INTERNATIONAL HEALTH NEWS

Your Gateway to Better Health!

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Welcome to the 173rd issue of International Health News. This month marks the 12th anniversary of our publication on the Web and, with it, my last issue as editor. It has been a great 12 years!! However, it is time to turn the reins over to someone with fresh ideas. So, beginning with the February 2007 issue your editor will be William R. Ware, PhD. Bill, as you know, is a long-time contributor to IHN and his many well-researched and thought-provoking articles have added substantially to the value of IHN over the past few years.

Bill is not planning on any major changes to the format or the philosophy of IHN. We will continue to focus on developments in alternative, complementary and preventive medicine, especially in regard to diet, supplements, vitamins, exercise and lifestyle. We will also continue to seek out and report on the latest research in the fight against arthritis, cancer, heart disease and other degenerative conditions, while keeping a sharp eye out for warnings about dangerous medical procedures and serious adverse effects of pharmaceutical drugs.

In this issue we bring you the final installment of Bill's extensive research into the prevention of breast cancer. While the medical literature presents conflicting evidence as to the causes and risk factors of breast cancer, there is an emerging consensus that limiting alcohol consumption and ensuring an adequate vitamin D and iodine intake are important preventive measures. Maintaining an ideal weight, getting regular exercise and avoiding smoking are other measures which will help prevent not only breast cancer, but other degenerative diseases as well.

Also in this issue we report that soy protein helps reduce cholesterol levels, green tea protects against heart disease, turmeric (curcumin) may be an effective treatment for arthritis, and much more.

Please bear in mind that the cost of publishing this newsletter is solely defrayed by income made from our on-line vitamin store. Without this, there would be no IHN. So, if you need to restock your supplements, please remember that by ordering through my on-line vitamin store you will be helping to maintain the web site and database, and the publication of IHN. You can find the store at http://www.yourhealthbase.com/vitamins.htm.

Also, please don't forget to take a look at our brand new 440-page book "The Prostate and Its Problems". You can find it at http://www.yourhealthbase.com/prostate/book.htm.

Wishing you and your family a happy Holiday Season and good health in the coming New Year,
Hans

Highlights

New analysis supports use of soy protein for cholesterol reduction

NEW ORLEANS, LOUISIANA. Soy protein is widely recommended to combat high blood cholesterol, or hypercholesterolemia, a main risk factor for cardiovascular disease. Researchers from Tulane University School of Public Health and Tropical Medicine set out to quantify the cholesterol-lowering ability of soy protein supplements. They explain that not all previous studies support these claims. The team undertook a meta-analysis of 41 randomized controlled trials dating back to 1982 in which supplementation in the form of isolated soy protein was the only intervention. Adults with and without hypercholesterolemia took part. The amount of the protein consumed ranged from 20 grams to more than 61 grams per day.

The researchers pooled the study results and found a significant benefit on total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides - another type of blood fat linked to atherosclerosis. Mean serum total cholesterol was reduced by an average of 5.26 mg/dL, LDL cholesterol by 4.25 mg/dL, triglycerides by 6.26 mg/dl, and HDL cholesterol was raised by 0.77 mg/dL. The findings were supported by an overall dose-response effect, that is, the greater the amount of soy consumed, the greater the effects. However, the figures are smaller than those found in earlier meta-analyses. This is probably due to more stringent limits on the studies included here.

The findings echo those of a recent research analysis by the American Heart Association, which found that isolated soy protein lowers LDL cholesterol by only a few points, and that supplements containing isoflavones (compounds found in soybeans) are ineffective. The researchers conclude that, while the cholesterol benefits of soy may be small, they are not insignificant - even a small decline could have an important effect on the prevalence of high cholesterol in the general population. They recommend replacing foods high in saturated fat, trans fats, and cholesterol with soy products such as tofu, tempeh and soy nuts.

Reynolds, K. et al. A Meta-Analysis of the Effect of Soy Protein Supplementation on Serum Lipids. The American Journal of Cardiology, Vol. 98, September 1, 2006, pp. 633-40

Role of C-reactive protein in development of heart failure

ROTTERDAM, THE NETHERLANDS. Inflammatory compounds are increasingly thought to contribute to heart failure, contributing to many aspects of the condition. Currently, the most easily-measured marker of such inflammation is C-reactive protein (CRP). Elevated CRP has been linked to adverse outcomes in heart failure, and can predict heart failure among those at high risk.

Researchers from Erasmus MC in Rotterdam examined CRP levels and the development of heart failure in a group of 6,437 men and women aged 55 years or above, who did not have heart failure at recruitment. Serum CRP levels were measured with a high-sensitivity test, and the participants were grouped into four categories depending on CRP concentration. Overall, those in the highest quarter had a 2.64 times higher risk of heart failure than those in the lowest quarter. However, the risk was very different for men than for women. Men's risk was 4.37 times higher in the top quarter, and women's was only 1.86 times higher. Both were significant, but when other cardiovascular risk factors were taken into account, the link with CRP became statistically insignificant for women (1.42 times higher risk). It remained significant, but smaller, for men (3.73 times higher risk).

The researchers conclude that CRP is "strongly and independently associated with occurrence of heart failure in men", but in women, "the association is weaker and does not persist after accounting for established cardiovascular risk factors". They believe that these results may reflect important sex differences in the origins of heart failure. Coronary artery disease may be a more common underlying factor among men, whereas hypertension may be a more common cause in women. The authors also suggest that some of the established heat failure risk factors may play a larger role for women than for men. This study provides further support for the theory that CRP is involved in the development of heart failure, especially in men.

Kardys, I. et al. C-reactive protein and risk of heart failure. The Rotterdam Study. American Heart Journal, Vol. 152, September 2006, pp. 514-20

Drinking green tea may protect against death from heart disease

SENDAI, JAPAN. Green tea has been the subject of much research on the prevention of cancer and heart disease. The polyphenols contained in green tea are thought to have antioxidant properties and have been widely studied in the laboratory and in animals. But prospective studies involving humans are lacking.

A team of researchers from Tohoku University Graduate School of Medicine investigated the health effects of green tea consumption in a group of 40,530 healthy Japanese adults aged 40 to 79 years. Participants were recruited in 1994 and followed for up to 11 years. In this time, 4,209 deaths occurred. Consumption of green tea seemed to have a beneficial effect on risk of death from all causes and from cardiovascular disease, but not cancer. Men who drank five or more cups a day had a 12 per cent lower rate of all-cause mortality than those who drank less than one cup. There was a smaller, non-significant benefit for one cup or more a day. In women, the link was stronger. Mortality risk was 18 per cent lower with three to four cups a day and 23 per cent lower with five or more cups, both significant.

When causes were looked at separately, death from cardiovascular disease was stronger than for all causes combined, especially in women and especially for death caused by stroke. Risk of death from cancer was not significantly linked to green tea consumption. The findings did not alter significantly when several relevant factors were taken into account in the analysis. Lower risks of death from cardiovascular disease and stroke have been linked to green tea consumption in two earlier prospective studies. But green tea was not associated with lower all-cause mortality in another study, and has been linked previously to lower cancer mortality, in contrast with this study.

The authors conclude that, although the benefits of green tea were more pronounced among women, possibly due to factors linked to smoking, it remains important for men too. Clinical trials are now warranted, they conclude.

Kuriyama, S. et al. Green Tea Consumption and Mortality Due to Cardiovascular Disease, Cancer, and All Causes in Japan. The Ohsaki Study. The Journal of the American Medical Association, Vol. 296, September 13, 2006, pp. 1255-65

Editor's comment: There is considerable clinical evidence that EGCG (the active component in green tea) is effective in the prevention of several types of cancer. EGCG is available in supplement form with one capsule corresponding to about 6 cups of green tea.

Dose and coating of aspirin tablets affect response

SAN DIEGO, CALIFORNIA. One of the aims of short-term aspirin therapy is to prevent thrombosis, stroke and heart attack by inhibiting platelet aggregation, and therefore "thinning" the blood. But the success of aspirin therapy has been found to vary depending on factors such as the dose and preparation, as well as differences in patient's sensitivity to the drug.

Researchers from Atlantis Laboratory Systems set out to investigate the reasons behind varying anti-platelet success rates in aspirin therapy. They gave healthy volunteers tablets of either 81mg or 325mg aspirin which were either enteric-coated or uncoated, for six days. The 24 participants randomly assigned to the 325mg dose showed a greater initial antiplatelet response than the 24 participants on the 81mg dose, as measured with a testing system that reports values in aspirin response units (ARU). The tablets with an enteric coating (taken by 24 participants) led to a slower antiplatelet response, but only for the 81mg dose (taken by 11 of these 24 participants). Significant day-to-day variations were found in the responses of the individual participants, but on day seven (once therapy had finished), there was no statistical difference between the mean response in all of the groups, regardless of dosage or coating. The participants' platelet aggregation had completely returned to normal by day 11 - five days after discontinuation.

The authors conclude that an 81mg enteric-coated dose requires significantly more time to reach the maximum protection against thrombosis compared with the other types studied. They conclude that the antiplatelet response was more rapid on a dose of 325mg aspirin per day than 81mg aspirin per day, and an enteric coating delayed the time of response for the 81mg dose. These factors are "important

mediators of the antiplatelet effects of aspirin in some patients", they write. The number of participants in the study was small, and none had cardiovascular disease, nevertheless the researchers felt that based on these findings, they would recommend that individual patients are monitored to "ensure the desired response to initiation or cessation of aspirin therapy".

Coleman, J. L. and Alberts, M. J. Effect of Aspirin Dose, Preparation, and Withdrawal on Platelet Response in Normal Volunteers. The American Journal of Cardiology, Vol. 98, September 15, 2006, pp. 838-41

Hope for turmeric therapy for arthritis

TUCSON, ARIZONA. Many arthritis sufferers use complementary and alternative medicine including dietary supplements, but the composition of supplements varies and their effectiveness is often unconfirmed. New findings suggest that certain preparations of turmeric (curcumin), with its anti-inflammatory properties, may be beneficial for arthritis.

The latest study comes from the University of Arizona in Tucson. Researchers investigated the effects and mechanism of turmeric, comparing the chemical composition of an experimental turmeric extract with products available over the counter. In experiments with rats they found that a turmeric extract free of essential oils had a significant impact on rheumatoid arthritis. This version could prevent acute and chronic arthritis, even reversing the disease after it had been induced, they report. Turmeric also held back joint destruction due to arthritis, and inhibited a protein that is linked to the inflammatory response. It was found to prevent the build-up of osteoclasts (cells that break down bone) in joints.

The researchers say they found an effective dose for rats, and calculated the equivalent for humans to be 1.5 milligrams per day of a portion of the turmeric root that makes up three per cent of dried turmeric powder. It would appear that turmeric dietary supplements share the same mechanism of action as several anti-arthritic drugs currently under development that target NF-kappa-B, a protein which induces inflammation. The inhibition of this protein, and of inflammatory genes activated by it, may be the central mechanism in turmeric's anti-arthritic effects.

Turmeric may also block other inflammatory pathways, given its chemical complexity, and the authors conclude that, just as willow bark provided relief for arthritis patients before the advent of aspirin, it would appear that the underground stem (rhizome) of turmeric may also hold promise for the treatment of joint inflammation and destruction. The researchers recommend that clinical trials be carried out to verify this effect and determine whether turmeric supplements can help prevent arthritis in the general population.

Funk, J. L. et al. Efficacy and Mechanism of Action of Turmeric Supplements in the Treatment of Experimental Arthritis. Arthritis & Rheumatism, Vol. 54, November 2006, pp. 3452-64

Strong evidence of folate link to colon cancer

MONTREAL, CANADA. The risk of colon cancer may be reduced if folate deficiency is identified and treated, suggests new research. Previous studies have indicated that a low dietary folate intake increases the risk of colorectal cancer. But this study claims to be the first to directly show a link.

Researchers from McGill University Health Center found that mice can "develop intestinal tumours due to low dietary folate alone". They explain that this research, which is consistent with previous epidemiological studies in humans, demonstrates a clear link between low dietary folate and the initiation of colorectal cancer in animals. None of the mice fed a normal diet developed tumours whereas one in four mice on the folate-deficient diet developed at least one tumour, they report. The possible mechanisms behind this effect were investigated. It may be that a low level of folate in the diet causes increased damage to DNA, contributing to the likelihood of tumor development. Low folate also appears to alter the behavior of genes which normally limit DNA damage.

An expert from the Institute of Cancer Research at the Canadian Institutes of Health Research (which financed the research) commented that the results of this study highlight how simply adding a

supplement to the daily diet could have tremendous long-term benefits to the individual and the health care system. But he pointed out that much more research will be needed before we will know for certain if folate has any protective effect for colorectal cancer. This is not a reason to consume excessive amounts of folate, he added, but to ensure that the recommended daily amount is taken through a healthy diet or a vitamin supplement.

The study follows an earlier finding by the same team suggesting that high folate diets can protect against heart disease. To increase folate levels in the general population, the US and Canada both require the addition of folic acid (the synthetic form of folate) to breads, cereals, flours, corn meals, pastas and rice.

Knock, E. et al. Low Dietary Folate Initiates Intestinal Tumors in Mice, with Altered Expression of G2-M Checkpoint Regulators Polo-Like Kinase 1 and Cell Division Cycle 25c. Cancer Research, Vol. 66, November 1 2006, pp. 10349-56

NEWSBRIEFS

Anesthetics could trigger Alzheimer's

Experts warn that general anesthetics may produce symptoms of Alzheimer's disease. Researchers from the University of Pittsburgh Medical School explain that anecdotal evidence on the link between surgery and cognitive problems dates back to the 1950s, but is still unclear. Trace amounts of anesthetic agents such as nitrous oxide, halothane and enflurane cause a decline in performance in psychological tests. Recent test tube and animal experiments support the theory that certain anesthetics can reduce the rate at which brain cells are produced and develop. Another possibility is that anesthetics affect the pattern of beta amyloid proteins - potentially forming clumps or "plaques" which are a main cause of Alzheimer's disease. The researchers have identified specific sites where the general anesthetic halothane interacts with beta amyloid protein. Just six hours of exposure to halothane, commonly used in Asia and Africa, is sufficient to trigger protein clumping similar to that seen in people with Alzheimer's.

Mandal, P. K., Pettegrew, J. W. and Mandal, R. Anesthetics and Alzheimer's disease. Presented at the annual meeting of the Society for Neuroscience at the Georgia World Congress Center, Atlanta, USA on Saturday, October 14, 2006 1:15-1:30pm

Simple method shows blood clotting triggers

A new technique has been developed which can help predict when and where blood clotting will occur. Researchers from the University of Chicago created the system using a simple laboratory model showing where blood clotting will take place using microfluidics - the study of tiny volumes of liquids. This allowed them to investigate blood clotting on surfaces that represent blood vessels and plasma on a tiny scale. They found that clotting occurs only when vascular damage is larger than a critical size. They also found that a blood-clotting protein called tissue factor can be present in blood without clotting necessarily taking place - it's the localization of it that makes a difference. Clotting has to occur at the right place at the right time, they explain. A strong, rapid clotting response is essential to stop bleeding at a wound, but at the wrong spot it can block blood vessels and be life-threatening.

Kastrup, C. J. et al. Modular chemical mechanism predicts spatiotemporal dynamics of initiation in the complex network of hemostasis. Proceedings of the National Academy of Sciences, Vol. 103, October 24, 2006, pp. 15747-15752

No proof of benefit for heart catheters

Pulmonary artery catheters may have no place in hospitals, according to intensive care specialists from Australia. Invented in 1968, the pulmonary artery catheter is now widely used in intensive care units to monitor critically ill patients' heart output and lung capillary pressure, in the belief that measuring and altering these variables would lead to better outcomes. But a team from the University of Sydney report on a recent evaluation carried out in the UK which concluded, "None of the trials show that using a pulmonary artery catheter benefits patients. A meta-analysis of 13 trials reported no overall effect of using these devices on mortality or length of hospital stay." A systematic review reached the same conclusions, they add, and the results are consistent across patient groups and in different countries. "Given that the use of pulmonary artery catheters increases the risk of important complications, continued use of these devices is difficult to defend," the authors write.

Finfer, S. and Delaney, A. Pulmonary artery catheters: As currently used, do not benefit patients. British Medical Journal, Vol. 333, November 4, 2006, p. 930-1

Lifestyle help prevents diabetes over the long-term

An intensive diet and exercise intervention is effective in the long-term for preventing impaired glucose tolerance from developing into diabetes. This is the latest finding from a diabetes prevention study based in Finland. A group from the National Public Health Institute in Helsinki observed a sustained reduction in the rate of type 2 diabetes among those given a lifestyle intervention. The study was based on 522 overweight, middle-aged people with impaired glucose tolerance. They were randomly given either an intensive lifestyle intervention or no intervention for an average of four years. A 58 per cent reduction in diabetes risk was found after the intervention, and three years later, the benefits were maintained - the risk was still 36 per cent lower in this group, mainly due to success in the goals of the intervention, such as weight loss, decreased intake of fat and saturated fat, increased fiber intake, and moderately intense physical activity 30 minutes per day or more.

Lindstrom, J. et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. The Lancet, Vol. 368, November 11, 2006, pp. 1673-79

Technique predicts heart failure outcome in elderly

Researchers have developed a simple seven-point system of assessing elderly heart failure patients. The team, from Washington University in St Louis, followed 282 elderly heart failure patients for up to 14 years and identified the main factors which affect survival. These are: advanced age, history of dementia, coronary artery disease, peripheral vascular disease, low blood sodium, high blood urea, and low blood pressure. By totaling how many of these health factors a patient has, mortality risk can be determined, so that more aggressive treatments (such as implantable defibrillators and pacemakers) can be considered. Four or more risk factors are linked to a low probability of six-month survival, whereas 0-1 indicates a good chance of five-year survival. "The system is easy to use, and the variables don't require any specialized testing - they are part of routine medical histories or basic lab tests," say the authors.

Huynh, B. C., Rovner, A. and Rich, M. W. Long-term survival in elderly patients hospitalized for heart failure. Archives of Internal Medicine, Vol. 166, September 2006, pp. 1892-98

RESEARCH REPORT

Primary Prevention of Breast Cancer – Part III

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IODINE AS A PREVENTIVE AGENT IN BREAST CANCER

The breast and thyroid are the principal accumulators of iodine. Venturi [1] and Cann *et al* [2] have hypothesized that dietary iodine deficiency is associated with breast pathology and cancer, and others have also discussed this hypothesis [3,4]. The evidence is as follows (see [1] and [2] for references):

- Clinical studies indicate that treatment with iodine reduces or eliminates the symptoms of some forms of benign breast disease. This is significant because some types of benign breast disease carry enhanced risk of developing breast cancer.
- The progression from intraductal hyperplasia to intraductal hyperplasia with atypia and then to ductal carcinoma in situ (see Part I) appears to be favored by low iodine status and reversed by iodine supplementation. Hyperplasia with atypia and intraductal carcinoma in situ carry an enhanced risk of developing invasive breast cancer [5].
- Traditional Asian medicine has long used iodine-rich seaweed to treat various types of benign breast disease, e.g. to soften breast tissue and reduce breast nodulation.
- Enhanced iodine accumulation in the breast occurs during pregnancy and lactation. It is common to find decreased breast tissue density and nodulation following pregnancy and lactation.

- Iodine reacts with fat to form iodolipids which are thought to be involved in the regulation of proliferation of breast tissue. Deficiency would lead to enhanced proliferation which could contribute to both benign breast disease and cancer.
- Thyroid dysfunction related to iodine deficiency is seen in some breast cancer patients.
- Iodine absorption occurs in the same ductal epithelium where the majority of breast cancer originates.
- Iodine is considered a prerequisite for normal breast tissue development in both animals and humans and in animal studies it has been shown that a deficiency results in benign abnormal tissue growth, malignant tissue growth and an increased sensitivity to carcinogens.
- Japanese women have the lowest breast cancer incidence in the world and have an average intake of about 12 mg/day of iodine from iodine-rich foods such as seaweed, products derived from seaweed, and fish. Some sources quote the Japanese intake as high as 45 or more mg/day. In countries where breast cancer is high, the iodine consumption is in the range of 0.1 to 0.2 mg/day, and may even be lower among women who avoid salt, the principal dietary source after fortification was mandated to combat an epidemic of goiter. It is important to note that Japanese women who live near the sea and eat lots of fish and seaweed products have an enhanced incidence of gastric cancer, and it is thought that this is due to very high levels of iodine intake.
- In rodents, iodine inhibits or delays induced carcinogenesis and reverses the pathological changes produced by iodine deficiency (cystic changes, periductal fibrosis and lobular hyperplasia).

There is clearly considerable circumstantial or anecdotal evidence in the above observations and a noteworthy lack of human studies and clinical trials, especially ones aimed at testing the hypotheses that iodine deficiency is a breast cancer risk factor and that supplementation with iodine will decrease the risk of breast cancer in North American or European women. However, two clinical trials discussed below address the question of treating some aspects of what some call *fibrocystic disease*. As discussed in Part I, fibrocystic disease is not generally benign breast disease of the type that carries a risk of developing into breast cancer, and there is considerable support for not using the term since it encompasses a variety of conditions, most of which are not really considered diseases. Nevertheless, the term continues to be used. The extent to which the problems covered under the umbrella term fibrocystic disease increase the risk of developing true benign breast disease or breast cancer over the long-term appears unknown.

With regard to the two trials, one used as an endpoint the elimination of breast pain and/or the reduction of micronodular growths, tenderness, fibrous tissue plaques and macrocysts [6]. The use of iodine therapy produced significant positive benefits for the majority of participants in the trial, which was multinational and placebo controlled. In the second study the endpoint was the elimination or reduction of pain from what is called cyclic mastalgia, which is breast pain that correlates with the phase of the monthly period [7]. Again, significant improvement was found with iodine therapy. The observed benefits of iodine therapy found in these two trials may or may not extrapolate to reduce cancer risk. However, in his book *Avoiding Breast Cancer* [8] McWherter describes a Canadian study where 3000 women living in Ontario were given an iodine preparation and followed for 10,000 woman-years. The incidence of breast cancer was half the rate of women in the same age bracket who did not take the iodine supplement. It does not appear that this study was published. McWherter uses iodine supplementation in his clinical practice at the FEM center in Texas where he specializes in breast care and the treatment of benign and malignant breast disease.

McWherter [8] also describes a small in-house study of iodine status where a single “loading dose” of iodine/iodide was given to nine consecutive breast cancer patients and urine samples collected. All showed deficiency as judged by the level of urinary iodine/iodide excretion which was significantly below what was considered optimum.

The formulation of the iodine supplement may be important. There is evidence that molecular iodine (I_2) is appropriate for breast tissue whereas the iodide ion as in potassium iodide is active in the thyroid. Supplementation increases the loading of both breast and thyroid tissues, and large doses must be given to increase the load in both. Typical therapeutic doses are 6 mg/day. One convenient source is Lugol’s Solution, which is a mixture of molecular iodine and potassium iodide and provides approximately this dose in one drop. SSKI, a saturated solution of potassium iodide contains 19-50 mg/drop. The proprietary formulation called Iodoral contains 12.5 mg of iodine/iodide per tablet in the same proportion as Lugol’s solution. McWherter

mentions in his book that he uses Lugol's solution in treating benign breast disease. It takes a number of months to see benefit [8]. Lugol's solution is available over the Internet and at some compounding pharmacies.

It is probably safe to say that nobody knows what the optimum daily intake of iodine is. In the US, the average daily intake is estimated at about 0.25 mg/day. Table salt is fortified with potassium iodide (KI) or potassium iodate (KIO_3). In the US, this has raised the iodine status in low-iodine regions (the so-called goiter belt) to the point where goiter is uncommon (but not unknown). It is also generally agreed that iodine deficiency can cause hypothyroidism, mental retardation, and cretinism (severe mental retardation accompanied by physical deformities). Fortification of table salt has also resulted in decreased incidence of cretinism. However, many households do not use iodized salt, and salt avoidance is common because of concerns over hypertension. This leads one to suspect that the average consumption is just enough to prevent the deficiency diseases mentioned above from becoming noticeable, but the daily intake is very low compared to, for example, the intake by Japanese women. Those who have been active in research in this area regard a daily intake of a few hundred micrograms (few tenths of a mg) to be way too low for optimum health.

The circumstantial and anecdotal evidence presented above should be sufficient to prompt human studies designed to examine the iodine-breast cancer hypothesis. The potential benefits could be huge, but the safe limit of iodine intake would be an aspect of such studies, given the possible connection between very high intakes and gastric cancer, although the intakes responsible for this risk enhancement would appear to vastly exceed therapeutic doses used in the context of breast disease and would, no doubt, never be used in studies. Endocrinologists who consider one mg/day excessive and dangerous will raise concerns about supplemental iodine causing either hypothyroidism or hyperthyroidism, although there does not appear to be any significant evidence that a dose of 6 mg/day will cause either disorder except under unusual circumstances. The study on the relief of cyclic mastalgia used a proprietary preparation called IoGen at doses up to 6 mg/day for 6 months without evidence of any adverse effects [7]. The formulation is made by Symbollon Pharmaceuticals, a company which is now enrolling women for a one-year, FDA-approved randomized trial of 6 mg/day of iodine derived from taking IoGen for periodic breast pain associated with symptomatic fibrocystic breast disease. It is significant and instructive that those who believe doses of one mg per day or more are dangerous were unable to block this US government approved study. For more information regarding this trial and a list of participating sites in the US, consult http://clinicaltrials.gov/show/NCT00237523. Individuals wishing to try iodine supplementation should consider doing so under the supervision of a physician.

Space does not permit a more detailed discussion of the potential role of iodine in breast cancer prevention. The reader is referred to an article available free online by Dr. Donald W. Miller, MD, professor of cardiovascular surgery at the University of Washington (http://www.lewrockwell.com/miller/miller20.html).

SOY AND SOY ISOFLAVONES

Interest in the hypothesis that soy foods and the phytoestrogens they contain reduce the risk of breast cancer extends over several decades [9]. Soy is a rich source of isoflavones which have chemical structures similar to estrogen and under certain experimental conditions bind to estrogen receptors and exert estrogen-like activity.

Three recent reviews of the literature are available [9-11]. The most ambitious which is by Trock *et al* concludes that while soy intake may be associated with a small reduction in breast cancer risk, the results must be interpreted with caution due to the potential of exposure misclassification, confounding, and lack of dose response, and in addition there are some experimental results suggesting adverse effects [11]. Gikas and Mokbel simply conclude that "there is no clear evidence that phytoestrogen intake influences the risk of developing breast cancer" [10] and Messina *et al* report the conclusion of a recent workshop—more and better research is needed [9]. Even the American Soybean Association recently withdrew their petition to the FDA that, if successful, would have allowed the claim that there was an inverse association between soy protein intake and breast cancer risk [12].

ORAL CONTRACEPTIVE USE AND HORMONE REPLACEMENT THERAPY

ORAL CONTRACEPTIVES

The use of reproductive hormones as contraceptives began in 1960 and since then an estimated 200 million women have used them. Since most types of hormonal contraceptive contain an estrogen as well as a progesterone component, it is not surprising that questions would be raised regarding the possible impact on breast cancer risk. In a 1996 review (frequently referred to as the *Collaborative Group Study* or the *Oxford Study*), 54 studies were available for analysis which involved over 53,000 women with breast cancer and over 100,000 who were free of breast cancer [13]. These studies included data for oral contraceptive (OC) use by all age groups and a wide range of duration-of-use. This review concluded the increased risk ranged from 24% in current users to 16% 1-4 years after stopping, and 7% 5-9 years after stopping. No evidence of risk was found for those having cancer diagnosed 10 or more years after discontinuing OC use or diagnosed in women over 45 years of age. In this study there was no duration-of-use effect, no pill-type effect and no effect of age at first use. The results were statistically significant.

In contrast to the 1996 Collaborative Group Study, Marchbanks *et al* [14] found in a large case-control study reported in 2002 that for women diagnosed between 35 and 64 years of age, current or former OC use was not associated significantly with increase breast cancer risk, nor were OCs implicated in risk associated with a family history. An important difference between this study and the Collaborative Group Study was that the latter included women who were younger. Consistent with the Marchbanks *et al* study, a recently reported large French follow-up study found no increased breast cancer risk associated with prior OC exposure once a woman reached menopause [15].

Because young women appear to be more susceptible to breast carcinogenesis than older women, there has been considerable interest in the question of OC use in the teen years, the period leading up to the first pregnancy and the period prior to the onset of menopause. The following recent studies are of interest:

- A Swedish case-control study published in 2005 and limited to women diagnosed prior to age 41 found that OC use before age 20 was associated with a 110% increase in risk, whereas OC use before having the first child carried an enhanced risk of 63%. For women diagnosed prior to age 36, there was a 53% increased risk *per year of OC use prior to age 20.* While each year of OC use prior to age 20 resulted in a significant increase in risk of early-onset breast cancer, there was no risk associated with use after age 20 [16].
- In a US study involving women 20 to 54 years of age, all premenopausal, for those developing cancer before age 35 recent use of OCs increased the risk by 126% [17].
- In another US case-control study the subjects were 20-44 years of age at diagnosis. For women < 35 years of age, the results when stratified by the dose of the estrogen component gave a risk of 262% for high vs. 91% for low dose [18].
- A large prospective study [19] with more than a 7-year follow-up conducted in Norway and Sweden enrolled women aged 30-49. Current or recent use of OCs at enrollment was associated with a 60% increase in breast cancer risk. In the 30-39 age group, the significant enhanced risk was 50%, 70% and 50% forever use, current use, or former use respectively, as determined at enrollment. Lower but significant risk was found for the 40-49 age group. This study found enhanced risk associated with use before first full-term pregnancy and also that long-term users were at higher risk.
- A meta-analysis (an analysis of studies) just published addresses the risk of OC use both during the premenopausal period (age < 50) and as well during the period prior to the first full-term pregnancy [20]. All of the cases in this analysis of case-control studies developed cancer prior to age 50. Compared to non-users, ever-users of OCs had a 19% increased risk of breast cancer. For women who had had one or more child, the increased risk was 29% in general and 44% if OCs were used prior to vs. 15% for use after the first pregnancy. Use of OCs for 4 years or more prior to the first pregnancy carried an enhanced risk of 52%. All of these results were found to be statistically significant.

Therefore, while one recent study cited above found no risk for OC use after age 20, the other studies did not confirm this conclusion and enhanced risk for use at younger ages was commonly found. Furthermore, these results lend credence to the suggestion that the disagreement between the 1996 meta-analysis and the study of

Marchbanks may be due to the quite large risk factors associated with OC use by young women, an age group mostly absent from the latter study. These results with younger women are consistent with the enhanced susceptibility of carcinogenesis among this age group and especially among those who have yet to bear a child, and in addition, are consistent with the association between breast cancer risk and the magnitude and duration of estrogen exposure. Nevertheless, there is the widespread belief that OC use is benign in this context, a belief that may well be correct if a woman has not developed breast cancer for 10 years after cessation of use or has entered menopause. Unfortunately, most of the studies available involved older and frequently stronger formulations of the pill than are currently prescribed, and these modern formulations may carry reduced risk, as suggested by one study cited above. Whether these low-dose formulation will carry a small but significant risk will take a number of years to determine, given the apparent lag time between exposure and clinical presentation of this disease, the variety of formulations and modes of administration and the relatively recent introduction and use of these low-dose formulations. The one study cited above that relates to more modern low-dose formulations still found significant risk [18].

Thus there is a risk-benefit problem which may not even be fully appreciated by most women, and this problem goes well beyond the question of contraception. As Burkman points out in an interesting review published in 2001, oral contraceptives provide protection against ectopic pregnancy, reduce the risks of ovarian and endometrial cancer, protect against pelvic inflammatory disease, reduce the incidence of benign breast disease, provide relief from menstrual disorders, reduce the risk of colorectal cancer, improve bone mineral density and finally reduce the risk of rheumatoid arthritis [21]. On the other side of the ledger, aside from the potential increase in breast cancer risk, there is an increase in risk of venous thrombolism and of stroke due to blood clots. Thus this is far from a simple matter. For example, any intervention that reduces the risk of ovarian cancer is important given that this type of cancer is difficult to diagnose before it is too late to treat with more than palliatives measures. Also, avoiding unwanted pregnancy can be very important for some individuals and carry great weight in the decision making process if other methods of contraception are rejected for one reason or another. The decision is particularly challenging for someone who has yet to have her first full-term pregnancy or is a teenager, since as discussed above, the evidence of risk is particularly strong and consistent for this situation. Thus there is a considerable challenge for obtaining guidance, especially if one is associated with a medical culture where the 10-minute office visit is the norm!

HORMONE REPLACEMENT THERAPY AND RELATED ISSUES

A recent review [22] presents a question which puts the hormone replacement therapy (HRT) matter in clear perspective: "…why, for decades, since the mid 1960s, were millions of women prescribed powerful pharmacological agents already demonstrated, three decades earlier, to be carcinogenic?" Yager and Davidson in their review of estrogen carcinogenesis in breast cancer [23] briefly examine the early evidence. In a meta-analysis of 51 studies involving over 160,000 women published in 1997, it was found that use of HRT or ERT (estrogen replacement therapy) for more than 5 years was associated with a statistically significant 35% increase in risk of breast cancer. The recent results of the Women's Health Initiative study (WHI) which also found significant risk in HRT (but not ERT) should have come as no surprise. This study also reported increased risk of venous thrombosis, cardiovascular disease and stroke [24]. The WHI study finally had an impact, was featured big-time in the media and reduced the prescription rate for HRT dramatically, leaving women with few adequately tested options to deal with severe menopause-related symptoms. The surprising fact is that up until then there was evidently insufficient concern to frighten women or change prescribing practices, in spite of at least 51 studies already in the peer review literature that collectively waved a red flag. This is in fact such an interesting phenomenon that in June of 2004 a group of historians, epidemiologists, biologists, clinicians and woman's health advocates gathered to examine the causes and implications associated with the question posed at the start of this section [22].

It is important to realize that HRT in North America has in recent decades almost always involved estrogens derived from horse urine and progesterone-like synthetic chemicals, generally denoted by the term *progestins*, but frequently confused with and erroneously equated to natural progesterone produced endogenously. The great appeal to the "industry" of synthetic progestins is that they can be mass-produced, patented, blessed with regulatory approval, and aggressively marketed. These progestins are now under scrutiny as principal actors in increasing the risk of breast cancer [25]. The estrogens produced from horse urine, also termed *conjugated* and these chemically modified conjugated estrogens actually contain a mixture of nine different estrogens.

In sharp contrast to the HRT generally used in North America, in Europe natural estrogen (estradiol) and other sources of progesterone have been popular for a number of years, primarily due to tradition [26]. In France a widely used HRT involves transdermal or injected estradiol and micronized progesterone or progesterone derivatives not used in North America. In a French prospective cohort study with a follow-up of almost 6 years, it was found that HRT that used estrogen and micronized progesterone gave no increased risk of breast cancer, whereas combined therapy that used synthetic progestins gave results that confirmed the above discussed increase in breast cancer [27]. Micronized progesterone is made from yams or soy, has a molecular structure identical to human progesterone, and micronization enables steady, even absorption. It is available in North America. In another French study reported in 2002, similar results were obtained, i.e. there was no increase in breast cancer in a cohort where 83% used transdermal estradiol gel and a source of progesterone other than the synthetic progestin used in North America [28]. In both of these studies, the results were statistically significant. Two conclusions are evident. There appear to be HRT protocols using bio-identical estrogen and progesterone that do not increase the risk of breast cancer, protocols that have been used in Europe and in particular in France for some time. Also, these results should focus even more attention on synthetic progestins such as medroxyprogesterone acetate as potentially part of the problem with enhanced breast cancer risk.

The term *hormone balancing* is encountered in discussions of HRT as well as in the more general context of female health and ageing issues. This term generally implies the use of natural so-called bio-identical estrogens and progesterone (i.e. identical to those produced by humans) for HRT. This is a complex subject and physicians who specialize in this area attempt to optimize the use of hormones for each patient, taking into account menopausal status, presence or absence of ovaries and/or uterus, age, and plasma hormone levels. Proper and successful orchestration involves monitoring and adjusting dose levels, ratios of estrogens, etc. and monitoring plasma levels. The goal, of course, is to minimize the risks and maximize the benefits. This approach also permits taking advantage of the potential beneficial effects thought to be associated with natural progesterone [8]. It appears debatable whether or not sufficient information is available to permit ascertaining the breast cancer risk associated with various hormone balancing protocols commonly suggested since more hormones than just estrogen and progesterone are frequently involved. Nevertheless, the French studies provide some evidence of safety for natural based HRT using estradiol and micronized progesterone. Readers interested the subject of hormone balancing may wish to consult *Avoiding Breast Cancer* by J. McWherter, MD [8] and *Hormone Balance* by Carolyn Dean, MD [29]. These two books will provide a starting point and an introduction to this rather complex subject. Incidentally, some experts (probably most!) in this area discourage self-testing with saliva test strips followed by self-medication with over-the-counter hormone preparations, and recommend that any use of hormones should be done under the supervision of a physician with experience in this area. But there is a potential problem. Some physicians who include hormone balancing in their programs aimed at prevention and treatment of breast and menopausal problems report considerable trouble with poor accuracy and precision of commercial laboratory hormone assays and incorrect formulations of estrogen and progesterone products by compounding pharmacies. This may be an area worth exploring during consultation.

Hormone balancing in general can go beyond manipulating doses of bio-identical estrogen and progesterone. Two other commonly used substances are testosterone and dehydroepiandrosterone, better know simply as DHEA. The latter is available over-the-counter in the US. Testosterone and DHEA are termed androgens. Testosterone is secreted by both the ovaries and adrenal gland whereas DHEA and its sulfate are adrenal androgens which can be converted into testosterone. Testosterone can be further modified by aromatase-mediated chemistry to give estrogen. This is not the case for methyl testosterone, a form frequently used in combination with conjugated estrogen for the treatment of low libido or other problems associated with oophorectomy or menopause. Methyl testosterone is termed non-aromatizable. It can cause adverse changes in lipid profiles and some physicians do not recommend its use [30].

There have been a number of studies regarding the potential risk of testosterone, both endogenous and exogenous. A recent large, multicenter case-control study nested in a prospective study (serum levels were measured before breast cancer developed) found that the highest serum testosterone levels gave about double the risk when compared to the lowest levels. Subjects were postmenopausal and did not use HRT [31]. This result is consistent with and similar to that found by Key *et al* [32] in a reanalysis of 9 prospective studies which also used serum levels where it was found that when the highest vs. the lowest serum testosterone quintiles were compared, there was a 122% increase in breast cancer risk. For all women taken together, the risk increase was 45%, and there was little dependence on the time from measurement to diagnosis. All these

results achieved statistical significance. Similar results were reported in 2005 based on data from the Nurses' Health Study [33]. In a recent paper, Lillie *et al* examined the question of bias in these studies and found that the association between increased testosterone levels and increased breast cancer risk is unlikely to be due to bias or the lack of adjustment confounding [34].

In a recent study from Harvard of combined estrogen (conjugated) and testosterone hormone replacement in postmenopausal women, a significant increase in breast cancer risk was also found [35]. Most of the participants had been given methyl testosterone. However, the addition of testosterone to conventional HRT (conjugated horse estrogens and synthetic progestins) also increases the risk of breast cancer, although the relative risks were somewhat lower than those found by Key *et al* for non-HRT users [36]. The studies regarding breast cancer risk based on serum levels that found enhanced risk were mostly with postmenopausal women. For premenopausal women, studies are limited. However, two recent studies found a positive association between blood levels of testosterone and breast cancer [37,38]. Noteworthy by their absence are studies designed to access the breast cancer risk associated for women undergoing testosterone only replacement intended to bring levels up to the normal range [30] and the study cited above where risk was found with testosterone replacement therapy, subjects used mostly conjugated estrogen and methyl testosterone and thus the investigation does not directly address the question, although it does point to danger associated with one protocol. The use of methyl testosterone also confuses the issue. Thus the significance of the observed breasts cancer risk associated with testosterone replacement therapy at physiologic levels remains unclear.

The enhanced risk associated with DHEA therapy for postmenopausal women is smaller than that found for testosterone (19-69%), but the data are more limited [31,32]. Page *et al* found no association with either DHEA or DHEA sulfate in premenopausal women [39]. Kaaks *et al* [31] caution that while adequate levels of DHEA (or its sulfate DHEAs) may contribute to better bone mineral density, well-being and libido without significant effects on endometrial tissue, the association with increased risk of breast cancer "strongly caution against the use of DHEAs for postmenopausal hormone replacement." This warning was based on serum level data. How this relates to DHEA therapy intended to treat low levels is unclear.

These results for testosterone and DHEA are fairly recent, and some physicians using hormone balancing which includes these two hormones may be unaware of this literature. The two above cited books ignore or downplay the possibility that the use of testosterone or DHEA might enhance the risk of breast cancer as does the 2005 position statement from the North American Menopause Society, which, while citing the study of Key *et al* discussed above, fails to tell the reader the results [40]. However, in the latest edition of her book *Dr. Susan Love's Breast Book* the author cautions against both the use of testosterone and DHEA because of the possible connection with increased breast cancer risk[41]. Obviously more research is needed.

Women with high endogenous androgen levels (so–called hyperandrogenic) probably are totally unaware that this situation exists. But if for some reason these levels were measured and found high, is there anything that can be done to reduce them? Otherwise this subject is rather academic. In fact, there has been considerable interest in this question in Italy. Two studies have reported decreases in serum levels of testosterone brought about by a dietary intervention which included reductions in total fat and refined carbohydrates, an increase in the ratio of omega-3 to omega-6 polyunsaturated fatty acids, and increased intakes of foods rich in dietary fiber and phytoestrogens [42,43]. Other studies are ongoing [44]. The same group involved in these studies has shown that elevated testosterone levels in treated breast cancer patients are strongly associated with an increased risk of recurrence, and that a dietary intervention similar to the one described above reduced the recurrence rate [45]. This result is consistent with a just reported study that found the metabolic syndrome was a prognostic factor for breast cancer recurrences [46].

Finally, an important area of concern and interest is the use of unopposed estrogen therapy (no synthetic progesterone) and the risk of breast cancer. A study from Harvard just recently published addresses this question with an analysis of data from the Nurses' Health Study. In this prospective study, 11,508 postmenopausal women who had had a hysterectomy and reported estrogen use were included in the follow-up. The cohort was later expanded to a total of 28,835 participants. Users of unopposed estrogen (conjugated) were found to be at increased risk of breast cancer, but only with very long term use (> 20 years) [47]. This result is consistent with that found in the Women's Health Initiative Study discussed above which involved a much shorter follow-up and found no enhanced risk. These results, although based on a limited number of studies, should

provide some reassurance for women using this approach to deal with estrogen deficiency associated with a hysterectomy or menopause. They should however be concerned about continuing the therapy past 20 years.

THE SPECIAL CASE OF HIGH RISK IN GENERAL AND GENETIC RISK (BRCA 1/2) IN PARTICULAR

As discussed in Part I, high risk can refer to having the BRCA1 or BRCA 2 mutation, but is can also refer to the presence of genetic risk inferred from family history that may not be related to the BRCA genes. This high risk level may prompt the recommendation of pharmaceutical or surgical intervention. The pharmaceutical intervention generally involves tamoxifen, an estrogen receptor modulator used mainly in treating breast cancer rather than for primary prevention. Randomized, controlled clinical studies testing the efficacy of tamoxifen for primary prevention utilize cohorts judged to be at high risk but in fact at enrollment there was for most studies no *a priori* information available regarding BRCA status. Pooled analysis [48] of several studies found an overall reduction in the incidence of breast cancer in the treated vs. placebo groups of 38%. Risk reduction was seen only when the cancers found were estrogen receptor positive. In a preliminary report just published [49] which involves a trial at the Royal Marsden Hospital in the UK, 2500 high-risk women were randomized to either tamoxifen or a placebo. At the time of the report, 70 cases of breast cancer had been observed and they were equally divided among the placebo and tamoxifen groups, i.e. no benefit from treatment. It is not clear why. The Marsden cohort had a much higher percentage of individuals with high risk based on family history rather than reproductive history, the presence of benign breast disease, atypical hyperplasia, etc.

Because of the importance of the question, does tamoxifen reduce the risk of breast cancer in individuals carrying the BRCA mutations, for two of these studies the number of BRCA carriers was determined later. Unfortunately, in both studies, the number of carriers was too low to provide any meaningful results. One study involved 13,388 treated participants and yielded only 19 BRCA carriers in the 288 cancer cases that developed. Only cases were tested [50]. In the other, which involved the above mentioned Royal Marsden Hospital study, out of 70 cases only 4 were carriers [49]. Again, the numbers are so small that meaningful analysis is impossible. Thus, if a woman is found on genetic testing to be a BRCA carrier, there appears to be no statistically significant evidence, based on randomized, controlled clinical trials, that tamoxifen will reduce the risk of developing breast cancer, provided this is the only factor contributing to a high-risk classification.

The problem of side effects associated with tamoxifen chemoprevention is nicely summarized by Bergh [48]. Based on pooled studies, treatment of 14,192 (not a typo) women for five years prevented (or deferred!!) 132 estrogen receptor positive cancers. The “expense” in side effects when treated vs. untreated subjects were compared was that 53 vs. 22 developed endometrial carcinoma, 118 vs. 62 had a thromboembolic event (e.g. deep vein thrombosis or pulmonary embolism), and 59 vs. 39 had a cerebrovascular accident or stroke. Incidentally, tamoxifen also appears to increase the risk of cataracts. Not a comforting score card nor the profile of a benign therapy. Thus physicians who must advise BRCA carriers are in a difficult position with regard to risk vs. benefit. Also, as Powles points out [51], the clinical trials of tamoxifen for primary prevention in cohorts deemed high risk have treated very large numbers of women but only a few actually developed breast cancer in either the treatment or placebo arms. The big percentage differences in breast cancer cases between the treated and placebo arms may be impressive (e.g. 50%) but the actual number of cases in each arm is negligible compared to the total number of participants treated and thus exposed to the risk of serious side effects. In other words, the absolute number of breast cancer cases prevented was very small. Another problem associated with seeking guidance from clinical trials is that, compared to the long times associated with risk of developing breast cancer, clinical studies of chemoprevention that run only 5 years may not be very informative, but very long trials may not be operationally or financially feasible and also involve long-term exposure to the risk of side effects. These are issues that the BRCA carrier may wish to explore with her physician before agreeing to undergo prophylactic therapy with tamoxifen or related drugs.

The BRCA carrier does have more effective primary preventive options that are evidence based—bilateral mastectomy or the removal of both ovaries. The former is profoundly disfiguring with potential psychological problems, although breast reconstruction has progressed significantly. Bilateral mastectomy yields approximately a 90% reduction in risk. Removal of the ovaries (oophorectomy) yields a 56% reduction of risk of breast cancer for BRCA 1 carriers and *perhaps* a 46% for BRCA 2 carriers [52]. An important consideration is

that the risk of ovarian cancer, which is considerably enhanced in BRCA carriers, is also reduced by about 90% by oophorectomy. Even better results were reported recently at the annual meeting of the American Society of Clinical Oncology. It was reported that removal of both ovaries and fallopian tubes reduced the risk of breast cancer by 70% [53]. But oophorectomy has its own set of side effects since it amounts to surgically induced menopause which, if severe symptoms develop, leads to the need for treatment, and childbearing now becomes vastly more complex. However, when confronted with an estimated lifetime probability of 60-80% for having breast cancer, some women do indeed elect one or both of these radical preventive measures.

Serious questions can also be raised in the case of young women as to the long-term effect of oophorectomy as it relates to the resultant estrogen deprivation. A study from the Mayo Clinic just published in the *Lancet* (Oncology) addresses this issue [54]. Researchers investigated the impact of prophylactic bilateral oophorectomy on mortality. It was found that women having this surgical intervention before the age of 45 years had a 67% increase in overall mortality compared to controls. This increase in mortality was seen mainly in women who had not received post-surgical estrogen replacement up to age 45. There was increased risk of non-cancer related mortality unless estrogen replacement occurred. Premature estrogen deficiency that was not compensated throughout the post-surgical period up to age 45 increased the risk of cardiovascular disease, osteoporosis, bone fractures and neurological diseases. There was also an increased risk of estrogen-related cancers despite oophorectomy, but this was attributed partly to preexisting conditions. The authors point out that current practice involves prescribing estrogen after women undergo prophylactic bilateral oophorectomy before menopause, but whether they receive treatment up to age 50 is unclear, and the results of the Women's Health Initiative trial have prompted a striking reduction in the use of estrogen alone as well as estrogen plus progestins for all ages. They suggest that the results of the Women's Health Initiative study might not apply to women with natural or surgical menopause before the age of 50 years, and that this practice should be reconsidered.

Finally, there is growing interest in more intensive screening as a partial solution to the high risk associated with BRCA carriers or those with a high-risk profile from family history and other factors. Intensive in this context generally means adding additional imaging such as MRI to mammography. To quote Dr. A.S. Whitemore of Stanford University School of Medicine [53], " Putting myself psychologically in the shoes of a young women with a BRCA 1 mutation, I certainly would get MRI screening of the breasts. I would be religious about it. I would not have a mastectomy; I would just get very good screening." An aspect of this philosophy is that one avoids the heavy costs in side effects associated with surgical or pharmacological risk reduction measures and simply takes the risk of cancer developing with the hope of early enough detection to permit successful treatment. A woman electing this approach should consider researching the extent of local expertise with this relatively new application of MRI and perhaps seek out a center specializing in the monitoring of BRCA carriers and others at very high risk, even if some travel is involved. This approach also allows one to postpone irreversible therapy while waiting for better non-surgical preventive measures to be developed, an option that may be very attractive to younger BRCA carriers.

OTHER RISK FACTORS AND PREVENTIVE ACTIONS

RISK ASSOCIATED WITH RADIATION EXPOSURE

It is generally acknowledged that radiation exposure is associated with increased breast cancer risk and is cumulative, but at low doses the risk is usually boarding on negligible [55]. For example, enough is known about the dose vs. risk to estimate that even a number of ordinary chest x-rays would only yield a relative risk of about 1.02, i.e. a 2% increase in risk, which is close to insignificant [56]. However, the picture changes a bit when age is factored in. For example, the extensive use of x-rays to monitor children with scoliosis significantly increased the risk of breast cancer in later life [57]. The number of x-rays taken ranged from a few to over 70. Exposure started at an early age, mostly before 14. It is well known that the sensitivity to radiation in this context is high in this age group [55]. Increased breast cancer risk is also seen in individuals, frequently young, who are given high dose radiation for Hodgkin's lymphoma and as well as in others who receive therapy that exposes the breasts to radiation. The benefits presumably outweigh the risks from therapeutic radiation in such situations.

However, an interesting situation is presented by BRCA carriers. In a just reported multi-national study [56], the risk of chest x-rays was examined in a cohort study of 1,610 women who had the BRCA 1/2 mutation. Compared to the above-mentioned groups where cumulative radiation exposure was high, this cohort had

exposure only from routine chest x-rays, which according to the author's estimate, put them at least a factor of 10 lower in exposure as compared to groups where enhanced risk from x-rays was found. In this cohort of BRCA carriers, any reported exposure to chest x-rays was associated with an increase in breast cancer, the risk was increased in women aged 40 or younger and in women born after 1949, and the risk was particularly high for those exposed only before the age of 20. These results were described as clinically significant, given the already high risk among BRCA carriers and the potential for a two- to three-fold increase in risk associated with chest x-ray exposure. These results also raise the issue of potential risks associated with mammographic screening which is often recommended on an annual basis for BRCA carriers starting at age 30.

ENVIRONMENTAL ESTROGENS AND COSMETICS

The role of estrogen in the etiology of breast cancer is well established and this raises questions concerning the potential contribution from cosmetics and many chemicals in the environment that can enter the human breast and may have estrogenic activity. For example, parabens (esters of p–hydroxybenzoic acid) widely used as preservatives in underarm cosmetics (deodorants) have been implicated. These chemicals have inherent estrogenic and other hormone related activity and absorption might explain the clinical observation showing a disproportionately high incidence of breast cancer in the upper outer quadrant of the breast, just the local area of frequent and long-term application. Parabens have also been found in human breast tumors [58,59]. The fact that many chemicals thought to carry potential risk tend to accumulate slowly over the years is a worrisome aspect as is the possibility that while individual levels of a given chemical may not be dangerous, a number can act together to produce significant risk. The list of chemical candidates is long. The bottom line appears to be that no one knows the nature or seriousness of the risk and that more research is needed. However, such research is very difficult and in most situations, also presents ethical issues which prevent direct human testing. A discussion of individual chemicals and the associated evidence of risk are beyond the scope of this review. The reader is referred to a very recent and comprehensive review [60].

ASPIRIN AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN BREAST CANCER PREVENTION

A large number of studies have appeared concerning the potential of aspirin and other non-specific non-steroidal anti-inflammatory drugs (NSAIDs, e.g. ibuprofen) and specific COX-2 inhibitors such as Celebrex for the primary prevention of breast cancer. Epidemiologic studies have given conflicting results. Four large prospective cohort studies published between 1996 and 2005 [61-64] with long-term follow-up involving over 390,000 women and over 9000 observed breast cancer cases found mostly no significant evidence of benefit from the use of aspirin, ibuprofen or other NSAIDs and one study found a modest increase in risk associated with long term use [63]. Only about half of case-control studies yielded evidence of significant benefit [65]. When very large cohort studies with long follow-up yield evidence of no benefit and case-control studies are inconsistent, it is hard to make a case for the benefits of the intervention in question. As regards the specific COX-2 inhibitors, a recent case-control study found significant benefit associated with Celebrex and Vioxx but only 10 cases were compared to controls in the analysis [66]. Given the potentially serious gastrointestinal toxicity associated with long-term use of NSAIDs and the well publicized cardiovascular risks associated with the use of COX-2 inhibitors and perhaps even some non-specific NSAIDs taken at high dose [67,68], it is not surprising that there appears to be a reluctance among experts to recommend the use of any member of this class of drug for long-term primary prevention of breast cancer [69]. It should be mentioned, however, that the evidence that NSAIDs appear to play an important preventive role in colorectal cancer seems generally acknowledged as is the role of inflammation as a factor in the initiation and progression of a number of cancers [70].

The target of both specific (COX-2) and non-specific NSAIDs are the cyclooxygenase enzymes (COX-1 and COX-2) which, among other actions, convert the omega-6 fatty acid arachidonic acid (AA) to prostaglandins. The COX- 2 derived prostaglandin PGE_2 (a so-called eicosanoid) is inflammatory and related to cancer through activating cell proliferation and migration, angiogenesis (development of tumor blood supply) and inhibiting apoptosis (normal programmed cell death) [70]. Both specific and non-specific NSAIDs inhibit the production of this prostaglandin through enzyme inhibition. Another way to suppress AA derived eicosanoids such as PGE_2 is through a low intake of its precursor linolenic acid, the dominant omega-6 fatty acid in food, and a high intake of omega-3 fatty acids, especially the long-chain acids EPA and DHA discussed above. Experimental data suggest that a ratio of dietary omega-3 to omega-6 fatty acids needs to be 1:1 or 1:2 in order to provide protection against the development of cancer through the manipulation of the AA tissue concentration [71]. In most Western countries the dietary omega-3 to omega-6 ratio ranges from 1:10 to 1:50. It has been suggested that failure to obtain consistent results in studies that examined the effect of high dietary intakes of omega-3 fatty

acids (e.g. from fatty fish consumption) is due to the overwhelming effect of high levels of AA and thus the impossibility of reducing the omega-3 to omega-6 ratio down to say 1:2 [72]. The point is that some of the same end results produced by NSAIDs may be achievable, apparently without side effects, by adjusting the omega-3 to omega-6 balance, generally by increasing the consumption of fish and/or supplementation with eicosapentaenoic acid (EPA), one of the omega-3 essential fatty acids found in fatty fish and fish oil [73] and reducing the consumption of the linoleic acid (found in vegetable oils like corn, soybean, sunflower and safflower oil, in meat and in many prepared food products). Individuals who consume large quantities of linoleic acid, the omega-6 precursor of AA, may be unable to achieve a beneficial omega-3 to omega-6 balance simply by eating fish once or twice a week or, in many cases, every day. The measurement of the cellular AA/EPA ratio in blood cell phospholipids, a test mentioned above that is now available at some clinical and diagnostic laboratories, can provide guidance as to current status and progress in suppressing tissue AA and its conversion to pro-inflammatory prostaglandins [73]. Someday there may be studies that examine the relationship between cancer risk, the omega-3 and omega-6 dietary intake *and the resulting cellular ratio of AA to EPA*. This would eliminate a serious shortcoming in past studies mentioned above that examined the relationship between diet, inflammation and cancer. Barry Sears argues on the basis of extensive data that bringing the AA/EPA ratio down to 2 to 4 should have significant health benefits, especially with regard to inflammation-mediated illnesses, and the list of such disorders is long [73].

CONCLUSIONS

Fairly strong evidence has been presented concerning risk reduction associated with limiting alcohol consumption or taking folic acid supplements to counteract the adverse effects of drinking. Premenopausal women should perhaps be concerned about high intakes of animal fat, red meat, high-fat dairy products and all women should consider limiting foods rich in omega-6 fatty acids and eating more foods high in omega-3 fatty acids or even supplementing with EPA and DHA. Avoiding oral contraceptives during the teenage and early adult years also appears justified from the breast cancer risk standpoint, but this is clearly a complex issue. Vitamin D is perhaps the most important micronutrient in the context of breast cancer prevention as well as other health issues, and both prudent sun exposure and supplements appear worth considering. Iodine intake and status appear to be much more important than generally recognized, and iodine supplementation is part of the breast cancer prevention program some physicians use. Avoiding HRT and limiting ERT to a few years if symptoms associated with menopause are intolerable appear indicated, but so-called hormone balancing may turn out to be an attractive option. Other actions that are supported by evidence and can be described as potentially effective involve not smoking, making exercise a life-long habit, and taking very seriously the matter of weight loss after menopause as well as obesity in general. Evidence has been presented concerning the merits of sleeping in total darkness.

Finally, there is the special case of high-risk individuals, identified either because of strong family history indications or because genetic testing has revealed a BRCA mutation. Women in this position should consider seeking advice and perhaps consider undergoing surveillance from a physician or a clinic specializing in this area. The side effects of medical prevention, be it through drugs or surgery, are of such a magnitude that these interventions must be carefully weighed for risk vs. benefit. A second opinion seems highly desirable. The most conservative approach seems to be very active surveillance with multiple imaging techniques done at a center specializing in high-risk individuals, and in addition, frequent examinations. There is evidence suggesting that BRCA carriers should minimize x-ray exposure but this is incompatible with frequent mammograms. Life is rarely simple when dealing with the risk of cancer or cancer itself. For those with high risk of breast cancer, the risk of ovarian cancer is also a very serious issue which women in this category should insist be addressed with the best possible surveillance protocols available.

This review has concentrated on preventive aspects that are based on clinical or epidemiologic studies. Results that failed to achieve statistical significance by the usual criteria based on confidence intervals (limits) have by and large been ignored. It turns out that there are a number of actions a woman can take that are rather solidly evidence based. Much fascinating research involving cell culture studies has been omitted even though it gives a glimpse of potential future preventive interventions. Finally, screening by mammography and its relation to primary prevention has been omitted intentionally from this review. It is a complex and highly controversial topic which may be the subject of a future review. For now, the interested reader is referred to the comprehensive

and up-to-date review by Ralph Moss, Ph.D. which can be purchased for a nominal amount at http://www.cancerdecisions.com

REFERENCES

1. Venturi S, 2001. Is there a role for iodine in breast diseases? Breast. 10(5):379-382.
2. Cann SA, van Netten JP, van Netten C, 2000. Hypothesis: iodine, selenium and the development of breast cancer. Cancer Causes Control. 11(2):121-127.
3. Smyth PP, 2003. The thyroid, iodine and breast cancer. Breast Cancer Res. 5(5):235-238.
4. Aceves C, Anguiano B, Delgado G, 2005. Is iodine a gatekeeper of the integrity of the mammary gland? J Mammary.Gland.Biol.Neoplasia. 10(2):189-196.
5. Derry DM, Breast Cancer and Iodine. Trafford Publishing, Victoria, BC, 2001.
6. Ghent WR et al., 1993. Iodine replacement in fibrocystic disease of the breast. Can.J Surg. 36(5):453-460.
7. Kessler JH, 2004. The effect of supraphysiologic levels of iodine on patients with cyclic mastalgia. Breast J. 10(4):328-336.
8. McWherter J, Avoiding Breast Cancer. A.E. Rosebud, Dallas, 2006.
9. Messina M, McCaskill-Stevens W, Lampe JW, 2006. Addressing the soy and breast cancer relationship: review, commentary, and workshop proceedings. JNCI Cancer Spectrum. 98(18):1275-1284.
10. Gikas PD, Mokbel K, 2005. Phytoestrogens and the risk of breast cancer: a review of the literature. Int.J Fertil.Womens Med. 50(6):250-258.
11. Trock BJ, Hilakivi-Clarke L, Clarke R, 2006. Meta-analysis of soy intake and breast cancer risk. JNCI Cancer Spectrum. 98(7):459-471.
12. Martinez ME, Thomson CA, Smith-Warner SA, 2006. Soy and breast cancer: the controversy continues. JNCI Cancer Spectrum. 98(7):430-431.
13. 1996. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet. 347(9017):1713-1727.
14. Marchbanks PA et al., 2002. Oral contraceptives and the risk of breast cancer. N Engl J Med. 346(26):2025-2032.
15. Dumeaux V et al., 2005. Previous oral contraceptive use and breast cancer risk according to hormone replacement therapy use among postmenopausal women. Cancer Causes Control. 16(5):537-544.
16. Jernstrom H et al., 2005. Impact of teenage oral contraceptive use in a population-based series of early-onset breast cancer cases who have undergone BRCA mutation testing. Eur.J Cancer. 41(15):2312-2320.
17. Althuis MD et al., 2003. Breast cancers among very young premenopausal women (United States). Cancer Causes Control. 14(2):151-160.
18. Althuis MD et al., 2003. Hormonal content and potency of oral contraceptives and breast cancer risk among young women. Br.J Cancer. 88(1):50-57.
19. Kumle M et al., 2002. Use of oral contraceptives and breast cancer risk: The Norwegian-Swedish Women's Lifestyle and Health Cohort Study. Cancer Epidemiology Biomarkers Prevention. 11(11):1375-1381.
20. Kahlenborn C et al., 2006. Oral contraceptive use as a risk factor for premenopausal breast cancer: a meta-analysis. Mayo Clin Proc. 81(10):1290-1302.
21. Burkman RT, 2001. Oral contraceptives: current status. Clin Obstet.Gynecol. 44(1):62-72.
22. Krieger N et al., 2005. Hormone replacement therapy, cancer, controversies, and women's health: historical, epidemiological, biological, clinical, and advocacy perspectives. J Epidemiol Community Health. 59(9):740-748.
23. Yager JD, Davidson NE, 2006. Estrogen carcinogenesis in breast cancer. N Engl J Med. 354(3):270-282.
24. Modena MG et al., 2005. New evidence regarding hormone replacement therapies is urgently required transdermal postmenopausal hormone therapy differs from oral hormone therapy in risks and benefits. Maturitas. 52(1):1-10.
25. Campagnoli C et al., 2005. Pregnancy, progesterone and progestins in relation to breast cancer risk. J Steroid Biochem.Mol.Biol. 97(5):441-450.
26. Stahlberg C et al., 2003. Hormone replacement therapy and risk of breast cancer: the role of progestins. Acta Obstet.Gynecol.Scand. 82(7):335-344.
27. Fournier A et al., 2005. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Int.J Cancer. 114(3):448-454.
28. de Lignieres B et al., 2002. Combined hormone replacement therapy and risk of breast cancer in a French cohort study of 3175 women. Climacteric. 5(4):332-340.
29. Dean C, Hormone Balance. A Woman's Guide to Restoring Health and Vitality. Adams Media, Avon, MA, 2005.
30. Basaria S, Dobs AS, 2004. Safety and adverse effects of androgens: how to counsel patients. Mayo Clin Proc. 79(4 Suppl):S25-S32.
31. Kaaks R et al., 2005. Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. Endocr.Relat Cancer. 12(4):1071-1082.
32. Key T et al., 2002. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. JNCI Cancer Spectrum. 94(8):606-616.

33. Missmer SA et al., 2004. Endogenous estrogen, androgen, and progesterone concentrations and breast cancer risk among postmenopausal women. JNCI Cancer Spectrum. 96(24):1856-1865.
34. Lillie EO, Bernstein L, Ursin G, 2003. The role of androgens and polymorphisms in the androgen receptor in the epidemiology of breast cancer. Breast Cancer Res. 5(3):164-173.
35. Tamimi RM et al., 2006. Combined estrogen and testosterone use and risk of breast cancer in postmenopausal women. Archives of Internal Medicine. 166(14):1483-1489.
36. Tworoger SS et al., 2005. Plasma sex hormone concentrations and subsequent risk of breast cancer among women using postmenopausal hormones. JNCI Cancer Spectrum. 97(8):595-602.
37. Micheli A et al., 2004. Endogenous sex hormones and subsequent breast cancer in premenopausal women. Int.J Cancer. 112(2):312-318.
38. Yu H et al., 2003. Plasma sex steroid hormones and breast cancer risk in Chinese women. Int.J Cancer. 105(1):92-97.
39. Page JH et al., 2004. Plasma adrenal androgens and risk of breast cancer in premenopausal women. Cancer Epidemiology Biomarkers Prevention. 13(6):1032-1036.
40. Position Statement: The role of testosterone therapy in postmenopausal women. Position statement of the North American Menopause Society. Menopause 12[5], 497-511. 2006.
41. Love SMwKL, Dr. Susan Love's Breast Book. Da Capo Press, Cambridge MA, 2005.
42. Kaaks R et al., 2003. Effects of dietary intervention on IGF-I and IGF-binding proteins, and related alterations in sex steroid metabolism: the Diet and Androgens (DIANA) Randomised Trial. Eur.J Clin Nutr. 57(9):1079-1088.
43. Berrino F et al., 2001. Reducing bioavailable sex hormones through a comprehensive change in diet: the diet and androgens (DIANA) randomized trial. Cancer Epidemiology Biomarkers Prevention. 10(1):25-33.
44. Franco B, 2006. Androgens and breast cancer. Int.J Gynecol.Cancer. 16 Suppl 2:493.
45. Berrino F et al., 2005. Serum testosterone levels and breast cancer recurrence. Int.J Cancer. 113(3):499-502.
46. Pasanisi P et al., 2006. Metabolic syndrome as a prognostic factor for breast cancer recurrences. Int.J Cancer. 119(1):236-238.
47. Chen WY et al., 2006. Unopposed estrogen therapy and the risk of invasive breast cancer. Archives of Internal Medicine. 166(9):1027-1032.
48. Bergh J, 2003. Breast-cancer prevention: is the risk-benefit ratio in favour of tamoxifen? Lancet. 362(9379):183-184.
49. Kote-Jarai Z et al., 2006. BRCA1/BRCA2 mutation status and analysis of cancer family history in participants of the Royal Marsden Hospital tamoxifen chemoprevention trial. Cancer Lett.
50. King MC et al., 2001. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA: The Journal of the American Medical Association. 286(18):2251-2256.
51. Powles TJ, 2002. Anti-oestrogenic prevention of breast cancer--the make or break point. Nat.Rev.Cancer. 2(10):787-794.
52. Eisen A et al., 2005. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. J Clin Oncol. 23(30):7491-7496.
53. Vanchieri C, 2005. Risk reduction works for BRCA mutation carriers--with heavy costs. JNCI Cancer Spectrum. 97(14):1032-1033.
54. Rocca WA et al., 2006. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol. 7(10):821-828.
55. Ronckers CM, Erdmann CA, Land CE, 2005. Radiation and breast cancer: a review of current evidence. Breast Cancer Res. 7(1):21-32.
56. Andrieu N et al., 2006. Effect of chest X-rays on the risk of breast cancer among BRCA1/2 mutation carriers in the international BRCA1/2 carrier cohort study: a report from the EMBRACE, GENEPSO, GEO-HEBON, and IBCCS Collaborators' Group. J Clin Oncol. 24(21):3361-3366.
57. Morin DM et al., 2000. Breast cancer mortality after diagnostic radiography: findings from the U.S. Scoliosis Cohort Study. Spine. 25(16):2052-2063.
58. Darbre PD, 2003. Underarm cosmetics and breast cancer. J Appl.Toxicol. 23(2):89-95.
59. Harvey PW, Darbre P, 2004. Endocrine disrupters and human health: could oestrogenic chemicals in body care cosmetics adversely affect breast cancer incidence in women? J Appl.Toxicol. 24(3):167-176.
60. Darbre PD, 2006. Environmental oestrogens, cosmetics and breast cancer. Best.Pract.Res Clin Endocrinol Metab. 20(1):121-143.
61. Egan KM et al., 1996. Prospective study of regular aspirin use and the risk of breast cancer. JNCI Cancer Spectrum. 88(14):988-993.
62. Harris RE et al., 2003. Breast cancer and nonsteroidal anti-inflammatory drugs: prospective results from the Women's Health Initiative. Cancer Res. 63(18):6096-6101.
63. Marshall SF et al., 2005. Nonsteroidal anti-inflammatory drug use and breast cancer risk by stage and hormone receptor status. JNCI Cancer Spectrum. 97(11):805-812.
64. Jacobs EJ et al., 2005. Aspirin and other nonsteroidal anti-inflammatory drugs and breast cancer incidence in a large U.S. cohort. Cancer Epidemiology Biomarkers Prevention. 14(1):261-264.
65. Khuder SA, Mutgi AB, 2001. Breast cancer and NSAID use: a meta-analysis. Br.J Cancer. 84(9):1188-1192.

66. Harris RE, Beebe-Donk J, Alshafie GA, 2006. Reduction in the risk of human breast cancer by selective cyclooxygenase-2 (COX-2) inhibitors. BMC.Cancer. 6:27.
67. Graham DJ, 2006. COX-2 Inhibitors, Other NSAIDs, and Cardiovascular Risk: The Seduction of Common Sense. JAMA: The Journal of the American Medical Association.
68. Kearney PM et al., 2006. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ. 332(7553):1302-1308.
69. Crew KD, Neugut AI, 2006. Aspirin and NSAIDs: effects in breast and ovarian cancers. Curr Opin.Obstet.Gynecol. 18(1):71-75.
70. Wang D, Dubois RN, 2006. Prostaglandins and cancer. Gut. 55(1):115-122.
71. Simopoulos AP, 2004. The traditional diet of Greece and cancer. Eur.J Cancer Prev. 13(3):219-230.
72. Larsson SC et al., 2004. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. Am.J Clin Nutr. 79(6):935-945.
73. Sears B, The Anti-inflammation Zone. Harper-Collins Publishers, New York, 2005.

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