

Dear Readers,

It has been my privilege to work in the field of breast cancer for the past 32 years.

Many changes have occurred during that time. The sum of these changes has been the diagnosis of breast cancer at an earlier, more curative stage, when less surgery and less chemotherapy are needed. We are now able to consider strategies for the prevention of breast cancer. It is an exciting time full of promise. Though researchers and clinicians are essential in continuing to move the field forward, I believe that a well educated public is also critical. It is for this reason that this newsletter has been created. It is dedicated to all who have experienced breast cancer and those who are simply interested in being informed.



Breast Cancer Advisor

BY DR. SILVANA MARTINO • AUGUST 2011

BIOLOGY BASICS

To understand breast cancer, it is important to have some knowledge of the breast itself. The primary biological function of the breast is to prepare itself for milk production in anticipation of a pregnancy and the need to nourish a child. If one looks inside a breast, meaning if you removed the skin, you would find that the breast is primarily composed of fat. Within that fat, and distributed similar to the spokes of a wheel with the nipple being the center point, are located the milk making ducts of each breast. Each breast has approximately six to twelve milk producing ducts. It is these same ducts which make milk that give rise to breast cancers.

If you could see each of the milk making glands with your eyes, you would see that they resemble a structure that you are already very familiar with. Each duct looks like a bunch of grapes. (Let's make them red grapes since I favor red wine). As you know, a bunch of grapes is composed of a main stem with branches, at the end of which are located the grapes. Milk (similar to wine) is produced in the grape structures. The stems primarily serve the purpose of allowing milk to flow down and out through the nipple. If we simplify a bunch of grapes, it is really made up of two parts: grapes and stems of varying sizes. The stems are really little tubes that allow substances to move through them. Each of these two parts gives rise to a specific type of breast cancer. The grape like structures give rise to lobular cancers and the stems give rise to ductal cancers. Ductal cancers are far more common and account for about 85% of breast cancers. The remaining 15% are lobular in origin.

Let us now focus a bit more on the stem portions of the milk making duct system. Visualize each stem as a small tube. It has a wall which encircles an empty space (the lumen) similar to a straw. Milk flows through it. Cancer begins on the inside wall of the tube. When this process is just beginning, all of the cancer cells will accumulate within the lumen of the tube. They will tend to form a plug. This can be seen by the pathologist using a microscope on a biopsy specimen. At

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The Angeles Clinic FOUNDATION

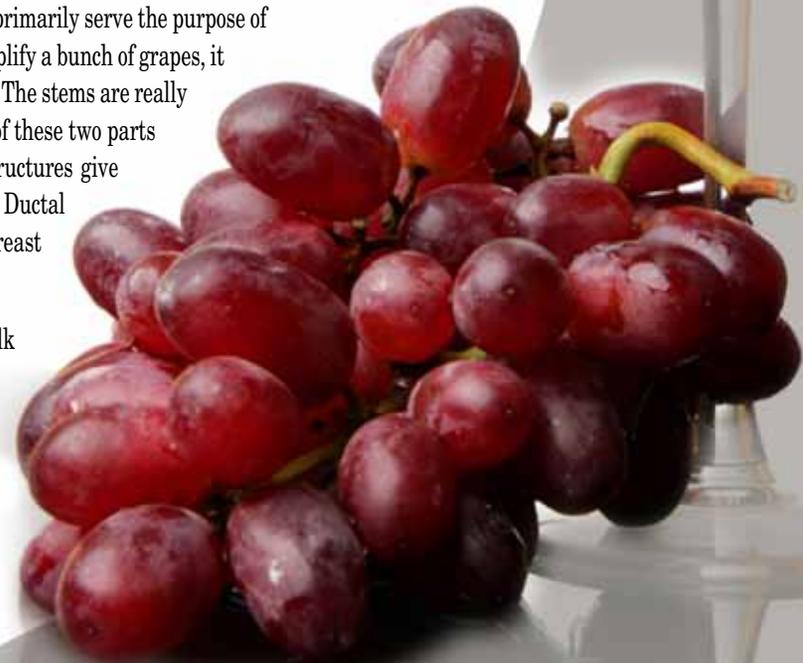
The Angeles Clinic Foundation is a nonprofit organization whose purpose is to sponsor and support programs, services, education, advocacy, and research related to cancer. Our goal is to make a difference in all aspects of the lives of people touched by cancer. Your support is important in the fight against cancer and the journey towards a cure.

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Biology Basics continued

this early stage of development, the cancer will be referred to as an in situ ductal cancer. Think of these in situ cells as a group of young children. As they grow up or mature, they will start to burrow through the wall of their tube. Once the wall is broken through, again a process that can be seen under a microscope, the tumor is then described as an invasive or infiltrating ductal cancer. The distinction between in situ and invasive (infiltrating) is very important. This is the tumor communicating that it is not made up of young children; rather it is now composed of more mature cells more like teenagers. Like teenagers, these are cells that now have a driver's license. They have acquired the ability to leave home (the breast) and travel to other parts of the body. As is typical of teenagers with a driver's license, they don't like to stay home. Likewise, cancer cells want to leave their place of origin. The manner by which cancer cells travel is simply for a small group of them to separate from other cells and then invade into a blood vessel or a lymph channel. Once this has been achieved, they can float in blood and lymph (which are primarily liquids) like a leaf on a river. Blood and lymph channels are the roads of the body. We are designed very much like a city. We have highways and minor roads, but they are all interconnected. So irrespective of where you start, you can reach all other areas.

Once a cell travels away from its place of origin, one of two things will happen to it. It will either be killed by one's own immune

system or it will land somewhere in the body and take up residence. The journey through the body is not an easy one. Most migrating cells will not survive the journey, but will be attacked and killed by the immune system. As you can see, a good immune system is very important. This is why taking good care of yourself and maintaining your immune system is so important.

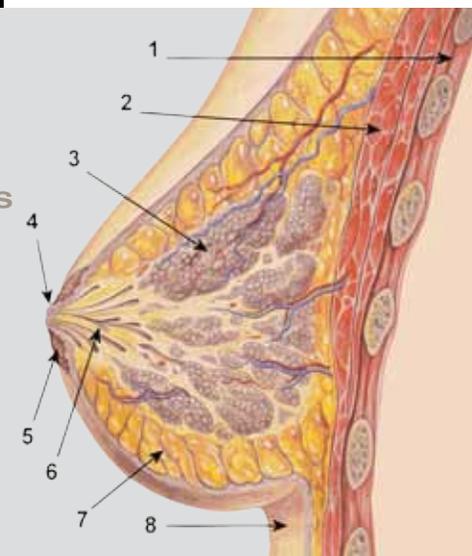
Thus far we have described the cancer process when its origin is the stem part of the bunch of grapes. We now turn our attention to lobular cancers which arise in the grape like part of the system. Think of it as a seedless grape. It has a pulp section and a covering or skin like portion. I am sure you know of someone who likes to peel the skin off the grape before eating it. It is very similar to that idea. These cancers start where the pulp is. As long as they are confined to this area, they are called lobular carcinoma in situ, similar to the ductal version. Once these cells are seen under the microscope to be breaking through the skin of the grape structure, they are then referred to as an invasive or infiltrating lobular cancer. As you can see, each type of breast cancer, ductal or lobular has an in situ phase and a more advanced infiltrating or invasive phase.

There is a distinction that needs to be understood between the two in situ phases. Though they carry a similar name which was given to them many years ago, they are not quite the same in behavior. Ductal carcinoma in situ behaves and is treated as a true cancer. Lobular carcinoma in situ, though once believed to behave and treated as a true cancer, is now viewed as a marker of risk where each breast is at equally high risk of developing a more advanced problem.

We will continue from this point and discuss the various stages of breast cancer in the next issue.

Anatomy of the Breast

- 1 Chest wall
- 2 Pectoralis muscles
- 3 Lobules
- 4 Nipple surface
- 5 Areola
- 6 Lactiferous duct
- 7 Fatty tissue
- 8 Skin



WHAT'S NEW

It is important to understand that medical research is a continuous process, and that new information is made available on a continuous basis via medical journals, meetings and the public media. As a researcher, it is important to have your results made public as quickly as possible so that you are given credit for it. In fact, your standing in the medical community, your reputation, your promotions, your income and your ego depend on it. For these reasons, many times results are made public when they are premature and often inconclusive. The public media loves premature reports, but fails to understand that premature data often turn out to be wrong.

Though new information is constantly being generated, there are certain journals and meetings that have a higher status where one prefers to present results. One of these meetings is ASCO (the American Society of Clinical Oncology) which took place in Chicago from June 3-7, 2011. This is an international meeting that takes place each year, usually in June. Attendance this year reached nearly 30,000. Because of its prominence, the media pays considerable

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What's New continued

attention to results presented at this meeting. They then select what they will report to the public. Of the many and varied results that were presented in the field of breast cancer, I have selected for review certain presentations that I anticipate will have the most impact on how we think and on treatment.

1 Breast Cancer Prevention

It is generally understood that preventing a disease is preferable to treating it after it occurs. Though we all accept this principle, it is not a common practice in western medicine. It part, because we do not often know how to prevent disease. Even so, there are things that can be done that have been shown to prevent breast cancer in some women. The most effective though least appealing therapy is the surgical removal of both breasts (bilateral mastectomy) before a cancer has developed. This is done in women who are at very high risk. It does not remove the risk completely, but reduces it by about 90%. For many women, this is not an acceptable approach. So, what else can be done? Actually, several alternatives can be considered. It has been known for several decades that if premenopausal women have their ovaries removed, they tend to develop less breast cancer. The presumed mechanism by which this happens is the reduction of estrogen production. This reduces risk by about 50%. This surgery is also not acceptable to many women. The remaining non surgical approach is the use of certain hormones that collectively also reduce estrogen levels in the body.

The first observation that this might be possible occurred with the drug tamoxifen. It was observed that women who already had one breast cancer and were being treated with this drug had a lower incidence of developing a second breast cancer in the opposite breast. This observation led to the question of whether this drug was not only capable of treating certain breast cancers, but might also have the ability to prevent a cancer from starting in the first place. This concept was tested in thousands of women who had not had breast cancer but who were at high risk. One half were given daily tamoxifen and half agreed to take a placebo. The results demonstrated that the group who took tamoxifen developed about half the number of breast cancers as the group given the placebo.

A second drug, raloxifene (Evista) which is similar but not identical to tamoxifen was studied next. Again, the group of women given the active drug had about half the breast cancers when compared to the group given placebo. A comparison of these two drugs was subsequently done, and found that they are about the same in effectiveness, but slightly different in side effects. Tamoxifen has more side effects, but may be a bit more effective as well. Tamoxifen can be used in women who are pre or postmenopausal, but raloxifene is used only in women who are postmenopausal.

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At the recent ASCO meeting, Dr. Paul Goss from Massachusetts General Hospital Cancer Center and Dana-Farber Cancer Institute in Boston, presented results on a new hormonal treatment for the prevention of breast cancer. These results were

also published in the June 10, 2011 online issue of The New England Journal of Medicine. The study which is still ongoing includes women from Canada, the US, Spain and France. Women age 35 and over were included. Each woman had to be postmenopausal. In addition, each woman had to be at a higher than average risk of developing breast cancer. They qualified if they had at least one of the following risk factors: age at least 60, a Gail risk score greater than 1.66% (a mathematical calculation based on certain features of personal and family history), or prior atypical ductal hyperplasia, lobular hyperplasia, or lobular carcinoma in situ found on a breast biopsy. They were also eligible if they had a prior diagnosis of ductal carcinoma in situ treated with mastectomy. Women were excluded if they were known to carry the BRCA1 or BRCA2 genes. Between February 2004 and March of 2010, 4560 women were randomly assigned (similar to a flip of a coin) to either the drug exemestane (2285 women) or to placebo

(2275 women) to be taken daily. Both groups were observed over time in the same manner with physical exams and mammograms to see if one group developed more breast cancers than the other.

At the time of this report, 43 invasive breast cancers have been diagnosed: 11 in the exemestane groups and 32 in the placebo group. The majority of the cancers were hormone positive, HER2/neu negative, and node negative. This is a statistically and clinically meaningful difference. Exemestane also appeared to reduce breast lesions that are known to be precursors of breast cancer such as ductal carcinoma in situ, lobular carcinoma in situ, and atypical ductal and lobular hyperplasia; suggesting that with time this treatment may show further reduction in invasive breast cancers.

Exemestane belongs to a family of hormones called aromatase inhibitors. It works by reducing estrogen production. The side effects of these drugs are somewhat different than tamoxifen and Evista. They can cause hot flashes, but these appear to be more tolerable than when caused by tamoxifen and Evista. There is no known toxicity to the eyes, no increase in uterine cancer, and minimal risk of blood clots. Some decrease in bone density and well recognized side effects of muscle, bone and joint aches can occur. Fatigue, insomnia and mood changes can occur with all three drugs.

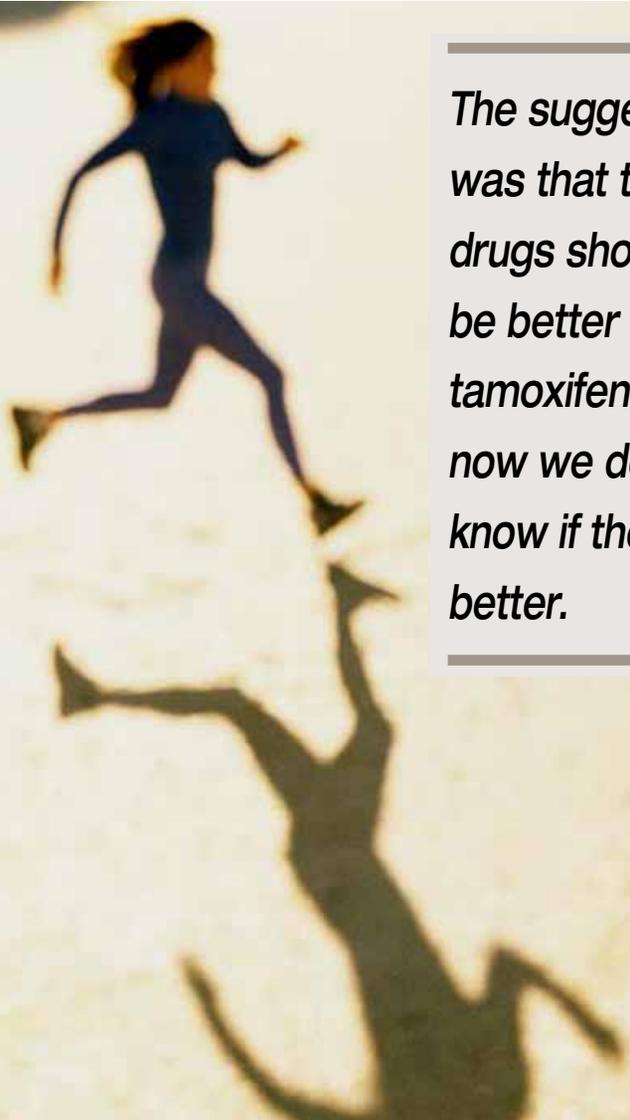
Is this new and important information? Yes, I believe that it is. We

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What's New continued

suspected that this family of hormones could reduce new breast cancers based on studies of these drugs when compared to tamoxifen in women being treated for breast cancer. The suggestion was that these drugs should be better than tamoxifen. Right now we don't know if they are better. That will take a direct comparison. But, this study demonstrates that they do work. Their list of potentially serious side effects is less than tamoxifen and Evista. Like Evista, they can



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only be used in women who are postmenopausal. Tamoxifen remains the only drug available for premenopausal women. Can exemestane be used now for this purpose? Medically, I believe that it can. How good is it in comparison to tamoxifen and Evista? We do not know. Will insurances pay for it? I doubt that they will until it receives FDA approval for this specific use. Can drugs that are similar to it such as anastrozole (Arimidex) and letrozole (Femara) be substituted for it? We don't know, and I would not. Does this now mean that those with ductal carcinoma in situ should be treated with exemestane?

The answer is no if they have had a lumpectomy. It may be yes if they have had a mastectomy, since this is the only group included in this study.

All the women who were on the placebo treatment will now be offered exemestane. So as in other prevention trials, we won't figure out how long one should be treated, whether the benefit continues beyond the treatment period, or if this therapy will reduce deaths from breast cancer. There are many important questions in medicine, but ethics prevent us from answering certain questions. We cannot sacrifice some people to science for the benefit of others.

Reference: Paul E. Goss, et al, Exemestane for Breast-Cancer Prevention in Postmenopausal Women, *New England Journal of Medicine*, downloaded from NEJM Media Center, June 04, 2011.

2 Radiation of Local Lymph Nodes in Early Breast Cancer

It is generally accepted that breast cancer often starts in more than one place in the breast.

Sometimes these areas are near each other, other times they are at a wide distance. Because of this pattern, the entire breast is generally treated. This can be accomplished by a mastectomy or by combining a lesser degree of surgery (a lumpectomy) with

radiation to the entire breast. Since breast cancer often travels to the surrounding lymph nodes, and since most of these lymph nodes are not surgically removed, guidelines have evolved recommending when radiation should include the lymph nodes. There are three major lymph node bearing areas that surround the breast: the arm pit area (axilla), the base of the neck area (supraclavicular), and a group of nodes located beneath the breast bone (internal mammary). The present practice is to radiate the nodes if tumor is found in at least 4 axillary lymph nodes. It should be noted that the lower portion of the lymph nodes in the axilla are usually radiated as part of doing the breast. However, the higher nodes in the axilla are not generally treated.

The data presented by Dr. Timothy Whelan at the June ASCO meeting addresses the question of whether additional radiation to the lymph node areas should be given in women with 1-3 positive axillary nodes and also some women with node negative disease when their surgery is a lumpectomy.

The study was conducted at 50 centers in Canada, the US, and Australia. A total of 1832 patients were randomly (like a flip of a coin) assigned to receive whole breast radiation or whole breast radiation plus radiation directed at the lymph nodes. They also received chemotherapy and hormonal therapy as per usual. They then were observed for approximately 5 years. The primary goal was to see if there was a difference in survival and a difference in side effect between the two groups. The women in the trial were generally young with a mean age of 53. Eighty five percent had 1-3 lymph nodes involved, with 5% having 4 or more nodes involved, and only 10% had no nodal involvement by cancer.

The results demonstrated that when nodal radiation was added, only 3.2% of the women had a recurrence in the breast area versus 5.5% when only the breast was radiated. Recurrences in distant parts of the body occurred in 7.6% when the nodes were radiated versus 13% when only the breast was radiated. The survival difference was small and not statistically significant with a survival of 92.3% if the nodes were treated and 90.7% if they were not. More inflammation of the lungs and lymphedema of the arm (swelling) were noted in the women who received nodal radiation.

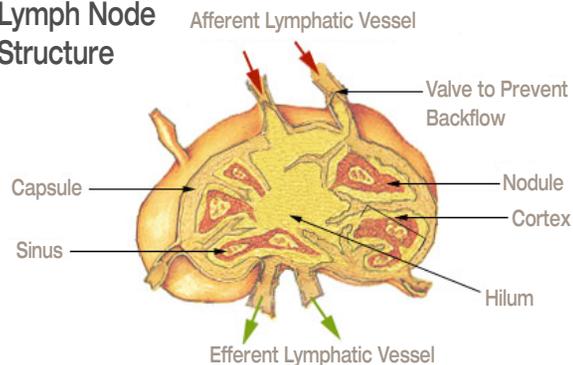
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What's New continued

Clearly one can see that there is some improvement with the addition of lymph node radiation both in recurrence in the breast area and away from the breast. This supports the basic concept that the more effective therapy is at controlling tumor in the breast area, the less likely the disease is to appear in other organs. The question is whether the difference is enough to make this procedure standard? The first thing that is obvious to me, is that there were too few women in the study who were node negative to feel that this study can be used to treat them in this manner. The only group one can relate this information to are those with 1-3 positive lymph nodes. I am sure that for many physicians this will provide enough reason to add radiation to the lymph nodes. I am not convinced yet that this should become standard therapy for all. I wish these numbers were more impressive and that the survival difference was more striking. Perhaps more time and a second large trial will convince me. For now, my bias is to pick and choose patients within this category that have a higher risk of recurrence such as those with larger breast cancers, a more aggressive pattern to their tumor or a lot of disease within these nodes and not add this treatment to everyone with any

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Lymph Node Structure



number of nodes involved. I may change my view in the future, but that is my judgment now.

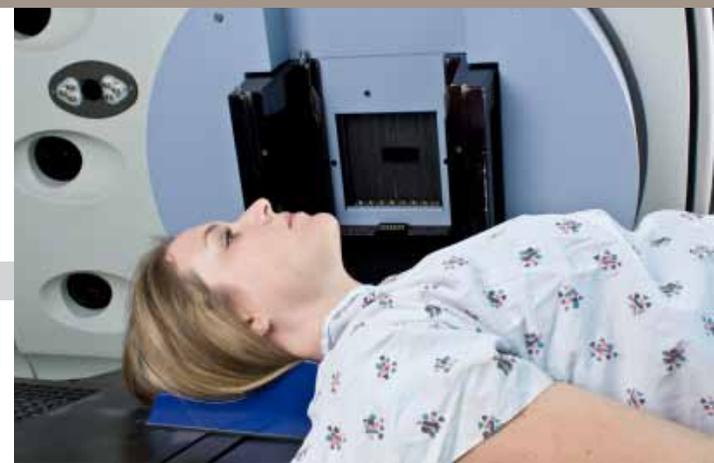
Reference: Timothy J. Whelan et al, NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer, abstract lba 1003, ASCO presentation, June 2011

3 Treatment of Brain Metastases in HER2/neu Positive Breast Cancer

There are certain organs in the body that are more commonly involved by breast cancer. The brain is one of these. This is more so in tumors that are HER2/neu positive and appears to also be true in triple negative breast cancers (estrogen, progesterone and HER2/neu all negative). Since the functions of the brain are so important, nature has provided extra protection in the form of a selective system called the blood/brain barrier designed to keep toxic substances from entering it. Most drug therapies that are used to treat breast cancer do not penetrate into the brain in adequate concentration to use them as sole treatment for brain metastases. It is believed that when there is tumor in the brain, this protective system is damaged and is perhaps less effective, so that drugs may enter in greater concentration. Even so, drugs alone are insufficient to treat brain metastases. Surgical resection and various forms of radiation are essential, and often used in combination.

In patients whose disease is HER2/neu positive, the drug trastuzumab (Herceptin) is commonly added to chemotherapy. Its use has improved survival over chemo alone even in advanced disease. Herceptin is not particularly good at getting into the brain, however.

In a poster presentation at the June ASCO meeting, researchers from the Medical University of Vienna, Austria presented some preliminary data using a combination of trastuzumab and lapatinib (Tykerb) a newer agent directed at the HER2/neu protein system with some promising results in patients with brain metastases. They looked back in their medical records and identified 80 patients with



HER2/neu positive brain metastases who were functioning well. They had a group who had been treated before HER2/neu therapies were available and a group treated after. Each patient had been treated with the best therapy of the time. They made the following observations. Patients who had received no drugs at all but simply surgery and or radiation to the brain had a survival of about 3 months. Those that in addition had been given some type of chemotherapy survived about 9 months. Those where trastuzumab had been added, lived an average of 12 months. The small group that had been given trastuzumab plus lapatinib was doing the best, with many still alive at the two year point.

It must be realized that this is a hodgepodge of patients, and also patients who in spite of their brain involvement were functioning well. So, they may not be the typical patient with brain metastases. The number of patients in the study is small, which makes any conclusion less reliable. But, the results seem reasonable, particularly since we know that lapatinib is much more capable of penetrating into brain tissue compared to trastuzumab. One must also realize that each drug you add to a treatment increases side effects. Though preliminary data is often misleading and should not be taken as fact, I believe this information may turn out to be important.

Reference: R. Bartsch, Systemic therapy and overall survival in patients with brain metastases from HER2-positive metastatic breast cancer, abstract 597, ASCO, 2011

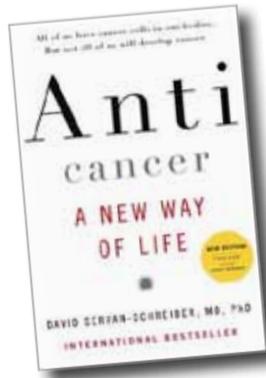
BOOK REVIEW

Anticancer A New Way of Life by David Servan-Schreiber, MD, PhD

This book was given to me by one of my patients as a Christmas gift in December of 2009, but I confess I did not read it until early this year. She felt that of all the books that she had read on cancer, this was the one that “opened her eyes and changed her path.” She hoped I would like it too. Well, I did like it. In fact, I liked it a great deal. The book was originally written in French and then translated into English. Its author is a physician who was diagnosed

with a brain tumor. It describes his experience both from a personal and medical perspective. Clearly, this experience changed how he lived his life. There are several excellent chapters on what he learned about diet, stress and fear management, meditation, and relationships. The sections on the immune system are particularly good. The book has a considerable review of scientifically based principles on how to live

a healthy life so the body has the best opportunity to heal. I agree with my patient that of similar books I have read, I consider this one particularly worth while.



QUESTIONS & ANSWERS

(Q) Dr. Martino, I am a 38 year old woman with a recent diagnosis of a 9 mm breast cancer which is hormone negative and HER2/neu positive. My lymph nodes were not involved with tumor. I am otherwise very healthy. My doctor has advised that I have Herceptin and chemotherapy. Is this necessary?

(A) I am assuming that since your doctor wants to give you chemo and Herceptin that the cancer was invasive. Neither Herceptin nor chemotherapy are standard treatments for non invasive disease. I am also assuming that the HER2/neu test was done on the invasive tumor and not on any non invasive part of the tumor. The answer to your question is not simple since the studies that have been done so far using Herceptin in treating early breast cancer were not designed to treat such small tumors. So, no one can tell you how much benefit you will receive. Because we know that even small tumors that are HER2/neu positive have a more aggressive behavior and are more likely to spread, many oncologists have chosen in the absence of clear data to treat even tumors that are 5mm or greater. This is probably more so in tumors that are hormone negative where hormonal therapy will not be used. Because you are young and healthy, it is expected that you will tolerate the therapy well. Most of us are more aggressive in our approach when we are dealing with a younger person as we feel that you naturally have many remaining years of life that one wants to protect. I suspect these are the various issues your doctor is considering in reaching a recommendation. Though not all would agree, I believe the recommendation is reasonable.

E mail your questions to:

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