BREAST CANCER—EXERCISE, PREVENTION, AND TREATMENT

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I have three goals in writing this article.

1) Acquaint women as well as men with the benefits of exercise for prevention of breast cancer and for its significant value during and after chemotherapy.
2) Insure that women understand the significance of ErbB2-positive breast cancer and the specific drugs available for its treatment.
3) Inform women of the importance of a definitive diagnosis regarding the type of breast cancer and the availability of sentinel node biopsy so that they can intelligently discuss the most effective management with their physician and *confirm availability.*

EFFECTIVE CANCER PREVENTION STRATEGY

There is accumulating evidence that regular physical activity is an effective cancer prevention strategy based on the effects of exercise-induced oxygen deprivation and acidosis on the genesis of cancer. The transition from normal tissue to cancer (carcinogenesis) is a prolonged, multi-step process governed by the adjustment of the tumor cells to its environment. If that environment is changed because of transient, systemic, exercise-induced oxygen deprivation and acidosis, it may be possible to interrupt critical evolutionary steps in carcinogenesis.[1] Even moderate exercise can produce significant reduction in blood pH. It is the belief of investigators that repeated, transient reductions in blood pH due to regular exercise alters the micro-environmental dynamics of the type of breast cancer that has its origin inside the milk ducts and that this will be sufficient to prevent or delay its final invasive transition.

Friedenrich and Orenstein[2] reviewed over 170 epidemiological studies and concluded that evidence for decreased cancer risk with increased physical activity was convincing for breast and colon cancer, probable for prostate cancer, possible for lung cancer and unknown for other sites. **In breast cancer, physical activity has been well documented to reduce cancer risk by almost 50%.**[3 4 5]

PREVENTABLE CAUSES

There are at least four causes of cancer that are possible for an individual to eliminate from their lives. They are tobacco use, physical inactivity, obesity, and poor nutrition– including too much alcohol. These are things that everyone can control, although it is more than simply "difficult" for a smoker to "quit" and an alcoholic to stop drinking. The need for these substances is intense and powered by physical need and centers deep in the brain. This type of intensity cannot be appreciated by those who have never been addicted to anything. But knowing this, we can then bring all the support that we can muster to a loved one who is willing to try. Exercise can help to fill the void.

INCIDENCE OF BREAST CANCER IN WOMEN AND MEN

Breast cancer is the second leading cause of cancer death among women in the United States, where, in 2009, there were 192,370 new cases among women and 1,910 among men. The deaths from breast cancer in that year alone were 40,170 women and 440 men.[6] About 20% to 30% of women with breast cancer will have a fast growing type known as Human Epidermal Growth Factor Receptor 2 (ErbB2-positive).[7 8 9] That's about 40,000 women each year diagnosed with ErbB2-positive breast cancer.

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2

The human epidermal growth factor receptor 2 (ErbB2; formerly HER2) gene is part of a family of genes that play roles in regulating cell growth. Amplification* of this gene occurs in a significant proportion of breast, ovarian, and gastric cancers, so that instead of having two gene copies of ErbB2, as would be the case in a normal cell, there are multiple copies, referred to as "ErbB2-positive." As a result, there is far more expression (activity) of the ErbB2 protein on the cell surface, resulting in tumors that are faster growing, more aggressive and less sensitive to therapy. An estimated 20 to 25 percent of breast cancers make these extra copies of the ErbB2 gene.[10]

Should the unthinkable suddenly become a reality, time is precious and finding information at that critical point of emotional turmoil would take time. If clinical diagnostic mechanisms are not in place to ensure that ErbB2 status is known, there is a chance that women who may benefit from this treatment will not receive it, putting them at significantly greater risk of their cancer coming back during the first few years after diagnosis. We are always reminded about the importance of self-examination, but an important safeguard for ALL women is INFORMATION regarding the types of cancer, its diagnosis and treatment and the availability of such treatment in local health care facilities.

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* **Gene amplification** is a cellular process in which multiple copies of a gene are produced, resulting in increased expression of the gene's trait. This usually occurs because of a serious genetic flaw in a cell or group of cells.

TREATMENTS

New drugs continue to be developed for the treatment of breast cancer, including the treatment of triple-negative breast cancer, newer ErbB2 (formerly HER-2) targeted agents in trastuzumab-resistant metastatic breast cancer, bevacizumab for metastatic breast cancer, and CYP2D6 inhibitors when given with tamoxifen. Time will tell.

Sentinal Lymph Node Biopsy

When a breast biopsy is positive for cancer, the sentinel lymph nodes are identified and removed for biopsy. This procedure is also performed for melanoma. When the results are negative, the necessity of axillary lymph node dissection is negated—saving the patient from much additional trauma and pain.

The sentinal nodes are the first nodes to receive the drainage from the site of cancer. If they show no sign of cancer, it is assumed that the entire lymph node drainage system for that site is free of cancer and need not be excised. Identification of these nodes is made by injecting a radio active substance with a short half-life into the biopsy site. The potential lymph drainage systems are then scanned and the first nodes to react are recorded. This recording accompanies the patient to surgery so that the surgeon can make small incisions and remove the few sentinal nodes, which are sent to pathology for evaluation.

Doxorubicin

Doxorubicin (Adriamycin) is one of the anthracyclines, an antibiotic and class of chemotherapy that is effective against several types of cancer including breast, uterine, ovarian, and lung cancers, leukemias and lymphomas. Their mechanisms of action are to inhibit and block DNA and RNA synthesis and create free oxygen radicals that damage the DNA and cell membranes.[11] Their main adverse effects are damage to the heart and vomiting. The threat of a dose-related cardiomyopathy largely limits the prolonged clinical use of doxorubicin. [12]

Trastuzumab

Trastuzumab (Herceptin®) only works in ErbB2-positive cases. Thus, the importance of a definitive diagnosis. If the cancer is ErbB2-negative, trastuzumab would be useless and an added unnecessary risk factor; if it is ErbB2-positive, the drug is specific. Trastuzumab (tras-tu-zu-mab) is a monoclonal antibody[†] that binds to the ErbB2 receptors on the plasma membrane of the tumor. This binding prevents the malignant

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[†] An antibody is said to be **monoclonal** when its binding sites are specific for one single antigen. (An **antigen** is any substance that causes your immune system to produce antibodies against it.)

cycle of the ErbB2 receptors. The cardiotoxic effect of transtuzumab seems to be because there are also ErbB2 receptors that protect the heart and they are disarmed along with those on the tumor, resulting in heart failure.[13]

Trastuzumab-DMI

Trastuzumab-DMI is an antibody-drug conjugate being studied. When used alone it is generally considered to be well tolerated in patients with ErbB2-positive breast cancer because ErbB2 is expressed at low levels in normal tissue, and therefore, damage to normal cells is minimized.[14] In fact, the results of phase I study of trastuzumab-DMI has just been published. [15] The conclusion was that the drug was associated with mild, reversible toxicity and substantial clinical effect with a maximum tolerated dose of 3.6 mg/kg every 3 weeks. Drug-related adverse events included grade </= 2 low platelet count (thrombocytopenia), elevated transaminases[‡], fatigue, nausea, anemia, low grade nausea, vomiting, loss of hair, or malfunction of nerves. There were no cardiac effects requiring dose modification.

The Taxanes—Paclitaxel and Docetaxel

The taxanes are produced by plants of the genus *taxus* (yews) and are used to produce various chemotherapy drugs including paclitaxel (Taxol) and docetaxel (Taxotere). Paclitaxel was first discovered in the bark of the Pacific yew tree.

Paclitaxel and docetaxel are mitotic inhibitors, i.e. they halt the mitotic phase of the cell cycle (Fig. 1). These agents prevent the cell from dividing, preventing cancerous growth. They are used to treat lung, ovarian, breast cancer; head and neck cancer, and advanced forms of Kaposi's sarcoma.

The mitotic phase of the cell cycle is the division of the mother cell into two daughter cells, genetically identical to each other and to their parent cell. This accounts for approximately 10% of the cell cycle. An animation of the process can be viewed on **www.cellsalive.com/mitosis.htm**

Fountzilas et al[16] in a phase II clinical study, found the combination of weekly paclitaxel and trastuzumab to be a safe and active regimen for patients with ErbB2-positive advanced breast cancer. A review by Petrelli[17] reported that paclitaxel was approved for the treatment of metastatic breast cancer when first-line anthracycline-based chemotherapy such as doxorubicin (Adriamycin) is contraindicated.

EXERCISE TO REDUCE CARDIOTOXICITY

In 2009 Wonders et al[18] reviewed the potential for the positive effects of exercise in mitigating the cardiac toxicity in women with ErbB2-positive breast cancer who are

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[‡] **Transaminases** are enzymes that catalyze chemical reactions.

treated with trastuzumab and doxorubicin. Although the cardioprotective benefits of exercise are well known in women undergoing breast cancer treatment,[19] [20] [21] its efficacy in patients receiving both of these drugs has not been examined.

It was once thought that physical activity would enhance the toxic effects of doxorubicin on the myocardium by enhancing free radical formation and mitochondrial changes. However, animal studies[22] have shown that both acute[23] and chronic exercise are protective against doxorubicin-induced damage to the heart because the increase in exercise-induced antioxidant capacity related to increased oxygen consumption protects cardiac cells against injury caused by oxidative stress.[24] [25] [26] [27] [28]

For Now—Aerobic Only!

"Before recommending resistance training during breast cancer treatment, we must have more information about cancer treatment effects on activated satellite cells in human studies." (Clarkson et al 2010[29])

Aerobic exercise. Epidemiological evidence has pointed to the benefits of physical activity in reducing breast cancer risk, which in turn has prompted the American Cancer Society to make specific recommendations for adopting a life style of physical activity as a guideline for protection against cancer. Their recommendations for exercise to prevent cancer and during and after treatment are the same: "that adults engage in at least 30 minutes of moderate to vigorous physical activity, above usual activities, on 5 or more days of the week; 45-60 minutes of intentional physical activity are preferable." These recommendations suggest participation in aerobic types of physical activity.

Resistance exercise. Effects of resistance exercise were not addressed specifically by the American Cancer Society. However, Clarkson et al have cautioned us regarding the effect of resistance exercise plus cancer therapy. In response to strenuous resistance exercise, muscle satellite cells are activated to reenter the cell cycle and proliferate, thus contributing their nuclear material into the muscle fiber to facilitate repair, regeneration, and hypertrophy. However, the role of cancer therapy is obviously to damage rapidly dividing cells, so there is a potential for the satellite cells that enter into the cell cycle to be damaged as well. Loss of these special cells may impair the maintenance of muscle mass.[30]

HOW DRUGS GET THOSE FIVE-SYLLABLE NAMES

In Italy and in France during the 1950s, a new strain of Streptomyces peucetius was found. In Italy it was from the area surrounding a 13th century castle—the Castel del Monet. This new strain produced a red pigment and an antibiotic that acted against tumors in mice. The two teams combined the name "Dauni", a pre-Roman tribe that occupied the area of Italy where the compound was isolated, with the French word for ruby, "rubis", describing the color--thus "daunorubicin."[31]

Clinical trials began in the 1960s, and the drug was successful in treating acute leukemia and lymphoma. However, by 1967, it was recognized that *daunorubicin* could produce fatal cardiac toxicity.[32] From this research, a new compound evolved given the trade name, "**Adriamycin**", after the Adriatic Sea; "**doxorubicin**" became the generic name. The drug was found to be especially useful in treating solid tumors. Unfortunately it remains cardiotoxic.[33]

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