INTERNATIONAL HEALTH NEWS

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The main feature of this issue is the continuation of Bill Ware's excellent article on breast cancer prevention. In it, Bill covers the effects of alcohol consumption, smoking, weight gain, and lifestyle factors. He also discusses the pros and cons of folic acid supplementation and reviews the evidence regarding the benefits of vitamin D, green tea, and regular exercise. Finally, Bill discusses emerging evidence on the possible effect of shift work, melatonin, and exposure to electromagnetic fields.

Also in this issue we present evidence that the use of vitamin D2 rather than vitamin D3 is discouraged; that a vitamin D deficiency is linked to greater risk of nursing home admissions, that grape seed extract may slow the growth of colon cancer, and that maternal smoking may hinder baby's immune system development. An information-packed issue!!

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Wishing you continuing good health,
Hans

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Muscle mass plays a central, but misunderstood, role in health

GALVESTON, TEXAS. The role of muscle mass and function in health may be underappreciated by researchers and physicians, a metabolism expert has warned. The author, from the University of Texas, explains that muscle provides amino acids for metabolism when dietary intake of protein is low, and helps maintain blood glucose levels. Muscle is also linked to many common diseases, so could increasing protein or amino acid intakes improve health?

Several studies support a central role for muscle protein in wholebody metabolism, including maintaining the protein content of the skin, brain, heart, and liver, all of which are factors central to survival. During critical illness, amino acids are in greater demand in the liver, immune system, and for wound healing. The author suggests that a patient with severe burns, for example, might require about four times the normal daily intake of protein.

Muscle also plays a potential role in the prevention of obesity, as muscle metabolizes more energy than stored fat cells. When a long-term perspective is considered, even relatively small differences (e.g. 10 kg) in muscle mass could have a significant effect on energy balance, states the author. Furthermore, evidence suggests that changes in the metabolic function of muscle play a more direct role

in the development of insulin resistance than previously thought.

Because of these links between overall health and muscle, the author offers three solutions to boost muscle mass and function: hormonal therapy, exercise, and nutrition. He calls for factors directly related to muscle, such as the maintenance of adequate muscle mass, strength, and metabolic function, to be included in future studies designed to demonstrate optimal lifestyle behaviors throughout the life span, including physical activity and diet. These factors should be taken into account as endpoints in recommendations for dietary intake, he concludes.

Wolfe, R. R. The underappreciated role of muscle in health and disease. The American Journal of Clinical Nutrition, Vol. 84, September 2006, pp. 475-82

Vitamin D3 should be used in preference to vitamin D2, say experts

WOLFVILLE, CANADA. The two major forms of vitamin D currently available in supplements are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Although considered very similar, emerging evidence suggests that vitamin D3 has greater bioefficacy. Unfortunately, vitamin D2 is still the predominant synthetic form used in North America.

Drawing attention to this are experts from Acadia University, who explain that sunshine exposure and fish consumption provide vitamin D in the form of D3, and that repeatedly vitamin D3 has been found to be the "more potent form of vitamin D in all primate species, including humans" at raising serum 25(OH)D concentrations. The authors believe that vitamin D2 should no longer be considered equivalent to vitamin D3, and even that it should not be regarded as suitable for supplementation. Supporting their argument are several plausible biological explanations for this greater bioefficacy, due to the different metabolic pathways followed by the two forms of vitamin D. The authors write that vitamin D2 has a non-physiologic metabolism, that is, it works differently to the body's natural function. Vitamin D2 also has a shorter shelf-life. The poorer stability and greater impurities in vitamin D2 powders may lead to a higher risk of toxicity than with vitamin D3. Care should be taken to distinguish the form of vitamin D used in clinical studies, the authors state, especially as metabolism of vitamin D2 can become impaired in older people.

In conclusion, they concede that vitamin D2, if given in high enough doses, can help prevent rickets, but state that the superiority of vitamin D3 is now well documented. "Continual application of vitamin D2 in clinical use, including in research trials, only serves to confound our understanding of optimal vitamin D dosing recommendations", they write.

Houghton, L. A. and Vieth, R. The case against ergocalciferol (vitamin D2) as a vitamin supplement. The American Journal of Clinical Nutrition, Vol. 84, October 2006, pp. 694-97

Lack of vitamin D increases risk of nursing home admission

AMSTERDAM, NETHERLANDS. Vitamin D deficiency is common among older people, so researchers from Vrije University set out to investigate whether lower vitamin D levels increase the risk of nursing home admission or early death in a large group of independent, community-dwelling older men and women. They recruited 1,260 participants aged 65 years or above and measured their serum 25(OH)D concentrations as a marker for vitamin D status. In the group, 10.1 per cent were deficient (less than 25 nmol/L) and 36.7 per cent were "insufficient" (25 to 49.9 nmol/L).

The individuals were followed from 1995/96 until 2003. During this time, 11.0 per cent were admitted to nursing homes, and 30.2 per cent died. These events were clearly linked to vitamin D status. Nursing home admission was 3.48 times more likely among those who were deficient and 2.77 times more likely among those who were insufficient, compared with individuals with high vitamin D status (75 nmol/L 25(OH)D or greater). Higher mortality was linked to lower 25(OH)D, but not significantly, so the authors conclude that lower serum 25(OH)D concentrations in older persons are associated with a greater risk of future nursing home admission and "may be" associated with mortality.

In an accompanying editorial, a nutrition expert from Creighton University, Omaha, Nebraska writes that insufficient nutrition may contribute to chronic disease, but that true causal connections between

specific nutrients and disorders are hard to establish, as most chronic diseases have a range of causes and take several years to develop. Vitamin D is one such nutrient. The present study makes biological sense, he writes, because low vitamin D can impair lower-extremity function, so can increase the risk of falls. He recommends that physicians assess and correct vitamin D status in their elderly patients, or even that a global intervention is considered, given the high rate of deficiency. The author suggests fortification of food, but this would probably require more solid proof than currently available. At the moment, "a substantial potential for reduction in the burden of chronic disease hangs in the balance", he concludes.

Visser, M. et al. Low serum concentrations of 25-hydroxyvitamin D in older persons and the risk of nursing home admission. The American Journal of Clinical Nutrition, Vol. 84, September 2006, pp. 616-22

Heaney, R. P. Nutrition, chronic disease, and the problem of proof. The American Journal of Clinical Nutrition, Vol. 84, September 2006, pp. 471-72

Editor's comment: While waiting for the experts to finish their debate, supplementing with 1000 IU/day of vitamin D3 would seem to be a highly commendable preventive measure.

Mixed results for pain management programs

LONDON, UNITED KINGDOM. A recent study has cast doubt over the effectiveness of self-management for arthritis. Such an approach may not reduce pain or avoid doctor visits, say researchers from the Royal Free and University College Medical School, London. The team investigated patient-centered self-management programs for osteoarthritis. They recruited 812 volunteers with osteoarthritis in their hips and/or knees and divided them into two groups. One group received six sessions on a self-management program plus an education booklet, and the other group received just the booklet.

After a year, those on the program had lower anxiety and depression levels and better confidence in managing their illness than the others, but no significant reduction in pain, physical functioning, or doctor visits. This contrasts with previous data suggesting beneficial effects on pain, so the authors call for further research. Despite these findings, the authors believe that self-management does provide certain benefits.

A similar finding was reported in a recent study of people with knee pain. A team from Keele University, UK found that personalized sessions with physiotherapists or pharmacists may reduce drug use, but don't reduce pain over the long-term. They recruited 325 adults over the age of 55 years with knee pain, and split them into three groups. Those given specialist help from a pharmacist or a physiotherapist showed significant improvements in pain after three months of treatment, compared with those given only a leaflet. However, when checked at six months and 12 months, the benefit had disappeared. Despite this, the treatment groups did use significantly fewer NSAIDs (non-steroidal anti-inflammatory drugs, such as aspirin and ibuprofen).

The researchers say that the participants may not have continued with their exercise or medication programs after treatment ended, but the 15-16 per cent drop in NSAIDs use has "important safety implications". NSAIDs can cause adverse reactions and illness, and are not recommended for long-term use, especially among older people. They report that both interventions were associated with high patient satisfaction, and add that participants in the physiotherapy group made fewer doctor visits than patients in the control group.

Buszewicz, M. et al. Self management of arthritis in primary care: Randomised controlled trial. British Medical Journal, published online October 13, 2006

Hay, E. M. Effectiveness of community physiotherapy and enhanced pharmacy review for knee pain in people aged over 55 presenting to primary care: pragmatic randomised trial. British Medical Journal, published online October 20, 2006

Editor's comment: There is ample evidence that osteoarthritis of the knee can be safely and effectively treated via supplementation with glucosamine sulfate (1500 mg/day) and acupuncture.[1-5] It would seem unethical to conduct a study ignoring this evidence.

[1] Reginster, JY, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo-controlled clinical trial. The Lancet, Vol. 357, January 27, 2001, pp. 251-56

[2] McAlindon, T. Glucosamine for osteoarthritis: dawn of a new era? The Lancet, Vol. 357, January 27, 2001, pp. 247-48

[3] Pavelka, K, et al. Glucosamine sulfate use and delay of progression of knee osteoarthritis. Archives of Internal Medicine, Vol. 162, October 14, 2002, pp. 2113-23

[4] Berman, BM, et al. Effectiveness of acupuncture as adjunctive therapy in osteoarthritis of the knee: a randomized, controlled trial. Annals of Internal Medicine, Vol. 141, December 21, 2004, pp. 901-10

[5] Vas, J, et al. Acupuncture as a complementary therapy to the pharmacological treatment of osteoarthritis of the knee: randomized controlled trial. BMJ, Vol. 329, November 20, 2004, pp. 1216-19

Vegetables may reduce the need for anti-cancer drugs

LEICESTER, UNITED KINGDOM. Further evidence on the anti-cancer action of vegetables comes from a recent study at the University of Leicester, where researchers found a molecule in certain vegetables that, in conjunction with drugs, may help hold back the development of breast cancer. The molecule, Indole-3-carbinol (I3C), has received attention for its potential in inhibiting cancer development. The research team found that I3C alters the receptors in three of the four cancer cell types they tested - possibly making the cells more vulnerable to anti-cancer drugs.

At October's National Cancer Research Institute Conference in Birmingham, UK, the researchers announced that although they need to carry out further studies on tumors removed from patients, "the potential benefits are clear". More precise evidence is now emerging on the benefits of specific substances present in fruit and vegetables, they explain, and these dietary agents do not harm normal cells when taken at doses which can slow down or kill cancer cells. Combining these substances with anti-cancer drugs may enhance the drugs' effectiveness and could allow reduced doses to be given to patients. This would be of great benefit, as most chemotherapeutic drugs are highly toxic, so the smaller the dose, the better. As dietary substances such as I3C have a track record of being safe for the patient, the researchers hope that the path to clinical trials will be relatively straightforward.

Speaking at the conference, nutrition expert Dr Sheila Bingham of the University of Cambridge said that this study supports the growing evidence that food can be important in altering our susceptibility to cancer and possibly survival from it, and may help to explain why fruits and vegetables are so important.

I3C is found in cruciferous vegetables such as broccoli, brussel sprouts, cabbage, cauliflower, kale, parsnips, turnips, and watercress, but the doses required in potential breast cancer treatments will need to be specially formulated to ensure they are high enough, delivered in the right way, and reaching the right areas. Previous research also points to I3C having a similar impact on colon cancer.

Moiseeva, E. P., Heukers, R. and Manson, M. M. EGFR and Src are involved in indole-3-carbinol-induced death and cell cycle arrest of human breast cancer cells. Carcinogenesis, published online September 6, 2006

Editor's comment: There is also emerging evidence that I3C may be effective as a sole agent in the prevention and treatment of prostate cancer.[1]

[1] *Sarkar, FH and Li, Y. Indole-3-carbinol and prostate cancer. Journal of Nutrition, Vol. 134, 2004, pp. 3493S-98S*

Aspirin may starve tumors of blood supply, but GI risks remain

NEWCASTLE, UNITED KINGDOM. Scientists have discovered a new anti-cancer property of aspirin which may aid the development of new treatments. Dr Helen Arthur and colleagues at Newcastle University have shown that aspirin limits the formation of blood vessels connected to developing tumors. The team explains that tumors cannot grow beyond the size of a pea without such blood vessels, formed through a process called angiogenesis. In the study, they found that aspirin has a direct effect on the cells of blood vessels which control angiogenesis. It caused a "striking reduction" in tubule formation. Salicylate, a remedy closely related to aspirin, had similar effects but selective Cox inhibitors (SC560 and Celecoxib) did not.

They report that high doses of aspirin or salicylate, well above therapeutic concentrations, lead to cell apoptosis (cell death) of the cells lining the blood vessels. They conclude that aspirin directly inhibits angiogenesis via a Cox-independent mechanism, which may underlie its cancer-protective effects. Previous studies have indicated that low doses of aspirin taken over long periods can reduce the risk of cancer - by as much as 50 per cent in the case of

bowel cancer. Aspirin seems to work against tumor formation in several ways, only one of which is to restrict the blood supply. But high doses of aspirin are toxic and anyone suffering from cancer should not take aspirin unless they are advised to do so by a doctor.

This point is reinforced by a study into long-term aspirin treatment to prevent heart attack. Dr Sonia Hernandez-Diaz of Harvard School of Public Health, Boston, and colleagues investigated the risk of gastrointestinal (GI) complications linked to aspirin. They took data from two anonymous databases of patient information, one from the UK and one from Spain. Analysis suggested that aspirin treatment may be responsible for one extra case of gastrointestinal complications for every 50 aspirin users per year in susceptible groups. Vulnerable patients include older men with a history of peptic ulcer. These groups are at higher risk of complications such as ulcer bleeding and intestinal perforation. They conclude that doctors consider a patient's risk of stomach ulcers before prescribing aspirin, as the risk might outweigh aspirin's benefits.

Borthwick, G. M. et al. Therapeutic levels of aspirin and salicylate directly inhibit a model of angiogenesis through a Cox-independent mechanism. The Journal of the Federation of American Societies for Experimental Biology, Vol. 20, October 2006, pp. 2009-16

Hernandez-Diaz, S. and Garcia-Rodriguez, L. A. Cardioprotective aspirin users and their excess risk of upper gastrointestinal complications. BMC Medicine, published online September 20, 2006

Editor's comment: A recent study involving over 22,000 healthy male physicians found no correlation between the regular use of aspirin and other NSAIDs and a reduced risk of colon cancer over the 18-year study period.[1]

[1] Sturmer, T, et al. Colorectal cancer after start of nonsteroidal anti-inflammatory drug use. American Journal of Medicine, Vol. 119, June 2006, pp. 494-502

NEWSBRIEFS

Grape seed extract may slow the growth of colon cancer

Early laboratory tests suggest that grape seed extract may help fight colon cancer. Researchers from the University of Colorado tested various doses of grape seed extract on human colon cancer cells in test tubes. The cancer cells were more likely to halt their normal growth cycle and die than cells not treated with the extract, with the biggest doses having the greatest effect. Next they injected human colon cancer tumors under the skin of mice, then funneled grape seed extract into the animals' mouths through a tube. The tumors grew more slowly in those mice, compared to those in mice without the extract. The team states that the study shows grape seed extract can attack cancer, but much more investigation will be needed before the extract can be tested as a human cancer treatment and preventive. And they warn that little is known about doses and side-effects of grape seed extract.

Kaur, M. et al. Grape Seed Extract Inhibits in Vitro and in Vivo Growth of Human Colorectal Carcinoma Cells via Induction of Cell Cycle Arrest and Apoptosis, and an Up-regulation of Cip1/p21. Clinical Cancer Research, Vol. 12, October 15, 2006, pp. 6194-6202

Reduction in sleep duration may add to children's obesity risk

Insufficient sleep could be adding to the rising obesity levels among children, says a researcher from Bristol University, UK. Distractions such as computers, cell phones, TVs and other gadgets should be banned from children's bedrooms, he says. Sleep may not be the only answer to the obesity pandemic, but its effect should be considered seriously, writes the expert, as even small changes in the energy balance are beneficial. Good sleep could be part of the obesity prevention approach, he believes. Sleep deprivation affects the metabolism, and previous research suggests that such effects on the metabolism can include insulin resistance, diabetes, and cardiovascular disease. Lack of sleep could re-program the part of the brain regulating appetite and energy expenditure. It could also trigger the release of ghrelin, a "hunger" hormone. Furthermore, fatigue due to lost sleep reduces levels of exercise - another causal factor in obesity.

Taheri, S. The link between short sleep duration and obesity: we should recommend more sleep to prevent obesity. Archives of Disease in Childhood, Vol. 91, November 2006, pp. 881-84

Maternal smoking may hinder immune development

Fetal exposure to cigarette smoke may weaken the immune system and explain the higher rate of infection among infants whose mothers smoked. Researchers from the University of Western Australia focused on the innate immune system, which provides protection until the baby develops an acquired immune system through contact with antigens. Immune responses of 60 newborns whose mothers had smoked during pregnancy were compared with 62 newborns whose mothers had not. Those exposed to tobacco had a significantly lower level of several immune compounds, including interleukin-6, interleukin-10 and tumor necrosis factor-alpha (TNF-a). Development of the acquired immune system was therefore slowed, the team said. They add that the findings could lead to more discoveries on the so-called "hygiene hypothesis" - the idea that early exposure to and immune response to bacteria plays a central role in the development of the immune system. Maternal smoking could potentially hold back these immune responses and raise the chance of future allergies.

Noakes, P. S. et al. Maternal smoking is associated with impaired neonatal Toll-like receptor (TLR) mediated immune responses. European Respiratory Journal, Vol. 28, October 2006, pp. 721-29

Insight into the energy supply of heart cells

Scientists have found a way to monitor energy supply in heart cells, potentially explaining how a heart attack can be triggered. A team from the University of Bristol, UK were able to make heart cells light up when energy is being produced, using a chemical found in fireflies called luciferase. They could then directly view energy levels in real time with a microscope and a highly sensitive camera. The study shows that when the heart is re-started after cardiac surgery or a heart attack, it can take a moment for energy production in the form of adenosine triphosphate (ATP) to begin. Knowing this, the team can explain why the heart may struggle to beat properly. This technology could lead to improved outcomes after heart attack or cardiac surgery when cells cannot make enough ATP.

Bell, C. J. et al. ATP Regulation in Adult Rat Cardiomyocytes. Time-resolved decoding of rapid mitochondrial calcium spiking imaged with targeted photoproteins. Journal of Biological Chemistry, Vol. 281, September 22, 2006, pp. 28058-67

Calcium tablets have a limited impact on fracture risk

Fracture risk is unlikely to be reduced by calcium supplementation in childhood, concludes a recent study. A team from the Menzies Research Institute, Tasmania, Australia analyzed studies on calcium supplements and children's low bone mineral density - an important risk factor for osteoporotic fractures. They took data from 19 randomized placebo-controlled trials of at least three months' duration, including a total of 2,859 children. These trials aimed to maximize peak bone mass, at least 90 per cent of which is obtained by the age of 18. Overall, analysis suggested that "calcium supplementation had no effect on bone mineral density at the femoral neck or lumbar spine" - the most important sites in the body for later fracture. However, there was a small effect on total body bone mineral content and upper limb bone mineral density. In conclusion, this small effect is unlikely to reduce the risk of fracture, either in childhood or later life, say the authors.

Winzenberg, T. et al. Effects of calcium supplementation on bone density in healthy children: meta-analysis of randomised controlled trials. British Medical Journal, published online September 15, 2006

Editor's comment: Without a commensurate adequate daily intake of vitamin D calcium supplementation is unlikely to have a beneficial effect on bone density.

RESEARCH REPORT

Primary Prevention of Breast Cancer – Part II

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BEVERAGES

ALCOHOLIC BEVERAGES

In sharp contrast to the parade of null results associated with the link between diet and breast cancer, for over two decades there has been a constant flow of convincing evidence in favor of the hypothesis that alcoholic drinks, even in rather small amounts, carry an enhanced risk of breast cancer. This body of evidence includes a number of prospective cohort studies. Dumitrescu and Shields [1] have very recently reviewed this subject. Significant points drawn from this review and other sources cited are as follows:

- The proportion of breast cancer attributable to alcohol (ethanol—ethyl alcohol) consumption among women in the US is 2.1%, i.e. about 14,000 cases per year out of about 667,000 cases. In Italy it is estimated to be as high as 10%. The figure for the US population is small because of the modest association between alcohol and breast cancer coupled with the generally low to moderate average level of alcohol intake among US women. A campaign to reduce alcohol consumption would thus have a small impact on overall breast cancer incidence in the US. In fact, a campaign for abstinence might increase overall mortality because of the beneficial effects of moderate alcohol consumption on cardiovascular disease risk [2]. For that small minority who consume large amounts on a more or less daily basis it appears to definitely be a risk issue [3].
- A collaborative analysis of 53 studies revealed a 32% increased risk (95% confidence limits 19-45%) for women with an intake of 35-44 g/day of alcohol, and a 46% (33-61%) increase risk for more than 45 g/day. One drink typically contains between 10 and 15 g of alcohol, and the normal-sized bottle or can of beer contains about 14 grams. Another way of summarizing the data is that the relative risk of breast cancer was found to be increased by about 7% for each additional 10 g/day intake of alcohol, i.e. for each daily extra drink over and above a threshold of about 10-15 grams of alcohol. Finally, the data can be viewed as follows: the cumulative incidence of breast cancer by age 80 years is estimated to increase from 8.8 cases per 100 women who are abstainers to 10.1 per 100 for those who consume 2 drinks per day and to 11.6 per 100 women who consume 4 drinks per day. The cumulative incidence by age 50 over this range from abstinence to 4 drinks per day changes from about 1.5 cases per 100 to

about 2 cases per 100 woman [4]. The relative risks given above tend to perhaps exaggerate the absolute risk. Also, the risk associated with one drink per day containing 10-15 g of alcohol does not appear to be statistically significant [5]. Thus drinking two or more cocktails to relax at the end of the day or two or more glasses of wine at dinner become a significant risk factor only if habitual to the point of being more or less a daily practice.

- Daily consumption of more than 15 g of alcohol throughout life is associated with a 33% increase in risk [6].
- Overall lifetime consumption rather than over any specific time of life may be more strongly associated with breast cancer risk although studies are in general inconsistent [6]. A study concerning whether or not frequent binge drinking among high school and college age women increases the risk in later life would be of considerable interest given the enhanced susceptibility to some risk factors during this age period.
- The consistency of study results is remarkable considering that they span diverse geographical populations, different age groups, varying levels of consumption and different study designs [6].
- Alcohol has been found to cause breast cancer in studies with mice and rats.
- While the mechanism of carcinogenesis due to alcohol is unknown, several plausible mechanisms exist including the perturbation of estrogen metabolism, mutagenesis by acetaldehyde, a metabolite of ethanol, oxidative damage and a potential influence on various metabolic pathways that involve folic acid.
- Alcohol consumption is associated with increased breast density as seen on mammography in both pre- and postmenopausal women. Increased mammographic breast density is a recognized risk factor for breast cancer with a fourfold to six fold increase in risk.

Observations in the late 90s that the risk of breast cancer due to alcohol consumption appeared to be modified by folate/folic acid intake resulted in considerable research into this subject. This is a very important aspect of breast cancer prevention since near or total abstinence for everyone is unrealistic, but taking one folic acid pill daily or being sure of adequate dietary intake has the potential of being both acceptable and effective. Also, for women of childbearing age, having an adequate folate status is recognized to be very important in connection with avoiding a folate-related birth defect, and taking folic acid after pregnancy has become evident is generally too late since the defect (neural tube) occurs very early in the fetal development. Thus it is of interest to examine the evidence. Note that folate and folic acid will be differentiated. As will be discussed below, the former is found in unfortified food, the latter is a synthetic chemical which is used in both supplements and food fortification.

If we restrict our attention to prospective cohort studies concerning the folate/folic acid—alcohol connection published between 2002 and 2006, there are six with a total of almost 270,000 women followed for an average of about 13 years [7-12]. Four of these studies provided quite strong and statistically significant results favoring the protective effect of dietary and supplemental folate/folic acid on the risk of breast cancer among women consuming more than one alcoholic drink per day. One, with a short follow-up, did not support the protective effect of folate/folic acid on breast cancer risk [7], and one found a favorable result, but the outcome was just shy of statistical significance [10]. The studies with favorable results did not stratify for menopausal status or were restricted to postmenopausal women.

If one attempts to average over total folate/folic acid intakes that were protective in these studies, the amount is at or above 350-400 micrograms/day. In a recent study involving 25,400 U.S. women [13], Stolzenberg-Solomon *et al* found folate from food for the first to fifth quintile ranged from 336 to 473 micrograms/day (mean quintile values, after mandatory fortification increased the dietary intake), and total intake from food and supplements ranged from 335 to 1210 micrograms/day. Only about 8% obtained amounts exceeding 412 micrograms/day from natural and fortified food, but 37% obtained between 307 and 412 micrograms/day from this source. Thus eating a diet heavy in folate/folic acid rich foods can provide an intake similar to that found to neutralize the effects of alcohol consumption, but in the cohort studied by Stolzenberg-Solomon *et al*, 39% would have needed supplements to bring the daily intake above 307 micrograms/day.

However, the folate/folic acid matter is somewhat more complicated than generally recognized. Folic acid, as found in supplements and also added to foods as part of government mandated fortification, is a synthetic chemical not found in nature. Its great merit is that it is both cheap and stable and solves what is probably an

impossible problem of extracting commercially significant amounts of folate from natural sources. While folic acid turns out to have more bioavailability than folate from food, only a limited amount is actually metabolized, and some of the remainder appears as free synthetic folic acid in the circulation system. The long-term effects of circulating unmetabolized folic acid are unknown, but alarming reports have appeared in the medical literature. In fact, concerns about the possibility of high serum levels of unmetabolized folic acid were already being raised as early as 1997 in response to fortification and the use of high-dose folic acid supplements (> 1 mg/day) in order to decrease the risk of neural tube defects [14]. Confirmation that the concern may be justified came in part from a study published in 2004 by Charles *et al* [15]. A group of 2928 women taking either a placebo, or 200 or 5,000 micrograms/day of folic acid for neural tube defect prevention were followed from the 1960's to 2002. For women randomized to the high doses of supplemental folic acid the risk of death attributable to breast cancer was twice as great as those on a placebo or low dose. This was a small study and the result could well have occurred by chance, and this study must be taken merely an indication of a problem with high does of folic acid. Incidentally, 5000 micrograms/day (5 mg/day) is no longer used for this purpose. Nevertheless, 5000 micrograms/day would, on the evidence of earlier and later work [14,16], definitely elevate serum levels of unmetabolized folic acid.

In a study sure to add to concern associated with this matter, Troen *et al* [16] have just reported that unmetabolized folic acid in plasma is associated with a reduced natural killer cell cytotoxicity in postmenopausal women. Women who consumed a folate-rich diet and used folic acid supplement at a dose of > 400 micrograms/day had reduced natural killer cell cytotoxicity compared to those consuming a low-folate diet and no supplements, and unmetabolized folic acid in the plasma was a biomarker for excess folic acid consumption. This is of concern because such a decrease in cytotoxic activity compromises the immune function. Natural killer cells also play a role in tumor cell destruction and may be part of the first-line host defense against carcinogenesis. While the actual mechanism associated with the increased breast cancer risk that appears to be associated with moderately high to high intakes of the synthetic chemical folic acid is unknown, this provides a plausible biological explanation for the alarming experimental and epidemiologic results.

Related to this issue is the paper already cited above in which Stolzenberg-Solomon *et al* [13] reported on a study supported by the National Institutes of Health wherein it was found that high intakes of folate/folic acid actually increased the risk of breast cancer both in abstainers and those who consumed alcohol. To achieve high intakes, supplements were necessary. Neither folate/folic acid from foods alone nor natural folate from unfortified foods were significantly associated with increased breast cancer risk, perhaps because of the limitation on daily intake. But women consuming 400 micrograms/day or more of supplement derived folic acid had a 19% higher risk of postmenopausal breast cancer compared to those not taking supplements. Those in the highest fifth of the study population in terms of total folate/folic acid intake had a 32% greater risk as compared to those in the lowest fifth. These results which were statistically significant, were based on a large sample size and were corrected for confounding. The levels of folic acid intake found in this study to enhance breast cancer risk were, as discussed above, in the range known to increase the probability of unmetabolized folic acid in the circulation. However, Stolzenberg-Solomon *et al* do not mention unmetabolized folic acid as a possible factor in their discussion of possible mechanisms. Nevertheless, taken together with the results of Charles *et al* and Troen *et al* it would seem that warning bells are ringing.

It is evidentially quite easy to find individuals taking 400 micrograms/day or more of folic acid in a multivitamin or B-complex pill or even a separate folic acid supplement and as well eating enough folate-rich foods and fortified foods to push the total folate/folic acid up to 600-800 micrograms/day or even higher, an amount that would produce unmetabolized folic acid [14,16]. Troen *et al* [16] found unmetabolized folic acid in the 78% of plasma samples from the cohort in his study. Thus it follows that until more is known about the risks of synthetic folic acid intake, caution is indicated. The common "B-50" B-vitamin formulation contains 1 mg/tablet and Life Extension's "Two-Per-Day" tablets contain an 800 microgram dose. Supplements containing only 200 micrograms per minimum dose are readily available and may merit consideration. The typical amount in a multivitamin is 400 micrograms per pill, which is just at the threshold of potential danger according to Stolzenberg-Solomon *et al for* a woman consuming a diet low in folate with little by way of enriched food products. Someone who has a high consumption of fortified cereal, bread and products made from fortified flour may have cause for concern regarding the high intake of folic acid and would thus want to question the amount of additional folic acid also being consumed in supplements, including that from a simple multivitamin. In this case, 400 micrograms per day of a supplement may be excessive. A point to remember is that only folate from

unfortified food appears safe at high intake, since all other sources are a synthetic chemical which is only metabolized to a limited extent and is responsible for the unmetabolized folic acid found in the blood of individuals ingesting large amounts of this chemical. The benefits of folic acid in the context of neutralizing the effects of alcohol consumption disappear, according to Stolzenberg-Solomon, at an intake exceeding about 400 micrograms per day and at higher intakes increased risk appears associated with an intervention intended to reduce risk. Having to deal with hidden sources of folic acid in fortified food only complicates this matter, especially when a single serving of breakfast cereal can provide 400 micrograms of folic acid in a form identical to that found in supplements.

There are other issues as well. In the last few years there has been increased interest in the relationship between risk factors, preventive actions and the tumor hormone receptor status, i.e. the histological estrogen receptor positive (ER+) or estrogen receptor negative (ER-) nature of the breast cancer that develops. How this estrogen receptor status influences the risk enhancement of alcohol and the risk reduction brought about by folate/folic acid is of interest because ER- tumors typically occur in only 20-35% of cancer cases. Thus there are two critical questions. First, is there an association between the adverse effect of alcohol and the tumor type that eventually occurs? Second, is the protective effect of folate/folic acid dependent on the histological type of tumor that occurs, i.e. does folate/folic acid protect against the occurrence of both histological types? As regards the first question, the literature is inconsistent with some studies finding no difference and others finding exclusively one or the other histological type influenced by alcohol consumption. One of the largest and most recent studies, which used data from the Nurses' Health Study and looked for risk factors for breast cancer according to estrogen receptor status, found no differential association with alcohol as a risk factor [17]. An earlier study found no differences for post menopausal and heterogeneous results for premenopausal women [18]. Other studies have been inconsistent [19,20].

In connection with the second question, a recently reported large prospective study [12], again based on data from the Nurses' Health Study, found that higher folate intake, when the alcohol intake was greater than 15g/day, reduced the risk of developing only ER- breast cancer. Stratification according to total folate for alcohol consumption greater than 15 g/day produced only one statistically significant result which was for folate ≥ 534 micrograms/day. Another study also found protection only for ER- cancer, but for some obscure reason, the highest level of alcohol consumption was ≥ ¼ drink a day with no stratification for much higher consumption, if it occurred at all [8]. The result that the effectiveness of folate/folic acid is restricted to ER- tumor formation is puzzling since folate/folic acid intake has been observed in numerous studies to reduce the risk of breast cancer all the way to that seen in abstainers. If folate/folic acid is only beneficial for a small percentage of the cohort in question, i.e. those who go on to develop ER- tumors, one would think that folate/folic acid would not have been found to be that successful. This, incidentally, is why the question of whether or not alcohol promotes both ER+ and ER- cancer is important. If it is confirmed by other prospective cohort studies that the alcohol induces both ER+ and ER- tumors, and that folate/folic acid inhibits the alcohol effect only for those that go on to develop ER- tumors, there would be serious implications simply because folate/folic acid intake would then provide no protection from the alcohol promoted development of ER+ tumors, which represent the majority of those observed. Given that a woman has no *a priori* knowledge of the histological tumor type that might develop, this result would imply that the only preventive action in this context is limiting alcohol to no more than one drink a day on average. Using folate/folic acid for prevention would in fact produce a false sense of security when consuming larger amounts of alcohol.

Additional studies related to the folate—ER+/ER- question appear to be urgently needed, especially since the result suggesting that only ER- cancer is influenced by folate is based, essentially, on only one significant and relevant result bobbing is a sea of non-significant results. Women who drink on average more than 15 g of alcohol per day (more than about 1 drink) may want to give consideration to optimizing their foliate/folic acid just on general principles. Others may elect to play it safe and keep their consumption such that it averages out to less than one drink per day until this critical uncertainty is resolved.

GREEN TEA, GREEN TEA EXTRACT AND BLACK TEA

Tea intake is estimated to be second only to water in terms of worldwide consumption as a beverage [21]. Cell-culture and animal studies have shown that green tea and green tea polyphenols have anticarcinogenic properties against breast cancer [22,23]. However, there has been only a limited number of prospective cohort and case-control studies. The most recent meta-analysis of the cohort studies yielded an indication of a

decrease in breast cancer risk for the highest vs. the lowest intake levels, but the result was not statistically significant. When a single case-control study was added to the analysis, the protective activity of green tea became statistically significant [21]. Similar less than definitive results were obtained in an earlier meta-analysis with a slightly different set of studies. Definite conclusions appear impossible considering the small number of studies, the lack of a consistent dose-response, and the absence of clinical intervention trial evidence. Typical intakes that were suggestive of benefit were in the range of 5-7 cups a day. Similar intakes can be achieved with green tea extracts, but for this option only cell culture and animal studies are available, although these generally provided evidence of potential benefit [22,23].

In a just published prospective cohort study from Japan, it was reported that green tea consumption was associated with reduced mortality due to all causes and due to cardiovascular disease, but not with reduced mortality due to cancer. Stratification of the cancer results did not include breast. The cardiovascular benefits were stronger for women than for men and appeared even at a level of consumption of 1-2 cups/day [24].

There is no statistically significant evidence concerning the merits of black tea in this context. Case-control and cohort studies are conflicting. In a recent meta-analysis, eight case-control studies yielded only a minor inverse (protective) relationship for black tea consumption and five cohort studies showed a modest increase in breast cancer risk [25]. However, for one specific type of breast cancer, i.e. lobular, black tea afforded a significant reduction in risk [25]. In general, studies of coffee and tea in the context of breast cancer risk have not examined the risk according to the estrogen receptor type of tumor that is involved or develops.

COFFEE

Epidemiologic studies of the association between coffee consumption and breast cancer risk have yielded inconsistent results. However, a recent case-control study that included large numbers of both pre and post menopausal women has just been reported [26]. A large and statistically significant beneficial effect of coffee consumption was seen with ≥ 4 cups /day of regular coffee (Odds Ratio 0.62, 95% CI 0.39-0.98), but only for premenopausal women. In another study just reported [27], the effect of coffee consumption was studied in women who carry the BRCA mutations which put them at high risk. In this multi-center case-control study, a strong and statistically significant protective effect was found for BRCA 1 cancers. The protective effect was not seen until the daily consumption reached a level of 6 cups of caffeinated coffee, but at this level of consumption, the benefit becomes impressive and statistically significant (multivariate Odds Ratio = 0.31, 95% CI 0.13-0.73). Only caffeinated coffee reduced risk, and a significant risk reduction was not found for women diagnosed after the age of 50. The mechanism of this protective effect, if it indeed exists, is unknown, but the authors suggest phytoestrogens in coffee as a potential explanation. Also, Baptista *et al* [28] have suggested that gene-specific deactivation of various pathways involved in carcinogenesis could be promoted by substances in coffee. More research is clearly needed.

WEIGHT GAIN, OBESITY AND ENERGY BALANCE AND LIFESTYLE

WEIGHT

Adult weight gain, both prior to and after menopause as well as postmenopausal obesity has in many studies been associated with the risk of postmenopausal breast cancer. There are also some studies that address the association of body fat and premenopausal breast cancer risk. In the past two years a number of studies have been reported which reinforce earlier studies and provide additional information. Among the issues involved are the use or non-use of hormone replacement therapy (HRT), the estrogen receptor status of the cancers found on follow-up, the presence or absence of hereditary predisposition (the BRCA mutation status), and when the weight gain occurred that ultimately influenced the risk. The highlights of these recent studies are as follows:

- Weight gain over the period from age 18 to menopause caries a significantly enhanced risk of postmenopausal breast cancer risk, with the risk increasing with the amount of weight gain. Weight loss or weight maintenance during these years reduces the risk [29-31].
- Among women who did not use postmenopausal hormone therapy, 24.2% of breast cancers could be attributed to a weight gain of 2 or more kg (4.4 lbs) since age 18 and 7.6% attributed to this weight gain since menopause [30].

- Hormone replacement therapy modifies the risk associated with adult weight gain. Women who experience adult weight gain and do not take hormone therapy have a greater *weight-associated* risk than those on hormone therapy [30,31].
- The association of breast cancer risk and adult weight gain appears to be restricted to those women who develop estrogen receptor positive tumors [31,32]. This is the most common tumor type.
- Postmenopausal obesity (BMI ≥ 30, BMI—weight in kg divided by the square of height in meters) or being overweight (BMI 25-29.9) were associated with statistically significant risk of breast cancer in non-users of HRT [32].
- Weight loss in early adult life (ages 18-30) protects against early onset BRCA-associated (hereditary) cancers [33] and weight control through dietary energy intake restriction is a justifiable action for risk reduction for these high risk individuals [34].
- Postmenopausal women with the highest energy intake, highest BMI and least physical activity had twice the risk of breast cancer when compared to those with the lowest energy intake, lowest BMI and greatest physical activity [35].
- For women who never used HRT, the sustained loss of 10 kg or more of weight since menopause was associated with substantial and significant reduction in the breast cancer risk (relative risk 0.43, 95% CI 0.21-0.86) compared to those who maintained weight after menopause [30].
- Compared to women with stable weight (± 2 kg—4.4 lbs) during adulthood, a long-term weight gain (measured from age 20) of 15-20 kg (33-44 lbs) resulted in a 50% increase in breast cancer risk during the postmenopausal years, but only among those not currently using HRT. Long-term weight gain did not increase the risk of breast cancer occurring during the premenopausal period of life. [36].
- High birth weight, high stature at age 14, low BMI at age 14, and peak growth at an early age (rapid growth between 8 and 14) were found in a recent study to all be associated independently with increased risk of breast cancer [37].
- The risk of premenopausal breast cancer decreases with increasing BMI and greater body fatness during childhood and this association is independent of adult BMI [38].

Eliassen *et al* comment in their paper [30] that given the poor success of sustained weight loss after menopause, women should avoid weight gain throughout adult life rather than count on losing weight after menopause. One of the most noteworthy aspects of the above results is the interaction between risk, weight gain and postmenopausal hormone use. A simple explanation of this phenomenon is that while adipose tissue is a source of circulating estrogen, the addition of exogenous hormones (not made internally), i.e. HRT, obscures the influence of enhanced hormone levels from fat tissue due to weight gain or obesity. The use of hormone therapy to negate the adverse effect of postmenopausal weight is obviously not a solution, given the increased risk of breast cancer now recognized to be associated with this intervention.

Finally, in an editorial, Michels and Willett [39] from Harvard comment that currently available data suggest the following description of a lifetime body build with the lowest breast cancer risk: “one would want to be born light, grow slowly but steadily into a chubby, short child, and to maintain one’s fat mass until one reached menopause, at which point one would want to shed the excess pounds immediately in order to keep the risk of breast cancer low.” This quote highlights the complexity of the matter under discussion. Michels and Willett also point out that lower BMI during adolescence is related to a lower risk of cardiovascular disease and diabetes. Thus encouraging a relatively high BMI during adolescence may be undesirable from the standpoint of overall health.

SMOKING

In 2002 Terry and Rohan published a review of the literature concerning smoking and the risk of breast cancer [40]. At that time, the results were inconsistent although there was some indication of increased risk associated with long-term use of tobacco. In 2006 Cui, Miller and Rohan updated the subject with a further review of the literature and an update on their prospective cohort study [41]. Eight new studies had been reported. Three case-control studies and all the prospective cohort studies (three also) found increased risk for breast cancer associated with long-term cigarette smoking. In addition, two case-control and five cohort studies have examined the association between smoking before the first full-term pregnancy and breast cancer risk. All of the case-control studies and four of the five cohort studies found smoking before the first full-term pregnancy increased the risk of breast cancer. In the authors’ prospective study, the highest breast cancer risk was found among women who smoked 40 years or more (RR 1.50, 95% CI 1.19-1,89). Positive associations were found

with smoking duration, intensity, and cumulative exposure. They also observed that the lower the age at which smoking commenced the higher the breast cancer risk.

Thus there appears to be fairly strong evidence that breast cancer can be added the list of adverse outcomes associated with long-term heavy smoking, a list which includes lung cancer and cardiovascular disease. One would hope that such a dismal report card, including the added risk associated with smoking prior to first pregnancy, would discourage teenage girls from taking up the so-called "habit" but it is probably true that this group does not scare easily. Obviously any woman who smokes should consider the evidence presented above as providing a strong incentive for quitting.

EXERCISE

It is well known that exercise and physical activity have a beneficial effect on many aspects of health. In the context of breast cancer, most of the attention has been directed at the question of exercise and its intensity during adolescence and early adulthood and how this impacts the risk of in later life. Lagerros *et al* [42] have performed a meta-analysis of 23 studies (4 prospective cohort and 19 case-control) that provide considerable insight into this question. Overall, exercise during adolescence and young adulthood resulted in a significant 20% reduction in later breast cancer. This result was significant for women diagnosed after menopause and was almost significant for premenopausal cases. Both moderate and vigorous levels of physical activity were equivalent. It is also possible that adolescent physical activity carries over into adult life. There is also some recent evidence suggesting that increased physical activity even in the postmenopausal period can reduce the risk of breast cancer [43].

NIGHT WORK, NIGHT LIGHTS, ELECTROMAGNETIC FIELDS AND THE MELATONIN CONNECTION

It is generally recognized that our genetic makeup and thus our human biochemistry has, because of negligible mutation rates, undergone essentially no change since the Stone Age. It can be surmised that our ancestors by and large slept in the dark (in caves, make-shift shelters, or under forest cover, etc.) except when sleeping in the open on moonlit nights. Also, during the day, our Stone Age ancestors were exposed to daylight rather than much weaker artificial light. This picture is in sharp contrast to modern living with night lights, illuminated bedside clocks and displays on electronic equipment in the bedroom, street lights illuminating sleeping areas, shift work, long periods on night-shift, and insomnia, all of which interfere with total darkness during the hours that would normally be set aside for sleep. Also, the indoor daytime light intensity is only a fraction of that found outdoors. This aspect of modern living appears to have significant repercussions.

A population susceptible to this alteration in light exposure is the shift worker, and thus it was natural to look for enhanced disease risks in cohorts such as nurses and other health care workers, airline personnel, etc. In connection with breast cancer and shift work, a recent meta-analysis of 13 studies is of considerable interest. Studies included were of the following design: prospective cohort, nested case-control within a prospective study, retrospective case-control, or incidence studies where the referent group was the general population. Studies involved flight attendants, nurses and other individuals whose occupation involved night work. The aggregate estimate for all the studies was a statistically significant 48% increase in occupational risk of breast cancer. The results were similar when stratified for the type of occupation. Residual confounding did not appear to be significant. The fact that the risks for flight attendants and other night occupations were essentially the same was taken by the investigators to indicate that increased radiation exposure experienced by flight attendants is not a factor [44].

Two of the studies [44,45] were of prospective cohort design and were based on the Nurses' Health Study and the Nurses' Health study II, the former involving mostly postmenopausal and the latter premenopausal women. Increased risks of breast cancer were 39% in the former and 79% in the latter (reference 15 in [44]) both statistically significant, when shift workers were compared to those who just worked days. For the premenopausal cohort, the increased risk was apparent only after 20 years of rotating shift work whereas for the other study, it was after 30 years.

While the biological mechanism for the above observations is unknown, a popular theory involves the suppression of secretion of the hormone melatonin brought about by the presence of light during the night hours. Humans have numerous vital biological processes that vary reproducibly over each 24-hour period. The general term applied to this phenomenon is "circadian rhythm." Light controls the circadian related processes, i.e. the

body uses light to determine where it is in the 24-hour period. Presumably this involves responding to both light and darkness. The principal actor is the pineal gland which is responsible for the secretion of the hormone melatonin, a process which is triggered by darkness during the hours when one is normally asleep. Light can acutely suppress melatonin secretion and disrupt the human circadian system [46]. In fact, it has been found that low melatonin levels, as measured by a biomarker in first morning urine, is associated with a significant increase in breast cancer risk [47]. The acute suppression of melatonin secretion by light during the night would thus be expected to increase risk and help explain the night-shift results.

It is also possible that disruption of the circadian rhythm by light exposure during childhood and adolescence may affect the lifetime risk of breast cancer since these developmental periods may be times when the female is particularly vulnerable [48]. For now, this is just a hypothesis, but having children become accustomed to sleeping in total darkness seems reasonable, given the evidence presented above concerning shift work.

Night-shift work has also been identified as a risk factor for colorectal cancer in the Nurses' Health Study. Nurses working night-shifts for 15 years or more had statistically significant multivariate (adjusted for confounding) relative risk of colorectal cancer of 1.35 (95% CI 1.03 to 1.77) [49]. The relationship of night-shift work to other cancers does not appear to have attracted much attention. However, melatonin is under investigation for use in cancer treatment, either alone or as an adjunct to conventional therapy [50]. A detailed review of melatonin and cancer can be downloaded free from the Life Extension website (www.lef.org, January 2004 issue of the magazine *Life Extension*).

Thus the question—what to do. For many on shift work, there is generally no choice. It is part of the chosen profession such as nursing or being a flight attendant. No studies have been conducted or even appear to be in progress that address potential solutions to this problem. However, there is a large literature on the subject of improving the performance of night-shift workers by attempting to adjust their circadian clocks. The most frequently seen suggestions involve (a) having a room at work that is very brightly illuminated (i.e. mimics outdoor light intensities) where breaks can be taken; (b) wearing dark glasses for the commute home in the morning; and (c) going to bed at once in a totally dark room. Whether such a protocol would have any impact on the risk of breast cancer remains to be seen, but if the increase in risk requires 20-30 years to develop, it seems unlikely that a study could be conducted. Another potential solution would be to take melatonin, which is available over-the-counter in some countries including the U.S. and Canada. However, no one appears to have studied the long-term effects of taking this hormone, even though it is thought to have a number of interesting properties including acting as an antioxidant and in cell culture studies, being an anti-cancer agent [50].

Exposure to relatively weak electromagnetic fields (EMFs) such as found in the residential or occupational setting have repeatedly been suggested as a risk factor for breast cancer. A biological basis was provided by the observation that EMFs could inhibit the normal nocturnal rise of melatonin levels. Feychting and Forssén [51] have recently reviewed the evidence (up to and including 2005) associated with both workplace and residential exposure to low-frequency (50-60 Hz) EMFs. Included were studies on electric blanket use, a commonly quoted example of residential exposure. From the sum total of evidence available the authors conclude that no significant increased risk is associated with low-frequency EMF exposure. However, Davis *et al* recently reported that residential nocturnal exposure to EMFs decreased a urinary marker for melatonin [52]. In addition Schernhammer and Hankinson [47] found a decreased risk of breast cancer associated with an increase in this marker in a case-control study nested in the Nurses' Health Study II. Unfortunately, these two studies used a different urine collection protocol which makes it difficult if not impossible to ascertain if the marker level changes observed by Davis *et al* are significant in this context since they were very small compared to the range of marker concentrations found by Schernhammer and Hankinson and in this latter study, significant risk reduction was seen only at levels of the marker indicating high nocturnal melatonin levels.

MICRONUTRIENTS

MULTIVITAMINS

If one searches the medical literature database PubMed with the linked keywords *breast cancer* and *multivitamin* in either title or abstract, one finds essentially nothing of interest in the past 10 years. This reflects the practice of focusing on individual micronutrients. This is unfortunate since there is considerable evidence of the benefits

derived from taking a multivitamin in the context of prevention of many health problems. Micronutrient deficiencies are related to cancer risk and multiple deficiencies are common. The evidence includes the observation that micronutrient deficiencies can mimic radiation or chemical damage to DNA causing both single and double-strand breaks and oxidative damage or both [53,54]. The double-strand chromosomal aberration is a strong predictive factor for human cancer (for a detailed discussion of this subject and the evidence supporting taking a multivitamin/mineral supplement daily, see the research review in the *International Health News* newsletter of September-October 2004 titled *A Metabolic Tune-up?? What Is This All About*? which was inspired by the extensive research of Bruce Ames and coworkers at the University of California, Berkeley). This section will be devoted to individual micronutrients.

VITAMIN D [55]

Among the micronutrients, vitamin D has received the most attention. This interest partly derives from the results of a number of studies indicating that solar ultraviolet radiation (UV) exposure is associated with a reduced risk of breast cancer as well as other cancers [56]. Individuals with a high level of exposure will have the highest levels of vitamin D and its metabolite 25-hydroxy vitamin D (see the IHN Research Report on Vitamin D in the May and June 2004 issues for a detailed discussion of vitamin D and health). In a recent study by Grant [56], 12% of breast cancer deaths among white American women and 16.5% among black American women were attributed to inadequate exposure to solar UV radiation. Supporting evidence comes from studies of serum levels of 25-hydroxy vitamin D. In a recently reported meta-analysis of two studies [57,58], Garland *et al* found that women who consume 1000 IU of vitamin D in addition to the normal background amount consumed or generated per day had a 10% lower risk of breast cancer, and in addition, an intake of 2700 IU was estimated to yield a risk reduction of 50% for an individual weighing 70 kg (154 lbs [59]. These intakes vastly exceed those found in prospective or case-control studies of the relationship between vitamin D intake and breasts cancer, which is probably why such studies have been inconclusive (the top quartile or quintile of intake rarely exceeds >500 or >700 IU per day. An daily intake of 1000 IU is being commonly recommended by scientists working is this field [60] (see also the above cited IHN Research Report). While some might be concerned that 2700 IU per day would be toxic, a recent study by Heaney *et al* [61] found that even 10,000 IU per day had no adverse effects. It is well known that if one sunbathes until the skin just shows a slight pink, the estimated generation of vitamin D is equivalent to the oral intake of between 10,000 and 20,000 IU. It is also important to realize that in northern latitudes (>35°-40°N) the amount of UV that is active in producing vitamin D in the skin is low to negligible in the winter months and vitamin D deficiency is common among those living in these higher latitudes or the equivalent in the southern hemisphere. Sun exposure or even prolonged sunbathing in the winter in Boston or Edmonton does not generate significant vitamin D. In addition, individuals with dark or black skin need twice the exposure to achieve the same Vitamin D production. Also, the current recommendation to avoid all sun exposure unless a sunscreen is used has had an impact of deficiency levels, since sun screens decreases the natural generation of vitamin D. Thus lifestyle, attitude toward sunscreens, and where one lives all have a significant influence on vitamin D status, and, according to the study discussed above [56], the incidence of breast cancer. The National Academy of Sciences—Institute of Medicine has set 2000 IU per day as the safe upper limit for vitamin D intake (see [60] for a current discussion of toxicity and recommended intake).

Low vitamin D status is also implicated as a risk factor in colon cancer, colonic adenomas, prostate cancer and ovarian cancer. The evidenced in general comes from dietary, serum and geographical studies [60]. The impact of vitamin D deficiency in connection with bone health, hypertension, diabetes, and rheumatoid arthritis is discussed in the above-cited IHN Research Report along with the necessary information to interpret the standard blood test for vitamin D status (25-hydroxy vitamin D). In the study of Garland *et al* [59] the 50% risk reduction for breast cancer was achieved with blood levels of 25-hydroxy vitamin D > about 50 ng/mL (125 nmol/L).

The hypothesis has also been recently advanced by a group including eminent vitamin D researchers and epidemiologists that the remarkable and recurrent seasonal aspect of influenza is due to low vitamin D levels in the winter [62]. The authors of this study suggest that even 2000 IU/day in the winter may be insufficient to fully protect against influenza, especially for the elderly.

Women living in northern latitudes and those who avoid sun exposure clearly need to be concerned about their vitamin D status. In the context of intakes of for example 1000 IU per day, food sources are not significant, and at least during the winter months, supplementation with the D3 form of vitamin D (not the D2 form) appears to be

necessary. Whether supplementation is necessary in the summer is obviously a strong function of the total unprotected sun exposure.

VITAMINS A, C AND E

Aside from cell-culture studies, there appears to be no evidence of significance regarding the role of these three vitamins in breast cancer prevention and there is some evidence that intakes of vitamin C in excess of 300 mg/day was associated with an increase in risk [63-65]. However, Zhang has reviewed a large number of studies concerning vitamin C and breast cancer risk and reports no association [66]. If vitamin C increased the risk, presumable it would have been seen in at least some of these studies.

CALCIUM AND MICRONUTRIENTS IN DAIRY PRODUCTS

Two reviews published in 2005 both found in general no association between the consumption of dairy products and breast cancer [67,68]. However, a large cohort study restricted to postmenopausal women published in 2005 found that dietary calcium and/or some other component of dairy products may modestly reduce the risk of breast cancer in postmenopausal women, an effect that was stronger with estrogen receptor positive cancers [69]. Also, another prospective cohort study found that for premenopausal women, high intakes of low-fat dairy products were linked to lower breast cancer risks, but it was impossible to separate the effects of vitamin D and calcium [70]. This last mentioned study is consistent with the result that vitamin D and calcium from food and supplements was associated with lower levels of mammographic breast density which is a surrogate for lower breast cancer risk [71]. However, in this study as in others, the intake of vitamin D and calcium were tightly correlated, making it difficult to identify independent associations.

Thus the independent role of calcium is unclear in this context, and if dairy products are protective, the association is weak and the role of both estrogen receptor and menopausal status uncertain.

To be concluded next month.

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