form the database as to the appropriateness of the hypofractionation schedule in the adjuvant treatment of breast cancer. While each study used a slightly different schedule (ranging from 13-16 fractions and total doses from 39-42.9 Gy.), all had a similar goal; to deliver a shortened overall course of radiation that hopefully would be biologically equivalent to the more protracted treatment of 50 Gy in 25 fractions of 2 Gy. Recent ten-year updates for each trial comparing the two radiation time schedules affirmed the non-inferiority (notably < 2-3% difference) of hypofractionated as compared to standard fractionation with respect to tumor control , overall survival and appearance of the breast.

Despite these encouraging results validating the efficacy of the more time condensed radiation regimens, there was initial reluctance, at least in the U. S., to adopt the hypofractionation approach. This was likely because of the many variations in the details between the different studies, hence confounding the identification of "the optimal" regimen. The variations included differences in daily dose, total dose, discretionary use of a "boost dose" (additional dose directed solely to the surgical

continued next page

HOW TO RECEIVE FUTURE ISSUES

You may request future issues of this newsletter by e-mailing your request to:

smartino@theangelesclinic.org

GUEST WRITER continued

bed), the use of systemic therapies, tumor characteristics and inclusion of different types of patients.

Nevertheless, in recent years the utilization of hypofractionation has been steadily increasing. This trend is likely the result not only of updated 10 year follow-up results from the original studies, but also the report in 2015, of a large meta-analysis confirming the benefit and safety of this approach. Additionally, in 2010, the American Society of Therapeutic Radiation Oncology (ASTRO) guidelines were published which advocated the adoption of the Canadian fractionation schedule (42.7 Gy. in 16 fractions of 2.67 Gy.). They also suggested criteria detailing which patients were most appropriate for this approach.

REMAINING AREAS OF CONTROVERSY

There continue to be areas of controversy regarding which patients and which tumor characteristics are most appropriate for this abbreviated radiation approach. The recently closed RTOG 1005 trial promises further clarification as to the application of hypofractionation for specific high risk patient populations, including patients having: a) high grade tumors, b) pre-menopausal status, c) focal positive resection margins, d) high grade DCIS if < 50 years of age, e) hormone receptor negative tumor markers, and f) impact as to the use of pre- or postoperative chemotherapy.

COST

Several studies have confirmed that hypofractionation is delivered at a 25-30% lower cost as compared to the longer standard schedule. It also allows for more efficient utilization of treatment machines and patient convenience.

CONCLUSION

Over the last 20 years, there have been significant advancements in the application of radiation therapy for the breast-conserving treatment of early stage I/II cancer patients, including: a) identification of patient/ tumor specific prognostic variables predictive for in-breast recurrence, b) refinements in radiation therapy technologies (3D treatment planning, prone breast board, respiratory gating, intracavitary devices) so as to improve on dose homogeneity and decrease radiation therapy associated toxicities, and c) adoption of innovative treatment time schedules, (hypofractionated whole breast radiation, accelerated partial breast irradiation , intraoperative radiation), so as to broaden the application of post-lumpectomy therapy. In this modern era of personalized medicine, there is currently available a spectrum of radiation therapy delivery schedules ranging from a 6.5 week course of standard fractionated whole breast radiation, to a 3-4 week hypofractionation, to 5 day twice-a-day partial breast therapy, to single dose intraoperative therapy, to omission of radiation for especially favorable, low-risk , patients. The explicit goal should be to optimize both survival and local control without compromising breast cosmesis or patient safety. While mindful of pressures for cost containment, we should also remain respectful of the patient's priorities. The results of recent trials have confirmed that hypofractionation is a valuable option; for many the optimal choice. What remains unclear is the appropriateness of various fraction schedules for different molecular subtypes of breast cancer (luminal A, luminal B, HER2 positive and triple negative), which may exhibit different intrinsic sensitivity to different fractionation schedules.

C.Michele Burnison, MD
Amin Mirhadi, MD
Stephen Shiao MD, PhD
Radiation Oncology
Samuel Oschin Comprehensive Cancer Institute
Cedars-Sinai Medical Center
Los Angeles, CA