Review Article

A Detailed Study on Breast Cancer its Causes and Treatment

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ABSTRACT

Breast cancer is a very common disease that affects approximately 1 in 10 women. Breast cannot be considered a single disease as it is characterised by distinct pathological and molecular sub types that are treated with different therapies and have diverse clinical outcomes. There has been considerable investigation of the potential for soyfoods to reduce risk of cancer, and in particular cancer of the breast. Most interest in this relationship is because soyfoods are essentially a unique dietary source of isoflavones, compounds which bind to estrogen receptors and exhibit weak estrogen-like effects under certain experimental conditions. There is little clinical evidence to suggest that isoflavones will increase breast cancer risk in healthy women or worsen the prognosis of breast cancer patients. There is no evidence that isoflavone intake increases breast tissue density in pre- or postmenopausal women or increases breast cell proliferation in postmenopausal women with or without a history of breast cancer. The epidemiologic data are generally consistent with the clinical data, showing no indication of increased risk. Furthermore, these clinical and epidemiologic data are consistent with what appears to be a low overall breast cancer risk associated with pharmacologic unopposed estrogen exposure in postmenopausal women. While more research is required to definitively allay concerns, the existing data should provide some degree of assurance that isoflavone exposure at levels consistent with historical Asian soyfood intake does not result in adverse stimulatory effects on breast tissue.

Keywords: Breast cancer, Herbal plants, Isoflavonoids, estrogenic, antiestrogenic.

INTRODUCTION

Breast cancer is a type of cancer that originates in the breast(s). Breast cancer forms in tissues of the breast, usually the ducts (tubes that carry milk to the nipple) and lobules (glands that make milk). It occurs in both men and women. Breast cancer, disease characterized by the growth of malignant cells in the mammary gland. Breast cancer can strike males and females, although women are about 100 times more likely to develop the disease than men. Most cancers in female breasts form shortly before, during, or after menopause, with three-quarters of all cases being diagnosed after age 50. Generally, the older a woman is, the greater is her likelihood of developing breast cancer. Worldwide, breast cancer is the most common cancer among women, and in North America and Western Europe, where life spans are longer, the incidence is highest. In addition, in high-income countries, breast cancer is the leading cause of cancer death among women age 20 to 59.[1-2]

There are two main types of breast cancer:

Ductal carcinoma is the most common form of breast cancer. In this case, tumours form in the cells of the ducts (tubes that carry milk to the nipples). Ductal carcinoma can be invasive with the potential to spread or non invasive. This form of breast cancer accounts for about one in five new cases.[3]

Lobular carcinoma (cancer) occurs in the milk-producing glands, called the lobules. Lobular breast cancer can be non-invasive or invasive with potential to spread. About one in 10 breast cancer cases are invasive lobular cancer.

Three less common types of breast cancer are inflammatory breast cancer, triple-negative breast cancer, recurrent breast cancer.[4]

Inflammatory Breast Cancer: IBC is a unique type of breast cancer that occurs when cancer cells block the lymph vessels in the skin. As a result, the breast can become firm, tender, itchy, red, and warm due to increased blood flow and a build-up of white blood cells. When breasts become inflamed due to an infection or injury, they often become tender, swollen, red, and itchy. However, the underlying cause of IBC is unrelated to inflammation.Inflammatory breast cancer, or IBC, is rare, accounting for 1–3% of all breast cancers. [5]

Triple-negative breast cancer: If a pathology report states that breast cancer cells tested negative for estrogen receptors (ER-), progesterone receptors (PR-), and HER2 (HER2-), this means the cancer is triple-negative. These negative results mean that the growth of the cancer is not supported by the hormones estrogen and progesterone, nor by the presence of too many HER2 receptors. Therefore, triple-negative breast cancer does not respond to hormonal therapy or therapies that target HER2 receptors.[6-7]

Recurrent breast cancer: Recurrent breast cancer is cancer that has recurred, come back, after it has been treated. The cancer may come back in the breast, in the chest wall, or in other parts of the body.

Breast cancer, the most common form of cancer among women, also has the second highest morbidity rate worldwide (10.9% of all cancers). With an estimated 1.38 million new cancer cases diagnosed in 2008, it is also the

most common cancer in both developed and developing regions. About 69,000 new cases have been estimated in each of these regions (population ratio 1:4).Incidence rates vary from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe and are high (80 per 100,000) in developed regions of the world (except Japan) and low (40 per 100,000) in most developing regions. The range of mortality rates is much less (approximately 6-19 per 100,000) because of the more favourable survival of breast cancer in (high-incidence) developed regions. As a result, breast cancer ranks as the fifth cause of death from cancer overall (458,000 deaths), but it is still the most frequent cause of cancer death in women in both developing (269,000 deaths, 12.7% of total) and developed regions. where the estimated 189,000 deaths is almost equal to the estimated number of deaths from lung cancer (188,000 deaths).Statistical analysis suggests that 10% of patients with newly diagnosed breast cancer exhibit advanced or metastatic disease ,whereas approximately 30% to 50% of patients who are diagnosed with this disease at an early stage are prone to progress to a metastatic stage despite administered treatment such as chemotherapy and/or adjuvant therapies.[2] This suggests that despite much advancement in breast cancer treatment over the years, relapse of this disease with time (approximately 40% of all patients with breast cancer experience relapsed disease, with 60%-70% cases of relapse having metastasis)serves as a major roadblock to complete cure of this disease. The only established reason behind this is the underlying presence of a small 5 population of stem-like cells called cancer stem cells (CSCs), i.e. breast cancer stem cells (BCSCs). A recent hypothesis states that these CSCs originate from normal tissue stem cells; adult stem cells serve as ideal targets for malignant transformation because of their lengthy lifespan, and they are normally under tight control within a niche. Also these CSCs share certain properties with normal stem cells (noteworthy ones being the self-renewal capability), which leads to the generation of more CSCs and the ability to differentiate to form a variety of differentiated cells that are found in malignancy.[3] Additionally, CSCs pose a threat in the form of invasion that is resistant to current chemotherapy/radiotherapy, as well as distant metastasis. The concept of CSCs was first identified in hematologic malignancies and has been supported by abundant evidence over the years.[4,5] Tumors originate from cells having self-renewal capacity, an essential thrust for the future is understanding whether the CSCs exhibit this property on their own or acquire it during transitions, such as epithelial-to-mesenchymal transition (EMT) and mesenchymal-to-epithelial transition (MET). EMT is triggered through extracellular signalling of collagen or from growth factors such as fibroblast growth factors, epidermal growth factors, and platelet-derived growth factors (PDGFs) such as PDGF-A, PDGF-B, and PDGF-D. Through the process of EMT, molecular alterations in the form of loss of apical polarity, loss of epithelial cell junctions, reorganization of action cytoskeleton, acquisition of more spindle-shaped morphologic features ,and up regulation and down regulation of mesenchymal markers (fibronectin, N-cadherin, vimentin) and epithelial markers (Ecadherinepithelial-specific antigen) are acquired by epithelial cells. All these alterations constitutively aid in tumour growth and metastasis by a gain in stem-like properties through CSC generation. Also, it has been reported that mesenchymal stem cells (MSCs) are responsible for the initiation of EMT and they promote the entry of breast cancer cells into the bone marrow, which are then recruited by the tumour microenvironment and thus might play a critical role in cancer progression. In addition, bone marrow–derived MSCs also promote tumour progression through cytokine and growth factor production.[6] Further evidence of bone marrow–derived MSCs contributing to up regulation of EMT-specific markers in breast tumourigenesis has been reported in the recent past by Martin, elucidating the underlying role played by these MSCs in cancer progression.[7] Conversely, MET induction by inhibition of tumour necrosis factor-(TGF) and MEK-ERK pathways has resulted in improving Carcinogens accumulate in fatty tissues. Breasts are made up of, mostly, fatty tissues. The average woman comes into contact with innumerable carcinogens and toxins daily, from the soaps she washes with to the makeup she uses, not to mention pesticide residues, smoke and exhaust fumes, solvents, and cleaning compounds.

One more element of Dr Williams' research we should mention: breast cancer rates are higher in colder regions than in the warmer ones. He feels that looser clothing and the extra vitamin D from sun exposure could be responsible for this difference. This is something to consider in your plan to prevent breast cancer. The efficiency of induced pluripotent stem cell generation from fibroblasts.[8]

CAUSE AND SYMPTOMS

The exact causes of breast cancer are largely unknown, but both environmental and genetic factors are involved. Specific mutations in genes called HER2, BRCA1, BRCA2, CHEK2, and p53 have been linked to breast cancer; these mutations may be inherited or acquired. Mutations that are inherited often substantially increase a person's risk for developing breast cancer. For example, whereas some 12 percent of women in the general population develop breast cancer, roughly 60 percent of women who inherit mutations in BRCA1 or BRCA2 eventually develop the disease. Women who carry these mutations also have an increased risk of ovarian cancer. About 5 to 10 percent of men carrying BRCA2 mutations will develop breast cancer in their lifetimes; the risk is lower, about 1 to 2 percent, for men carrying BRCA1 mutations.

In addition to genetic mutations, other factors, including prolonged exposure to the hormone estrogen, as when menstruation starts before age 12 and continues beyond age 50, favour the development of cancer. In

postmenopausal women, breast cancer risk is increased markedly by elevated circulating concentrations of sex hormones (estrogens and androgens). Concentrations of these hormones have been found to be abnormally high in postmenopausal women who are obese, who drink alcohol, or who smoke. In addition, for all women, lack of exercise, obesity, use of oral contraceptives, alcohol consumption, smoking, and previous medical treatments involving chest irradiation are considered risk factors for breast cancer. Women who have had certain kinds of benign tumours are also more prone to developing breast cancer.

The most common symptom of breast cancer is an abnormal lump or swelling in the breast, but lumps may also appear beside the breast or under the arm. Other symptoms may include unexplained breast pain, abnormal nipple discharge, changes in breast texture, or changes in the skin on or around the breastvarious epidemiology studies have shown that smoking increases risk, as does increasing levels of regular alcohol consumption. An extra glass of wine a day will increase risk by about 7 per cent.

Dietary factors are clearly important. Various global studies show that women with breast cancer have much lowered levels of vitamin C, vitamin B-12 and long-chain omega-3. Research shows that tocotrienol vitamin E, fish oils and garlic appear to be particularly protective. Unfortunately, high street vitamin E is a usually a limited and synthetic copy of the real thing being usually the alpha-tocopherol form. Studies have shown that women with a history of breast cancer have lowered levels of the mammalian lignans enterodiol and enterolactone which are made from plant lignans in the intestine. One very good source is flax seed. Phytoestrogen levels (from green plants and pulses) are also low.

Women with lowered levels of vitamin D have a much higher risk of breast cancer. Professor Hollick of Harvard has stated that 25 per cent fewer women would die of breast cancer if they took adequate daily levels of vitamin D, the vitamin developed under your skin by the action of sunlight. Unfortunately, women in Britain do not see too much of the sun in winter. D3 is a supplement often used and 5000IU´s a day the level suggested. Vitamin K seems to aid the action of vitamin D. But it is important to note that various protective natural compounds and vitamins cannot be released from your food unless you have good levels of beneficial bacteria in your intestine. One study showed that women who had a history of taking antibiotics were twice as likely to develop breast cancer (Journal of the American Med Assn 2004, Feb 18; 291). Research, including clinical trials, suggests that such bacteria help release and so boost your vitamin levels (for example: K, B-12, folic acid, biotin), your immune system, the production of anti-cancer chemicals like sodium butyrate, whilst helping to bind to and remove heavy metals and oestrogenic chemicals from the body. Taking multi-strain probiotics may thus be advantageous. Women who exercise regularly (the best is a little - 20 minutes - every day) have less breast cancer and those with it have 50 per cent less mortality if they take daily exercise as part of their cancer-fighting regime.[9]

However by far the biggest risk factor is a heightened level of the hormone oestrogen. Oestrogen-driven cancer may well account for over 70 per cent of all breast cancers. Cancer Research UK has stated that Breast Cancer rates are rising at 2 per cent per year, while oestrogen levels are rising in women by 7 per cent. There are a number of possible reasons for this. For example: Women are having fewer children and breast-feeding them for shorter periods. Both factors (more children and breast feeding for 9 months or more) decrease risk. This may well be due to decreases in the lifetime levels of natural progesterone, a known oestrogen balancer. Women are starting their periods earlier and ending them later. Modern woman has almost twice the number of periods of her 16th century predecessors.

Women in the Western World consume large amounts of saturated fats and especially cows dairy. Saturated fat can provide the building blocks

For oestrogen in the body, Fat is also an excellent solvent and brings with it the animals hormones and pesticides from the fields. Several research studies from the Swedish experts at the Karolinska Institute suggest that a critical factor is the cow's hormone Insulin-like Growth Factor (IGF-1), which seems to stimulate hormones such as oestrogen and other localised cell factors that make your cells grow rapidly. The more dairy you consume, the greater your breast cancer risk according to Karolinska. Another study, this time by researchers in Denmark, amongst 117,000 girls showed that those who put on a big growth spurt between ages 8 and 14 eventually had a higher risk. Again, a finger was pointed at dairy. We have an article linking the level of saturated fat and cow's dairy consumption during a girl´s growing years with the incidence of cancer later in life.

Women now have more stressful occupations; many of these lead to sleep irregularities and deprivation (e.g. Nurses and Air Hostesses). Research shows that this results in lowered levels of the hormone melatonin, which seems to counter excess oestrogen under normal conditions. Melatonin is produced by the pineal gland about 90 minutes after falling asleep. If the room is not completely dark when you sleep, melatonin production can be affected (Blind women never develop breast cancer).But there are other reported causes you should be clear about:

The US State of Evidence report 2006 summarises the findings of more than 350 experimental, epidemiology and ecological studies and recommends new directions for the future in disease management. In particular it looks at the growing and vast amount of research on the effects of environmental pollution - like toxic chemicals and EMFs on the risks of developing the disease:

There is increasing evidence that various Electromagnetic Forces can also reduce these levels of melatonin whilst stimulating levels of IGF-1 and other hormones. This is not a modern myth. Scientists are growing increasingly worried by the electronic smog that surrounds us all from masts, to mobile phones, to Wi-Fi even electric blankets! One study even showed that EMF´s could reduce the effect of the breast cancer drug Tamoxifen!

The use of synthetic oestrogens: CRUK has provided data on the increased risks of breast cancer when women take an oestrogen based contraceptive pill especially if they take it after the age of 30. HRT is also a risk factor. Indeed research from the USA has shown that breast cancer levels declined by 7 per cent in 2005 as a direct result of women giving up HRT.

Xenon-oestrogens, or chemical oestrogen mimics: Increasingly, chemicals that mimic the action of oestrogen in the body are believed to be a significant and modern link to risk. Pesticides like DDT and Lindale were linked to 4-fold increases in breast cancer in Israel. They are banned for use in Western countries, but still sold to Third world countries for use on vegetables we import. Chemicals contained in common in home products like Household Cleaners, toiletry and personal care products may act as oestrogen mimics. For example chemicals in perfumes (which do not have to be listed on labels) like DEHP and toluene, BPA from plastic bottles, white lined cans and even kiddies toys, Phthalates from plastic bottles and packaging, Parabens, often used as a preservative, are all thought by experts to be capable of mimicking the action of oestrogen in the body. Worse Dr Ana Soto of Tufts has shown in her research that such toxins and their effects are cumulative´. In 2013, The World Health Organization report calls for BPA, Phthalates and Parabens to be banned.

Breast cancer may cause any of the following signs and symptoms.

- A lump or thickening in or near the breast or in the underarm area.
- A change in the size or shape of the breast.
- A dimple or puckering in the skin of the breast.
- A nipple turned inward into the breast.
- Fluid, other than breast milk, from the nipple, especially if it's bloody.
- Scaly, red, or swollen skin on the breast, nipple, or areola (the dark area of skin that is around the nipple).
- Dimples in the breast that looks like the skin of an orange, called peaud'orange.[10]

CHEMOTHERAPY

Chemotherapy is standard care for many women with breast cancer. While this treatment is often beneficial, there are some notable drawbacks, including the fact that breast cancer cells can become resistant to chemotherapy and that side effects can be debilitating and intolerable. Scientific evidence suggests that combining certain chemotherapy treatments with certain antioxidants at specific dosages can help improve drug effectiveness or reduce the severity of side effects. This issue is important because it has long been the opinion of many practicing oncologists that antioxidants should simply not be used concurrently with chemotherapy because it was believed that the combination might inhibit chemotherapy effectiveness. This reluctance stems, in part, from the fact that some chemotherapy drugs work by strongly promoting oxidation. This is especially the case for the class of chemotherapy drugs called anthracycline (Adriamycin and epirubicin), the alkylating agents (chlorambucil, cyclophosphamide, thiotepa, and busulfan) and the platinum drugs (cisplatin and carboplatin). Antioxidants, by definition, inhibit oxidation, so it was believed that antioxidants would prevent these chemotherapy drugs from working properly.Chemotherapy drugs that cause high levels of oxidative stress are thought to rely, in part, on using this stress mechanism to kill cancer cells. But oxidative stress might actually reduce the overall effectiveness of chemotherapy. Oxidative stress slows the process of cell replication, but it is during cell replication that chemotherapy actually kills cancer cells (Conklin, 2004), so slower cell replication can mean lower effectiveness of chemotherapy. One approach to addressing this problem is the addition of certain antioxidants at specific dosages to lessen oxidative stress, thus making the chemotherapy treatment more effective (Perumal and Shanthi, 2005).The interaction between chemotherapy and antioxidants is more complex than simply promoting and inhibiting oxidative stress, however. There are several mechanisms by which chemotherapy functions and antioxidants also have a number of different effects on the body. Each antioxidant has a different interaction with chemotherapy and this effect can even change based upon the dosage used.[11]

Chemotherapy drugs acting against breast cancer

- Tamoxifen
- Paclitaxel
- Docetaxel
- Doxorubicin
- Cyclophosphamide
- Methotrexate
- 5-Fluorouracil
- Vinca Alkaloids- Vincristine & Vinblastine
- Gemcitabine
- Epirubicin.[12]

Tamoxifen

Tamoxifen has been used since many years to treat breast cancer in women and men. It is majorly used to treat patients with early-stage breast cancer, as well as those with metastatic breast cancer. As adjuvant therapy, it helps to prevent the original breast cancer from returning and also helps to prevent the development of new cancers in the other breast. As treatment for metastatic breast cancer, the drug slows or stops the growth of cancer cells that are present in the body.

Estrogen can promote the growth of breast cancer cells. Some breast cancers are classified as estrogen receptor-positive, which means that they have a protein to which estrogen will bind. These breast cancer cells need estrogen to grow. Tamoxifen works against the effects of estrogen on these cells. [13]

Paclitaxel

Paclitaxel is a complex diterpintaxane obtained from bark of Western yew tree, which exerts cytotoxic action by a novel mechanism. [13]

Docetaxel

Docetaxel is the more potent congener of paclitaxel. [13]

Doxorubicin

Doxorubicin is a chemotherapy drug, a type of anthracycline antibiotic that is an anti-tumour drug. It is made from the bacterium Streptomyces. Doxorubicin can be used to treat early-stage or node-positive breast cancer, HER2-positive breast cancer, and metastatic disease. Doxorubicin is sometimes combined with Cyclophosphamide and/o r 5-fluorouracil to make a cocktail of breast-cancer fighting chemotherapy drugs. [13]

Cyclophosphamide

Cyclophosphamide is an anticancer drug that can be given either intravenously or orally in tablet form. The intravenous drug is clear. This drug is most often given with doxorubicin. Four to six cycles of treatment over three to six months are commonly administered for breast cancer. Chloramphenicol retards the metabolism of Cyclophosphamide. Cyclophosphamide Injection-200mg/15ml, 500mg/30ml and 1gm/50ml.

Methotrexate

Methotrexate is an anticancer drug that is usually given intravenously for women with breast cancer. This drug is most often given with both cyclophosphamide and 5-fluorouracil. Four to six cycles of the treatment over three to six months are commonly given for breast cancer.

5-fluorouracil

5-Fluorouracil is an anticancer drug that is given intravenously. It is pyrimidine analog. It belongs to the class of drug, Antimetabolites. This drug is most often given with both cyclophosphamide and methotrexate. This drug combination is referred to as "CMF".

Gemcitabine

Gemcitabine is a member of a general group of chemotherapy drugs known as antimetabolites. It is used in breast cancer.

Epirubicin

Epirubicin is a chemotherapeutic drug that is used for the treatment of breast cancer that has spread to the lymph nodes following breast cancer therapy. Epirubicin may cause an inflammation reaction (swelling, tenderness, or redness) at the site of treatment with radiation. [13]

Common Side Effects of Chemotherapeutic Drugs

Chest pain, Arthralgia Myolgia, Edema, Mucositis, Allergic reaction to Doxorubicin, may harm foetus in pregnant women, Possible future infertility greater danger of infections, In some cases, there is a risk of heart damage, Allergic reaction to Doxorubicin, may harm foetus in pregnant women, Possible future infertility greater danger of infections, Myelosuppression, Mucositis, Dermatitis, Diarrhoea, Cardiac toxicity. Some women who receive methotrexate experience mouth sores following treatment, Reversible alopecia (hair loss), and loss of appetite. Low blood cell counts (anemia, leukopenia, neutropenia and thrombocytopenia.[14]

DIAGNOSIS

Early diagnosis greatly improves the odds of survival. When detected early, breast cancer has a very high five-year survival rate, and patients who reach this stage often go on to live long, healthy lives. Survival rates are lower for cancers that have spread locally, and they are very low for cancers that have metastasized, or spread, to distant parts of the body. Breast cancer may be discovered by the patient during regular breast self-examination. When a self-exam is performed on a monthly basis, a woman becomes familiar with her breasts and can readily detect an abnormal change, such as a lump, a swelling, dimpling, or a change in contour, warranting immediate clinical examination. However, a change that is noticed through self-examination may not always be indicative of cancer. Alternatively, if the change found is cancer, the growth may already be fairly advanced. Before they are palpable, growths in the breast may be detected through a procedure known as mammography, which entails the use of X-rays to detect lesions in breast tissue. Mammography is often used for initial diagnosis, but, in order to confirm the presence of cancer, a tissue sample (biopsy) usually must be taken. If cancer is suspected to have spread (metastasized) to nearby lymph nodes, they must also be sampled. Metastasis generally begins in a so-called sentinel lymph node (the first lymph node invaded by cancer cells) and, in the case of breast cancer, spreads to axillary lymph nodes, which are located in and around the armpits. Once cancer has been diagnosed, the tumour's type and degree of invasiveness is assessed. Several imaging methods may be used to determine the degree of metastasis, including X-rays, computerized axial tomography (CAT) scans, or magnetic resonance imaging

(MRI). The presence of receptors for the hormones estrogen and progesterone is also determined because these receptors play an important role in the cancer's development and in decisions regarding the appropriate treatment.[15]

PREVENTION

Breast cancer cannot be completely prevented, but the risk of developing advanced disease can be greatly reduced by several means. For example, maintaining a healthy body weight, decreasing alcohol consumption, and ceasing to smoke each can contribute to a reduction in breast cancer risk. Early detection of subtle breast abnormalities is also important. Medical societies recommend monthly breast self-examination for all women over the age of 20, a breast exam by a health care professional every three years for women 20–39 years old, and a yearly mammogram for all women 40 and older. Women at high risk of developing breast cancer may benefit from taking Tamoxifen to reduce their risk. Women, who are at extreme risk, as determined by a very strong family history or the presence of mutated BRCA genes, may opt for preventive mastectomy. Reduce your dietary fat intake to no more than 20% of total calories. The optimum goal is 10%. Base your diet on rice, potatoes, corn, beans, whole grains and pasta. Eat lots of fresh organic vegetables and fruit. Stress the cancer-fighting foods - the protease inhibitors: fermented soy products, chick-peas, lentils, limas, and red, black and white beans; the cruciferous vegetables including broccoli, Brussels sprouts, cabbage and cauliflower; and the beta-carotenes including carrots, yams, sweet potatoes, tomatoes, green leafy vegetables, and squash. Eat plenty of fibre - that's whole foods. Avoid all dairy products and minimize or avoid animal protein. Avoid all hydrogenated oils: use only olive oils and fish oils, from natural sources. Add a tablespoon of raw flax oil to your diet daily. The Budwig Recipe is a must in preventing breast cancer. Every time you put any other oil (other than what is recommended here) into your body, you are asking for trouble: they wreck havoc on your hormonal system, and induce cancer causing hormones and prostaglandins (hormone-like chemicals) that cause cancer. [16]

For cancer prevention and battling an existing cancer, herbal plants and fermented soy products have been recently touted for many reasons.

Herbs and spices not only contain many phytonutrients but have amazing medicinal and health giving properties. Many have been used for thousands of years to cure adverse human conditions, infections and disease without the serious side effects that modern day drugs provide because they work with the body naturally as nature intended.

The body is clever machines which takes what it needs from plants and expel that which it doesn't. Interfering with this natural process by trying to kill off the pathogenic bacteria causing infection and disease will never work until the processes that take place on a molecular level are understood.

The human body cannot naturally deal with powerful synthetic chemicals which build up as toxins in the system. It needs the additional supportive phytochemicals which herbs possess.

To then treat side effects with more drugs adds to the burden already placed on the delicate weakened human system. The alternative is to use natural herbs as medicine instead which have been 'tested' for thousands of years by our ancestors. Every human body is so completely different, in its makeup, it is impossible to manufacture a 'one size fits all' drug. Certain basic elements are needed in so many different combinations and amounts that drugs will never heal without side effects. Drug companies have managed to persuade society that they have all the answers when in actual fact they have no idea of the consequences for humans that ingest large doses of single chemical elements over a long period of time. Many drugs and addictive substances (including coffee and sugar) block the absorption of nutrients and have adverse effects on the medicinal properties of many natural plant foods and herbs. Therefore the benefit of consuming natural plant foods will only be truly felt by those that do not take any synthetic drugs.

Morton Walker ["Phytochemicals in Soybeans," Health Foods Business, March 1995] points out that the isoflavone components of soy are similar to the drug tamoxifen in their anti-estrogenic effect (lowering estrogen), and should be used daily for any estrogen related malignancies such as breast cancer. Another isoflavone component, genistein... stops the proliferative growth of cells that can differentiate into cancer. Furthermore, Walker states that the anti-angiogenetic (stopping the growth of new blood vessels) properties of genistein are on a par with shark cartilage.

From the Tufts University Diet & Nutrition Letter [February 1995; 12:12], we see that that the phytoestrogens (plant estrogens found in soy protein) will prove to be an alternative to estrogen replacement therapy. Prememopausal women consuming soy protein are protected by this natural antiestrogen, and after menopause they provide the lift estrogen therapy normally provides, but without the cancer risk. From Earl Mindell's book Soy Miracle, we find that soy foods contain antioxidants, boost the immune system, are easier on the kidneys than animal protein, might slow down or prevent kidney damage, and can protect against osteoporosis. [17]

Rutin & Other Flavonoids

Flavonoids are beneficial antioxidants found in fruits and vegetables, especially red grape juice, green tea, soy, and many other legumes. One potential useful example of a beneficial flavonoid is monoHER, one of the most powerfully active antioxidants in flavonoid products, such

as Venoruton, which is used to treat varicose veins (van Acker and Boven, 1997). MonoHER is a derivative of the flavonoidrutin, obtained from many sources, such as buckwheat and the buds of the Chinese herb Saphora japonica. It is also found in propolis. The ability of flavonoids to protect the integrity of blood vessels may, in part, explain how they protect the heart.

Adriamycin can cause cardiomyopathy, a disease of the heart muscle that impairs the heart's ability to pump blood and deliver it to the rest of the body. Three studies found that flavonoids have a beneficial effect in protecting the heart against Adriamycin induced heart damage. The toxicity of Adriamycin to the heart is thought to be caused by oxidative stress. Flavonoids reduce oxidative stress, which may explain how they protect the heart. The studies, conducted in the Netherlands, found that the flavonoid monoHER almost completely protected the heart without influencing the antitumor effect of Adriamycin treatment against estrogen receptor-positive breast cancer cell. Rutin: Typical dosages range from 500 mg to 1,000 mg daily.[18]

Genistein

Genistein is an isoflavone found in legumes, especially soybeans. Isoflavones are antioxidants that counteract the damaging effects of free radicals in body tissues. Genistein has structural similarity to estradiol and therefore competes with estradiol for estrogen receptor binding. This blocks estradiol from stimulating cell growth. Isoflavones, such as genistein, also have antiangiogenic effects, blocking the formation of new blood vessels needed to support the growth of tumours. Genistein sensitizes cancer cells to apoptosis induced by chemotherapeutic agents including Taxotere, gemcitabine, and cisplatin. Apoptosis is the cellular programming in the DNA which instructs cells to self-destruct when they have reached the end of their intended life cycle. Apoptosis is a natural and desirable part of cellular growth, and cancer cells forget when they are supposed to stop growing, thus contributing to uncontrolled cell growth. Some chemotherapy drugs can help induce apoptosis in cancer cells. Genistein also directly inhibits breast cancer cell growth both in cell culture and animals.

A laboratory study from Japan showed genistein made estrogen receptor-negative breast cancer cells more responsive to Adriamycin treatment, thus increasing effectiveness. In contrast, no effect or even decreased drug effectiveness was noted in estrogen receptor-positive breast cancer cells. Another laboratory study from Japan showed that HER2/neu-positive breast cancer cells (which contribute to malignant transformation of cancer cells) were more sensitive to treatment when the combination of genistein and Adriamycin was used. A laboratory study conducted in Italy found that genistein increases the treatment effect of Adriamycin in both estrogen receptor-positive and estrogen receptor-negative breast cancer cells. This effect was even stronger in Adriamycin resistant breast cancer cells. When cancer cells become resistant to a chemotherapy drug, this lowers the drug's effectiveness. An important goal of cancer research is to identify compounds which can reduce chemotherapy resistance, and thus perhaps increase chemotherapy effectiveness. Genistein: A good product will use organic non-GMO genistein. Typical dosages range from 40 mg to 60 mg daily. One cup of soy milk will contain on average about 45 mg of genistein and the other related isoflavones.[19-25]

Quercetin

Quercetin is a flavonoid found in capers, apples, tea, onions, red grapes, citrus fruits, leafy green vegetables, cherries, and raspberries. Quercetin has anti-inflammatory activity, inhibits allergic and inflammatory reactions, and has strong antioxidant activity. An Italian laboratory study found that quercetin greatly increases the treatment effect of Adriamycin in estrogen receptor-positive Adriamycin-resistant breast cancer cell. Quercetin: Typical dosages range from 200 mg to 1,200 mg daily.[26]

All Trans Retinoic Acid (ATRA)

ATRA increased effectiveness of Taxotere in a laboratory study when estrogen receptor-positive and -negative breast cancer cells are pre-treated with ATRA three days prior to treatment with Taxotere (Wang and Wieder, 2004).[27]

Gamma-Linolenic Acid (GLA)

According to a US study (Menendez and Ropero, 2004), the omega-6 polyunsaturated fatty acid gamma-linolenic acid (GLA) and vitamin E, used in combination, enhance the effectiveness of Taxotere in human breast cancer cells (both estrogen receptor positive and negative). Gamma-linolenic Acid (GLA): Available as evening primrose oil, borage seed oil, and black currant seed oil. Typical doses range from about 300 mg to 3,000 g daily, usually with meals.[28]

Garlic

There has been concern that garlic may alter the way drugs are metabolized. In a study conducted at the National Cancer Institute, researchers found that garlic does notsignificantly affect the way Taxotere circulates through the body, but it may reduce the body's ability to clear Taxotere (Cox and Low, 2006). This could potentially increase levels of the drug in the blood. Garlic (from the garlic plant): Typical dosage is approximately one teaspoonful of fresh garlic or 1,000 mg to 3,000 mg of a standardized extract. Note that the active ingredient, allicin, is inactivated by cooking.[29]

Vitamin E

Palmar-plantar erythrodysesthesia (also known as hand-foot syndrome) is a painful feeling in the palms of the hands and the soles of the feet that can sometimes make the skin to turn a red or dark pink colour. The skin can

also develop ulcers, blisters, or sores. The chemotherapy drugs most likely to cause hand-foot syndrome are cyclophosphamide, Taxotere, Adriamycin, liposomal Adriamycin, etoposide, fluorouracil, hydroxyurea, mercaptopurine, methotrexate, mitotane, bleomycin, capecitabine, cytarabine, and thiotepa. In a human clinical study from Turkey, five patients treated with a Taxotere and capecitabine combination developed moderately severe palmar-plantar erythrodysesthesia (hand-foot syndrome). They started vitamin E therapy at 300 mg a day (equivalent to 450 IU) without dose reduction of chemotherapy. After one week of treatment, hand-foot syndrome symptoms began to disappear (Kara and Sahin, 2006).Note that the usual treatment for hand-foot syndrome is dose reduction of chemotherapy, which may lead to reduced effectiveness. This study is important because patients were able to continue at the therapeutic dose of chemotherapy with the help of adjunctive vitamin E. Vitamin E: Avoid synthetic vitamin E, such as alpha-tocopherol or succinate. Seek out the mixed tocopherols, particularly those containing the vitamin E fractions called to cotrienols and gamma-tocopherol. Typical dosage ranges from 50 IU to 800 IU daily.[30]

Grape Seed Polyphenol

Grape seed polyphenol increased effectiveness of Adriamycin against estrogen receptor-positive breast cancer cells and also reversed Adriamycin resistance in an animal study from China (Zhang and Zhou, 2004). Grape Seed extract strongly increases the treatment effect of Adriamycin in both estrogen receptor-positive and -negative breast cancer cells according to a US study (Sharma and Tyagi, 2004).Grape Seed Polyphenol (Grape Seed Extract): Sometimes products may combine grape seed extract with the extract called Resveratrol, the red wine antioxidant from the red pigment of grape skins. Typical dosages range between 50 mg and 200 mg daily.[31]

Green Tea Polyphenols

Epigallocatechin-3-gallate (EGCG) is the principal polyphenol found in green tea. In a laboratory study from China, it was demonstrated that green tea polyphenol improved effectiveness of Adriamycin in estrogen receptor-positive breast cancer cells that had become resistant to adriamyc intreatment (Zhu and Wang, 2001).Green Tea Polyphenols (EGCG): One cup of green tea contains between 10 and 400 mg of polyphenols depending on the source, amount of leaves used, and time the tea steeps. EGCG may be conveniently obtained from extracts. A good product contains 725 mg, standardized to 98% polyphenols, 45% of which is ECG.[32]

Vinca Alkaloids

Vinblastine and Vinblastine are vinca alkaloids. Both are mitotic inhibitor, and are used in cancer chemotherapy.[33]

DISCUSSION

The epidemiological data uniformly suggest there is no adverse association of soy protein or isoflavone intake on the prognosis of women with a history of breast cancer. The apparent benefits of soy consumption are not specific to any subpopulation, and a linear trend toward lowering the risk of recurrence and/or all-cause mortality is consistent across all cohorts regardless of ethnicity. No cohort suggested any interference with the effects of tamoxifen, with a trend toward an additive effect in the WHEL study and a statistically significant risk reduction on recurrence in the LACE cohort.

While all of the studies stratified for tamoxifen use, only 1 of the cohorts stratified for anastrozole use in postmenopausal patients. This was the smallest cohort with only 524 participants, a mere 86 of whom were on anastrozole. Despite this low power, the risk reduction of combining soy with anastrozole reached statistical significance when comparing the highest versus the lowest intakes. This intriguing result needs to be repeated in a larger population to verify the association. These results are intriguing and run contrary to in vitro and rodent studies that suggested proliferative effects of isoflavones on mammary tumors, and possible blockage of Tamoxifen santiestrogenic effects. There are several plausible reasons for this. Perhaps the simplest explanation is that the metabolism of isoflavones in rodents is not equivalent to humans. A recent experiment has suggested this may be the case.

In a study published by the esteemed isoflavone researcher KD Setchell in 2011, the metabolism of genistein in rodents and humans was compared.[34] Using rodent strains that have been used as models in isoflavone research (including Sprague-Dawly rats, and C57BL/6, nude, and transgenic AngptL4B6 mice), a study was designed to assess circulating levels of unconjugated versus conjugated genistein levels. Each rodent strain was given either soy-containing chow and/or a genistein supplement. Human comparison groups included "1) healthy adults who consumed single servings of soy nuts, soy milk, and tempeh; 2) healthy adults subchronically given soy milk; 3) healthy women orally administered 50 mg genistein; 4) healthy women orally administered 20 mg pure S-(-) equal; and 5) 6-mo-old infants fed soy infant formula and later, at age 3 y, a soy germ isoflavone supplement." This study found a vast difference in metabolism between rodent models and all of the human comparison groups. Humans conjugate nearly all of the ingested isoflavones (<1% unconjugated genistein in a steady state and <2% at peak concentrations.) Rodents however had much higher circulating levels of unconjugated genistein, ranging from 4.0% (+/- 0.6%) up to 30.1% (+/- 4.3%) and this varied tremendously by strain of animal. The authors note that these levels of unconjugated genistein represent up to 150 times the amount found in humans. Thus, extrapolation of isoflavone data from rodent studies to humans is not warranted and may be misleading. More to the point,

such extrapolation has mired the perspective of many practitioners into an assumption that is proving difficult to dispel, even in the face of evidence to the contrary.

It is important to note that a plant-based diet is widely accepted as the best dietary means of reducing risk of developing a variety of cancers. It is possible that soy intake was a surrogate for a broader plant-based diet in the above cohorts. In the WHEL study and the Shanghai study, total isoflavone intake was calculated given the dietary information provided and included intake of isoflavones from foods other than soy. Granted, soy is by far the most concentrated isoflavone foodstuff, but many other whole foods also contain isoflavones. In fact, in the United States 45% of isoflavones are ingested from beans and peas, 25% from tea and coffee, 10% from nuts, and 5% from grains.[35] Isoflavone intake may be a surrogate for the broader chemopreventative class of flavonoids and ultimately phytochemicals in general.

The epidemiological cohorts discussed here cannot be extrapolated to include those with stage IV breast cancer. The WHEL and LACE studies excluded those with stage IV disease specifically and the Shanghai study had only 485 participants in the stage III–IV category, rendering a low powered assessment that was not stratified by stage III versus IV. Thus, soy consumption in late-stage disease has no data on its safety. Further, there is some indication that it may be detrimental. One in vitro experiment demonstrated that isoflavones isolated from soy milk were capable of inducing mRNA patterns of expression that mimicked those gotten from 17-B estradiol when only the alpha receptor was available. However, isoflavones mitigated the effects of the alpha receptor when the beta receptor was present. At least in theory, this may be a consideration for late-stage breast cancer patients, where beta receptor expression can be limited or absent.[36]

In addition, both the LACE and the Shanghai cohorts found that there may be a detrimental effect at the highest doses assessed, although this associated risk did not reach statistical significance in either study. The LACE study found that women who had never used tamoxifen and were in the 95th percentile of isoflavone intake had a borderline significant increased risk of recurrence. The Shanghai study found that the linear dose relationship between soy intake and decreased recurrence and mortality appears valid up to 11 g/day of soy (approximately 40 mg isoflavones) after which there is a nonsignificant increase in risk. This dosage is corroborated by the After Breast Cancer Pooling Project, which concluded that 10 g/day of soy protein reduced the risk of both mortality and recurrence. Interestingly, this is very near the level of consumption found in elderly Japanese.[37]

CONCLUSION

This review of research, including laboratory, animal, and human studies, found data in most cases supporting the combination of antioxidants with chemotherapy. Much of the evidence available, however, is from laboratory studies rather than randomized, controlled human studies, so if patients and practitioners decide to use antioxidants, they are faced with some uncertainty as to which antioxidants to use and at which dosages. Further research should help to identify optimal dosing schedules and further investigate the wide range of nutritional and herbal therapies that exist for additional treatment candidates.

When a patient decides not to take antioxidants with chemotherapy, they should discontinue all antioxidants two weeks prior to chemotherapy and not resume until two to three weeks after the last session. The risk is that healthy cells may be less protected against chemotherapy and could include serious consequences such as organ damage and impaired immune function and, therefore, prevent the body's ability to fight cancer. The cancer itself may also be more able to develop resistance to chemotherapy. When a patient decides to take herbal medicine with chemotherapy, they should continue to take herbal medicine before, during, or after chemotherapy in consultation with a knowledgeable practitioner. The risk is that herbal medicine could interfere with chemotherapy and cancer cells not killed by the first round may become resistant to future treatment. The benefit is that herbal medicine may help chemotherapy work well, protect healthy cells against the harmful effects of chemotherapy, and reduce side effects.

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