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Welcome to our early October issue. We are taking a vacation, so thought we would send the issue out sooner rather than later. The highlight of this issue is, without a doubt, the first part of an excellent three-part series on the vital topic the prevention of breast cancer. Researched and written by our long-standing contributor Bill Ware, the articles cover risk factors and preventive measures including the role of diet and specific fat types, alcohol, smoking, exercise, supplements, and much, much more. This is tremendously important information!!

Also in this issue we present more evidence of the absolute necessity of ensuring an adequate daily intake of magnesium and vitamin D, and report that rheumatoid arthritis patients can reduce their risk of heart disease by supplementing with fish oil, a new study questions the safety of cell phones, and a vitamin E deficiency during a mother's pregnancy has been linked to asthma in children.

I sincerely hope you will enjoy and benefit from this information-packed issue. 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 continuing good health,
Hans

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Muscle strength linked to magnesium in older adults

PALERMO, ITALY. Magnesium is central to human health as it plays a role in a wide range of activities on the cellular level. A deficiency can lead to muscle weakness, fatigue and insomnia. This nutrient may therefore be essential for maintaining muscle

strength throughout life. Evidence from athletes supports a role for magnesium in avoiding damage to muscle cells.

Muscle mass and function can be compromised in older age, a condition known as sarcopenia. Researchers from the University of Palermo investigated the relationship between sarcopenia and magnesium status. They analyzed data from the Italian InCHIANTI (aging in the Chianti area) study. Data on muscle performance and serum magnesium, gathered at the same time, were available for 1,138 healthy men and women. Mean age was 67 years and the participants were considered representative of the general population.

Magnesium status was found to be significantly related to each of the measures of muscle strength - grip strength, lower-leg muscle power, knee rotation, and ankle strength. The link, found in both men and women, remained "highly significant" once

the results were adjusted for factors including age, sex, body mass index, and levels of several other nutrients. In case the link was due to magnesium deficiency among certain participants, the analysis was repeated excluding individuals identified as deficient and a highly significant relationship was still observed.

The researchers suggest that the explanation may lie in the importance of magnesium to metabolism, or the increased free radical production and proinflammatory effects of low magnesium. They conclude that serum magnesium is significantly, independently, and strongly linked to muscle performance in older people. Measurement of serum magnesium should be part of routine physical check-ups, they believe, but they add that it is not fully clear whether magnesium supplementation improves muscle function. Magnesium is found in green vegetables such as spinach, nuts (especially almonds), seeds, and

some whole grains. Excessive intake can interfere with calcium absorption.

Dominguez, L. J. et al. Magnesium and muscle performance in older persons: the InCHIANTI study. The American Journal of Clinical Nutrition, Vol. 84, August 2006, pp. 419-26

Editor's comment: A recent study carried out at the University of Tennessee found that less than 26% of older adults in the USA meet the Recommended Daily Allowance (RDA) for magnesium (320 mg/day for women and 420 mg/day for men). The Tennessee researchers concluded that a higher magnesium intake through the diet or via supplementation might provide an additional strategy for preventing osteoporosis. *(Ryder, KM, et al. Magnesium intake from food and supplements is associated with bone mineral density in healthy older white subjects. Journal of the American Geriatrics Society, Vol. 53, November 2005, pp. 1875-80)*

Certain mineral waters could boost calcium intake

OMAHA, NEBRASKA. Calcium is essential for healthy bones, yet intake in the general population falls below recommendations. Several calcium-fortified products have been produced by food and drink manufacturers. But could naturally calcium-rich bottled mineral water be a useful means to boost intake of calcium? A researcher from Creighton University analyzed data on the absorbability of calcium from naturally high-calcium mineral waters. Dr. Heaney explains that the studies so far indicate good bioavailability, but vary widely in their methods, so he set about evaluating the studies to reliably determine the nutritional value of these waters. He added to the findings his own previously unpublished data from laboratory tests on volunteers who consumed high-calcium water. Tests used to determine levels of absorption included measurement of urinary calcium, serum parathyroid hormone levels, bone resorption markers and protection of bone mass. Three of the seven studies included a comparison of milk against high-calcium mineral water.

Combined results suggested that the calcium in calcium-rich mineral waters is highly absorbable -

equal to milk in terms of absorbability. Dr. Heaney concludes that mineral water consumption potentially accounts for a substantial fraction of total daily calcium intake. For this reason, it may be a useful means to boost intake of the mineral, closing the gap between recommended and actual calcium intakes. He also examined the potentially important differences in waters relating to the "counter-ion" accompanying their calcium. In most cases this was bicarbonate, but was occasionally sulfate. Calcium sulfate has previously shown good absorbability when added to white bread and tofu. Taking into account the study methods, the researcher concluded that calcium bicarbonate and calcium sulfate showed no appreciable difference in absorbability.

Dr. Heaney adds that milk, an alternative major source of calcium, has the additional benefit of providing a broad range of other nutrients important for total body and skeletal health.

Heaney, R. P. Absorbability and utility of calcium in mineral waters. The American Journal of Clinical Nutrition, Vol. 84, August 2006, pp. 371-74

Population levels of vitamin E investigated

ATLANTA, GEORGIA. Research is continuing into the benefits of vitamin E supplementation. Much of the research to date has focused on measuring alpha-tocopherol, the major circulating form of vitamin E. However, population levels of gamma-tocopherol (the main form in the US diet) are uncertain. Some human and animal studies suggest that high gamma-tocopherol levels are associated with lower rates of cardiovascular disease and certain cancers. Therefore, gamma-tocopherol may contribute significantly to human health in ways not previously recognized. Importantly, supplementation with alpha-tocopherol may deplete gamma-tocopherol.

A team from the US Centers for Disease Control and Prevention has now determined levels of alpha- and gamma-tocopherol among a large group representative of the general population. They took information from the US National Health and Nutrition Examination Survey of 1999 to 2000. Concentrations of alpha- and gamma-tocopherol were available for 4,087 adults aged 20 years or above. Mean concentration of alpha-tocopherol was 30.09 umol per liter of blood serum, and that for gamma-tocopherol was much lower, at 5.74 umol

per liter. Older and female participants had significantly higher levels of alpha-tocopherol than younger and male participants. Lower rates were found in African Americans and Mexicans compared with whites. For gamma-tocopherol, levels were again higher in older persons, but no significant differences were found with gender or ethnicity.

The researchers conclude that serum levels of alpha- and gamma-tocopherol vary demographically among US adults. They add that the mean level of alpha-tocopherol has risen over the past decade or so, while the proportion of adults taking vitamin E supplements (predominantly in the form of alpha-tocopherol) increased from 4.1 per cent in 1987 to 11.4 per cent in 2000. Deficiency is rare, they write, and higher levels among older people and whites may be due to greater supplement use. Ongoing research into the effects of each form of vitamin E on health aims to discover the optimum serum concentrations and dietary intakes of the nutrient.

Ford, E. S. et al. Distribution of serum concentrations of alpha-tocopherol and gamma-tocopherol in the US population. The American Journal of Clinical Nutrition, Vol. 84, August 2006, pp. 375-83

Effects of vitamin B12 on cognitive function in older people

WAGENINGEN, NETHERLANDS. Deficiency of vitamin B12 is common among older people. As this vitamin is crucial for brain and nervous system functioning, researchers have proposed that supplementation may have beneficial effects on cognitive function in this group. However, randomized trial results have so far been inconclusive.

Researchers from Wageningen University carried out a large study with a long duration and rigorous cognitive tests. They investigated the effects of daily oral supplementation with vitamin B12 at a high dose (1,000ug) on adults aged 70 years or above with a mild deficiency. High-dose vitamin B12 supplements are considered to be safe and no upper safety level has been set in the US or Europe. Among the group of 195 participants, some were given 400ug folic acid alongside the vitamin B12, and others a placebo. Compliance was very high, with a mean of 99 per cent. After 24 weeks, vitamin B12 status and cognitive function were assessed. Vitamin B12 supplementation reversed

deficiency, and those taking folic acid showed raised folic acid levels in their red blood cells. Both supplementation groups had lower homocysteine levels, which is beneficial in terms of heart disease risk. Homocysteine was lowered to a greater extent in the combined supplement group, as expected based on knowledge of how the two nutrients interact.

However, neither supplement was linked to better results than placebo on tests of cognitive performance which covered attention, construction, sensorimotor speed, memory, and executive function. Participants in all three groups showed improved memory, but the researchers concluded that the supplementation regimes used in this study did not lead to improved cognitive function. This may be because a longer course of vitamin B12 is necessary to repair any existing cognitive damage. Despite the results, the authors write, these findings cannot exclude beneficial effects on cognitive function from longer-term vitamin B12 supplementation. Individuals who have had mild

cognitive impairment for less than six months may also be more likely to respond to treatment with vitamin B12.

Eussen, S. J. Effect of oral vitamin B-12 with or without folic acid on cognitive function in older people with mild vitamin B-12 deficiency: a randomized, placebo-controlled trial. The American Journal of Clinical Nutrition, Vol. 84, August 2006, pp. 361-70

Vitamin D deficiency common in non-Western pregnant women

THE HAGUE, NETHERLANDS. Vitamin D deficiency during pregnancy is an important issue for the bone health of mother and child, and the range of other functions recently linked to this nutrient. Vitamin D is produced in the skin following exposure to sunlight or other ultraviolet light, but the skin pigment in persons with darker skin absorbs some of the rays and causes vitamin D deficiency to be more likely when living in northern countries.

Researchers from the Municipal Health Service of The Hague gathered data on pregnant women from several ethnic backgrounds living in the Netherlands. Serum vitamin D was measured by midwives in 358 Western, Turkish, Moroccan, and other non-Western women during the 12th week of pregnancy. The Western women had a mean concentration of 52.7 nmol per liter. But concentrations in the other groups were significantly lower. Turkish women had a mean of 15.2, the Moroccan women 20.1, and the other non-Western women 26.3. Further analysis suggested that these differences were based on ethnicity rather than other factors that may be related to vitamin D status. More than 50 per cent of the women in all non-Western groups had a vitamin D deficiency, compared with 8 per cent of Western women, say

the authors. They conclude that the prevalence of vitamin D deficiency in pregnant non-Western women in the Netherlands is very high, and urge health services to include vitamin D status screening as routine for all pregnant non-Western women.

In an editorial, experts from the Medical University of South Carolina point out that the definition of deficiency used in the study was conservative - 25-hydroxyvitamin D concentration of less than 25 nmol per liter - so the rate of deficiency may be underestimated. They would like to see pregnant women achieve at least 80 nmol per liter, and discuss the necessary vitamin D intake. An intake of 200 IU per day is way too low, they believe. Instead, to increase vitamin D to meaningful concentrations, a daily intake of 2000 IU may be required. The authors call for further studies to establish the true vitamin D requirement during pregnancy.

van der Meer, I. M. et al. High prevalence of vitamin D deficiency in pregnant non-Western women in The Hague, Netherlands. The American Journal of Clinical Nutrition, Vol. 84, August 2006, pp. 350-53

Hollis, B. W. & Wagner, C. L. Vitamin D deficiency during pregnancy: an ongoing epidemic. The American Journal of Clinical Nutrition, Vol. 84, August 2006, pp. 273

Fish oil reduces heart disease risk in arthritis patients

ADELAIDE, AUSTRALIA. The potential benefit of fish oils on rheumatoid arthritis (RA) has been the subject of many previous studies. Overall, the results suggest that fish oil supplements containing the omega 3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can reduce stiffness and pain. But could these supplements also help reduce the increased risk of cardiovascular disease in RA patients?

A team from the Royal Adelaide Hospital investigated the effects of fish oil supplementation on several cardiovascular risk factors. They recruited 31 early RA patients all taking drug treatment for the condition, of whom 18 also chose to take fish oil. The dose was considered by the

researchers to be sufficiently high to have an anti-inflammatory action. After three years of supplementation, data from the patients who did not take fish oil was compared with data from those who did and reached a level of EPA greater than 5 per cent of total plasma fatty acids. Arachidonic acid, an omega 6 fatty acid which competes with omega 3 FAs, was lower in participants who reached the required level of EPA. It was 30 per cent lower in platelets and 40 per cent lower in peripheral blood cells. Serum thromboxane B2, a cardiovascular risk factor, was 35 per cent lower. Prostaglandin E2, a compound which RA drug treatment seeks to reduce, was 41 per cent lower.

Fish oil was also linked to positive changes in blood lipids, and a greater rate of remission after the 3 years - 72 per cent compared to 31 per cent in the non-fish oil group. The authors conclude that fish oil reduces cardiovascular risk in RA patients, and that this takes place via several biological pathways. They suggest that fish oil could potentially replace drug treatment for many RA patients. In this study, non-steroidal anti-inflammatory drug use was reduced by 75 per cent in the fish oil group between the start and finish of the study, compared with 37

per cent in the non-fish oil group. Added to which, RA drugs may themselves contribute to cardiovascular risk. Fish oil is a cheaper, safer treatment option and could also serve as a preventative measure against RA, the authors conclude.

Cleland, LG, et al. Reduction of cardiovascular risk factors with longterm fish oil treatment in early rheumatoid arthritis. Journal of Rheumatology, published online August 1, 2006

NEWSBRIEFS

New data adds to case against cell phones

The potential risk of malignant brain tumors from using cell phones continues to be investigated. A recent case-control study from University Hospital, Orebro, Sweden adds to the evidence. Analysis of data from 2000-2003 found a 2.6 times higher rate of brain tumor among those who used analog cellular phones, and a 1.9 times higher rate among those who used digital cellular phones. Using a cordless phone was linked to a 2.1 times increased risk. Greater time spent on the phones was associated with a higher risk. High-grade astrocytoma tumor had the strongest link to phone use. Such research faces many challenges. Estimating cell phone use is difficult and tumor latency periods are likely to be several years. Longer surveillance will probably be necessary to reach more reliable conclusions. The British Medical Association currently recommends a precautionary approach to cell phones while research remains inconclusive.

Hardell, L, et al. Case-control study of the association between the use of cellular and cordless telephones and malignant brain tumors diagnosed during 2000-2003. Environmental Research, Vol. 100, February 2006, pp. 232-41

Innovative eating disorder prevention for female students

An internet-based programme may help female students avoid eating disorders, say researchers from Stanford University, California. They recruited 480 college-age women to follow an eight-week program, "Student Bodies", which aims to promote healthy eating and a healthy body image while raising awareness of eating disorder risks. The women kept body-image journals and joined an online discussion group. In the general Western population, 0.5-3.7 per cent of women develop anorexia, and 1.1-4.2 per cent develop bulimia.

Women who followed the programme had a significantly lower rate of eating disorders than their peers. It particularly helped women who were overweight initially. None in this group developed an eating disorder over the next two years, compared with 11.9 per cent of comparable women not on the program. Among those already showing symptoms of an eating disorder, 14 per cent developed an eating disorder within two years, compared with 30 per cent of similar women not on the program.

Taylor, C. B. et al. Prevention of Eating Disorders in At-risk College-age Women. Archives of General Psychiatry, Vol. 63, August 2006, pp. 881-88

Vitamin E during pregnancy may prevent asthma in children

Pregnant women can reduce their baby's risk of asthma by consuming more vitamin E, suggests a team from the University of Aberdeen, UK. Their study included 1,861 children born to women recruited during pregnancy. At five years of age, the children whose mothers had a low intake of vitamin E during pregnancy had a significantly higher rate of wheezing and asthma. Rates were more than five times higher among those in the bottom fifth for maternal vitamin E intake than those in the top fifth. No links were found between the children's own nutrient intake and asthma. The team suggest that vitamin E has an effect on lung function and airway inflammation and that the effects could change at differing periods of prenatal and early life. The airways develop in the first 16 weeks of pregnancy, so vitamin E intake may be more important at this stage. Dietary modification or supplementation during pregnancy warrants further investigation, they conclude.

Devereux, G. et al. Low Maternal Vitamin E Intake during Pregnancy Is Associated with Asthma in 5-Year-Old Children. American Journal of Respiratory and Critical Care Medicine, Vol. 174, September 1, 2006, pp. 499-507

Fruit and vegetable juice could prevent or delay Alzheimer's disease

New data supports the possibility that fruit and vegetable juice may reduce the risk of Alzheimer's disease. A team from the Vanderbilt School of Medicine, Tennessee investigated the effect of polyphenols, an abundant form of antioxidant, on the oxidative damage which can produce Alzheimer's. They followed 1,836 Japanese Americans living in Seattle, USA for up to 10 years. Risk of Alzheimer's disease was 76 per cent lower among those who drank fruit and vegetable juices more than three times per week than among those who drank juices less than once per week. Drinking juice once or twice per week was linked to a 16 per cent lowered risk. The researchers suggest that these drinks may play an important role in delaying the onset of Alzheimer's disease, particularly among those who are at high risk. Polyphenols may prevent oxidative damage to the brain caused by amyloid beta plaques through halting the build up of amyloid beta by disrupting the action of hydrogen peroxide.

Dai, Q. et al. Fruit and Vegetable Juices and Alzheimer's Disease: The Kame Project. The American Journal of Medicine, Vol. 119, September 2006, pp. 751-59

Claims for genetic diabetes prevention may be overstated

Recent claims for the possibility of a genetic cure for diabetes are misleading, warn public health experts from the Erasmus MC University Medical Center in the Netherlands. They believe the media coverage surrounding a recent genetic discovery raise unrealistic expectations. A variant of the TCF7L2 gene was linked with type 2 diabetes. This offers a potential new insight into the development of diabetes, they write, but it is wrong to suggest the

discovery will lead directly to disease prevention. The authors explain that 45 per cent of the population would need a 100 per cent effective intervention to prevent 21 per cent of diabetes cases. These figures would not be a great enough incentive for lifestyle change, they suggest. Raising unrealistic expectations - even inadvertently - could distract attention from what can be done by applying what we already know to prevent diabetes and its complications, they conclude.

Janssens, A. C. J. W. et al. Editorial: Predictive genetic testing for type 2 diabetes. British Medical Journal, Vol. 333, September 9, 2006, pp. 509-10

Saturated fat really is bad for you!

Meals high in saturated fat can have an instant effect on heart disease and stroke risk, say scientists. A team from the Heart Research Institute in Sydney, Australia suggests that harmful effects can result from eating a single meal high in saturated fat, and a single meal high in polyunsaturated fat can be beneficial. They tested 14 healthy volunteers who ate meals which looked identical but varied in the type of fat used. The team found short-term changes in the level of low-density lipoprotein (LDL) cholesterol, which impacts on the body's ability to prevent the lining of the arteries from narrowing and forming artery-clogging plaque. The authors say that this adds to the evidence for aggressively reducing the amount of saturated fat in the diet. The study helps to explain how saturated fat supports the formation of plaques in the arterial wall, they add.

Nicholls, S. J. et al. Consumption of Saturated Fat Impairs the Anti-Inflammatory Properties of High-Density Lipoproteins and Endothelial Function. The Journal of the American College of Cardiology, Vol. 48, August 15, 2006, p. 715-20

RESEARCH REPORT

Primary Prevention of Breast Cancer – Part I

William R. Ware, Ph.D.
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“One of the most recalcitrant obstacles to reducing breast cancer incidence is a profound ignorance of the causes of sporadic breast cancer.” David M. Euhus, 2006 [1]

INTRODUCTION

One might think that guidance regarding primary prevention would come principally from an understanding of the mechanism of breast cancer carcinogenesis. The answer to the question, what causes breast cancer, should lead to answers to the question, how can it be prevented. However it is not that simple! DNA damage and cell matrix damage are two postulated mechanisms for cancer initiation and proliferation. This involves spontaneous mutations and as well DNA damage from a number of sources, which cause breast cells to behave in abnormal ways, some of which lead to tumor formation, invasive behavior, and metastasis. A search of the medical literature reveals numerous mechanistic studies probing the details of some aspect or other of breast cancer carcinogenesis, but there is a notable absence of any unifying theory, even in the area of hormonal involvement [2]. However, high blood levels of various estrogens have been clearly implicated as a risk factor for breast cancer. This conclusion is supported partly by a pooled analysis of nine prospective studies where blood was collected from healthy, cancer-free postmenopausal women who were then followed for an average of 5.4 years. The higher the levels of circulating estrogens, the higher the risk. While this does not prove a causal relationship, the authors suggest that other clinical and cell culture evidence makes the causal relationship quite likely [3]. The estrogen connection has recently been the subject of a comprehensive review [4].

Mainstream medicine for the most part views primary prevention of breast cancer as the use of pharmaceutical drugs, ovary removal or bilateral mastectomy, but restricts these interventions to those deemed high-risk, for example because of a genetic predisposition. Other preventive actions are outlined in the American Cancer Society (ACS) 2006 prevention guidelines as presented on their website are of interest: have several children and breast feed them for several months, don't drink alcohol, exercise regularly and stay slim and follow the ACS guideline for early detection of breast cancer. The guidelines mention the prescription drugs tamoxifen and raloxifene for high-risk women. So if a woman has already had her children and the last one is beyond breast feeding age, and this includes the vast majority of women concerned about breast cancer, then these recommendations boil down to exercise, keep weight down and avoid alcohol, period. Screening for early detection, for example by mammography, is not primary prevention. It has as its goal the early detection of cancer and is aimed at decreasing breast cancer-specific mortality and increasing overall survival. The success of mammography in accomplishing these goals is still being debated.

This review will examine the evidence associated with these and other potential preventive actions a woman can take for the purpose of primary risk reduction. The ACS guidelines in fact leave quite a lot unsaid.

NON-MODIFIABLE RISK (AND PROTECTIVE) FACTORS

Some would consider risk factors over which one has no control to be merely of academic interest. However, knowledge of these non-modifiable risk factors is in fact important, since their presence can encourage a woman to undertake aggressive investigation and implementation of preventive actions and interventions. The following are generally recognized as the principal non-modifiable risk factors for breast cancer [2,5,6]. While some of these factors are in theory modifiable, this would only apply to women of child bearing age who might elect to

breastfeed their children for extended periods, have a large number of children, etc. For most women concerned with breast cancer prevention, these are not really options.

- Age
- Age at menarche (first menstrual period)
- Age at first childbirth
- Age at the onset of menopause
- Height
- Strong family risk of prostate cancer
- Number of pregnancies including zero (nulliparous)
- Breastfeeding and its duration
- Family history, genetic and polygenic factors
- Benign breast disease found on biopsy

Breast cancer risk is very low (< 10/100,000) before age 25 and increases up to 100-fold by age 45. After menopause the age dependence varies according to location, with women in the US and Sweden for example experiencing a slower but continual rise to age 75, whereas in Japan where the risk is low anyway, the cancer incidence after 45 exhibits a plateau followed by a slow decline. All countries studied show the sharp increase during the reproductive years, a pattern that suggests the involvement of the reproductive hormones [6].

A younger age at menarche and first childbirth and a later onset of menopause all increase the risk of breast cancer. The risk also decreases with the number of children. It is widely believed that the lifetime exposure to endogenous (internally generated) reproductive hormones is an important factor in the etiology of the disease, and it has also in fact been demonstrated that mammary epithelial cell proliferation can be correlated with serum ovarian hormonal levels (e.g. estrogens) [4,6]. Estrogens and progesterone are involved in the control of cellular proliferation in the breast, and the risk of breast cancer associated with this increased rate of cell division is hypothesized to relate to a greater opportunity for the accumulation of random genetic errors (mutations) some of which could impact tumorigenesis. Early menarche and late menopause extend this exposure. The age at first birth has a dramatic effect on the relative risk. When the comparison is with women who have had no children (nulliparous), an age at first birth of 15 years yields a risk reduction later in life of about 60%. As the age of first completed pregnancy increases, the benefit slowly decreases until it disappears (same risk as nulliparity) at an age of 30—35 and then becomes an increasing positive risk factor until menopause. However, the benefits of early pregnancy appear only about 10 years after birth and in fact, the risk is enhanced during the first 10 years with the enhancement increasing with age. The mechanism associated with the benefits of an early first pregnancy is unknown but animal studies suggest that as the breast develops, growth includes an increase in the number of stem cells and differentiation from stem cells to functioning ductal and secretor cells, and this growth and development involves the possibility of mutations and malignant transformation. The important point is that the final differentiation occurs during the first pregnancy, leading to a small increased risk of malignant transformation in the short term, but also yields fully differentiated cells that have a much lower risk of transformation thereafter [2].

The role of breastfeeding as a cancer risk factor has been the subject of numerous studies. In a recent review, MacMahon points out that the association between breastfeeding and breast cancer risk is manifest only in areas where accumulated lifetime lactation exceeds 5 years. Thus in developed countries where the mean lifetime duration of lactation is < 9 months, the association, while potentially present, would be difficult to detect because of the small magnitude of the effect. Also, MacMahon comments that the very long durations of lactation in underdeveloped countries may be only a marker for other factors which also influence risk, such as under-nutrition [2]. However, lactation results in a substantial delay in reestablishing ovulation following a completed pregnancy, and this would decrease the lifetime number of ovulatory menstrual cycles, which would have the same effect as late menarche or early menopause, both known to reduce risk [7].

The connection between breast cancer incidence and above average height is curious. The mechanism responsible for the relationship is unknown, but it has been suggested that nutritional status, which might interact with genetic factors, is related to the gain in height in childhood and as well to an earlier onset of puberty [8].

Benign breast disease is also termed a *precancerous condition* [9]. Benign breast disease generally develops in the breast ductal system. Extra cells develop on the inner wall of a duct—termed hyperplasia. Some of these cells can transform into odd-looking cells, called atypia. Women with severe *atypical hyperplasia* have a 4- to 5-fold increase in the risk of breast cancer, and a family history of breast cancer increases this risk up to 9-fold [2]. If the hyperplasia intensifies and fills the duct with odd looking cells it is termed *ductal carcinoma in situ* (DCIS). When the abnormal cell growth expands through the ductal wall into the outside space and tissue, it is described as invasive cancer. Intraductal carcinoma requires treatment, generally surgical removal. Benign breast disease is generally identified on biopsy, but before it becomes invasive there is generally no palpable growth and evidence is generally from mammography. There are a number of other breast problems, most of which do not pose risk of progression to invasive breast cancer. These include swelling, pain, tenderness, lumpy breasts (not isolated breast lumps), nipple discharge, etc. that have historically been described as *fibrocystic disease*. A number of professionals in this field think that this term should not be used and the heterogeneous conditions it describes are not diseases at all [9]. However, the term is still used in both books for the lay audience and in the scientific literature. It is generally thought that this collection of disorders or physiological phenomena carry little or no risk of cancer. However, this may not be true for isolated lumps that a woman can generally differentiate from what is called “lumpiness” and the isolated lump demands professional attention and can indeed be cancerous. Some isolated lumps form as the result of ductal carcinoma in situ becoming invasive and developing into an extra-ductal cancerous lump. Lumps can also be cysts which, in general, are non-cancerous as in general are lumps attributable to fibroadenomas. However, professional advice should always be sought regarding lumps, if for no other reason, simply to alleviate anxiety. An informative discussion of this subject can be found in chapters 4 and 6 of Dr. Susan Love’s Breast Book [9].

Mutations in the tumor suppressor genes designated as BRCA1 and BRCA2 are responsible for 80-90% of all hereditary breast cancers, but only between 5 and 10% of all breast cancers are attributable to inherited genetic mutations. Women who carry these mutations have an increase in lifetime risk of breast cancer of between 35 and 84% by age 70 [10], which is roughly 10 times that of the general population. The presence of this gene mutation also dramatically increases the risk of ovarian cancer (10-50% increase in risk by age 70). Ovarian cancer is difficult to diagnose at an early stage with present technology and has a high mortality rate. Removal of the ovaries almost but not totally eliminates the risk of this cancer. One reason the risk reduction is not 100% is that there may be some ovarian tissue left behind during the surgery.

This brings up the issue of genetic testing. Recent guidelines from the US Preventive Services Task Force (USPSTF) [10] provide guidance as to when the risk of having the BRCA 1/2 mutations is high enough to justify the recommendation of genetic counseling and testing. These guidelines depend on family history and the following definitions are important: *relatives of the first-degree* are parents, siblings and offspring of the individual in question; *relatives of the second-degree* are grandparents and grandchildren, uncles and aunts, nephews and nieces, and half-siblings. Given these definitions, what is termed *increased-risk family history* is determined as follows and depends on the presence of any one of the following conditions: (a) two first-degree relatives with breast cancer, one of whom received the diagnosis at age 50 or younger; (b) a combination of three or more first- or second-degree relatives with breast cancer; (c) a combination of both breast and ovarian cancer among first- and second-degree relatives at any age; (d) a first-degree relative with bilateral breast cancer; (e) a combination of two or more first- or second-degree relatives with ovarian cancer regardless of age of diagnosis; and finally (f) a history of breast cancer in a male relative. Ashkenazi Jewish heritage entails enhanced risk and an increased-risk family history for this group is defined as any first-degree relative or two second-degree relatives on the same side of the family with either breast or ovarian cancer. In general, women with one, two or three or more first degree relatives with breast cancer have, compared to women who have no relatives with breast cancer, relative risks of 1.8, 2.9 and 3.9 respectively for eventually developing breast cancer [11].

In an editorial accompanying the publication of these guidelines [12], Burk points out that potential candidates for BRCA testing need to be aware of the following limitations associated with genetic testing and interpreting the results: (a) current testing is estimated to miss 12-15% of BRCA mutations; (b) other genetic causes of family related breast cancer are likely; (c) finding a gene variant of unknown clinical significance is estimated to occur about 13% of the time. While it is important to be aware of these limitations, they do not appear to be a significant deterrent to proceeding with testing if an increased-risk family history is present.

Omitted from these guidelines is the risk factor associated with a family history of prostate cancer. A recent study done in Sweden found that women with a family history of hereditary prostate cancer had a 1.58 times greater risk of developing breast cancer than a woman lacking such history. Hereditary prostate cancer was in this study defined as at least three first-degree relatives with prostate cancer or two affected first-degree relatives of age < 55 years (early onset). The risk of breast cancer was increased to almost a factor of 4 in women before the age of 65 years from families with a history of early onset prostate cancer [13]. Similar results were found in a French study [14]. There have been reports that carriers of BRCA2 mutations are at enhanced risk of prostate cancer [13], and a study involving Ashkenazi Jewish men also found the BRCA2 mutation associated with an increased risk [15].

The USPSTF takes the position that women who have increased-risk family history would benefit from genetic counseling that allows an informed decision about testing and preventive measures. Also, some high-risk women may want to know their status because it impacts on the cancer risk for their existing and future children and grandchildren. Thus test results can influence what are called fertility decisions. There is in fact evidence showing that BRCA testing affects family planning decision-making [16]. Technology exists that permits pre-implantation genetic testing and thus embryo selection, but there are a number of associated issues, both financial and ethical.

MODIFIABLE RISK FACTORS

ESTROGEN METABOLITES IN THE ETIOLOGY OF BREAST CANCER

The estrogens estrone and estradiol are both metabolized to yield a number of intermediate and end products. Interest in these estrogen metabolites as possible factors in breast carcinogenesis can be traced back to at least the early 1970s. By the early 1980s it was found that women with breast cancer had elevated levels of one of the metabolites, 16 α -hydroxyesterone. In a study published in 1997 which had a significant impact on research in this area, Kabat *et al* reported on a case control study [17] where the emphasis was on the ratio of two metabolites, 2-hydroxyestrone and 16 α -hydroxyestrone (2-OHE and 16-OHE). There were only 39 cases and 58 controls, and for the total group, no significant association with breast cancer risk was found for the ratio of these two metabolites. However, for postmenopausal women (23 cases vs. 28 controls) a significant increase in incidence of breast cancer was found for low values of the ratio of 2-OHE/16-OHE, but the confidence limits, while not including the null result, were huge. There was no control for alcohol or coffee consumption. While this one statistically significant result based on a very small number of cases eventually became a key part of the folklore of estrogen metabolites, even the authors suggested that until large prospective studies were conducted, the connection between this ratio and the risk of breast cancer would remain uncertain. Also, a serious problem with this and some subsequent studies was that individuals with cancer were compared to controls, whereas if the interest is in primary prevention, then this ratio should be examined in prospective studies where the participants are cancer-free at baseline.

After Kabat *et al* there appear to be only four prospective studies that relate to this question [18-21]. Two of these studies gave results that were statistically insignificant, one found that high, not low values of the ratio of 2-OHE/16-OHE were associated with increased risk, and one, which used mammographic breast density as a surrogate measure, also found high, not low values of the ratio were related to enhanced risk. Thus while cell culture evidence suggests that 16-OHE is pro-carcinogenic, has proliferative effects and down-regulates apoptosis (programmed cell death) and 2-OHE does not or only weakly influences these functions [22], epidemiologic prospective studies fail to confirm with consistent, statistically significant results the importance of the ratio of these metabolites in connection with the risk of cancer in initially healthy women. This view dismisses several suggestive case-control studies simply because they involved cases already diagnosed with breast cancer.

It is unfortunate that when one applies modern standards for evidence, the above-discussed studies by and large fail to achieve significance and also yield contradictory results. The reason this is unfortunate is that this metabolite ratio can be modified by dietary or supplemental intervention. The supplement in question is indole-3-carbinol, a compound found in such vegetables as broccoli. Supplementing with I3C or its first metabolite diindolylmethane (DIM) will generally shift the 2-OHE/16-OHE ratio to higher values, i.e. the production of 2-OHE is favored. This is an important aspect of Dr. E. J. Conley's protocol described in *The Breast Cancer Prevention*

Plan for cancer prevention [23] and DIM is part of Dr. J. McWherter's protocol described in the recent book *Avoiding Breast Cancer* [24]. While health benefits may result from taking I3C or DIM or eating lots of broccoli, such actions do not appear justified for breast cancer prevention by prospective cohort studies even if there is a shift in estrogen metabolism in favor of 2-OHE.

DIET AND BREAST CANCER

TOTAL FAT

For several decades the conventional wisdom connected total fat intake with breast cancer risk. Walter Willett in his book *Nutritional Epidemiology* provides a review of the historical data and discusses possible sources of confounding [25]. An international study published in 1975 showed a strong linear relationship between national total dietary fat intake and the death rates attributable to breast cancer. However, as Willett points out, one of the potential confounders, adult height acting as a surrogate for energy balance during development, produces almost the same international correlation as fat intake. As more and more studies were reported, it became evident that there was in fact no connection between breast cancer incidence and total fat consumption. Prospective follow-up studies are generally regarded as the most reliable in ascertaining risk [25] since they avoid recall bias and bias in control selection inherent to the case-control approach. Hanf and Gonder from the University of Göttingen have recently (2005) reviewed the evidence [26]. Of 12 cohort studies which examined total fat intake, the only statistically significant result was that in one study increasing total fat *decreased* the risk. Nine prospective studies of meat (red and white) failed in a pooled analysis to reveal any risk. And animal fat was not found to be significantly associated with risk. However, as discussed below, one study found in *premenopausal* women that animal fat, mainly from red meat and high fat dairy food, was in fact a risk factor. Aside from this one result, the conclusion based on a large number of prospective cohort studies is that there is no significant evidence that total fat intake is connected with breast cancer risk [27-29].

It is also significant that no large interventional study has demonstrated that a low-fat diet reduces the risk of breast cancer [26]. Consistent with this, the recently reported results from the Woman's Health Initiative (WHI) Randomized Controlled Dietary Modification Trial of postmenopausal women found no connection between the low-fat dietary intervention and reduced risk of breast cancer [30]. However, in spite of the extensive media attention, this study can hardly be considered definitive since by the end of the sixth year of follow-up the intervention and control groups differed by only 8.1% in the energy intake from fat and perhaps more importantly, adherence to the dietary program in the intervention group declined to 31% at year 6 and 19% at year 9. While the overall measures of benefit from the low-fat intervention failed to reach significance, women with an initial very high dietary fat consumption as a percentage of total energy (> 36.8%) at enrollment had a significant reduction in breast cancer risk, a result that merits further study.

One of the problems with many of the studies of breast cancer and total fat intake is that they involved only a small representation of premenopausal women. In 2003 research from Harvard based on the Nurses' Health Study II was reported which addresses this issue [31]. Dietary fat intake and breast cancer risk were assessed among over 90,000 premenopausal women between the ages of 26 and 45 at enrollment (mean age 43), starting in 1991. Food frequency questionnaires were used at baseline and again in 1995. After 8 years follow-up, the relative risk of breast cancer based on total fat intake was slight and only marginally significant (RR = 1.25, 95% confidence limits 0.98 to 1.59). However, the incidence of breast cancer associated with the intake of animal fat exhibited, for increasing quintiles compared to those in the lowest quintile of consumption, a significant trend of increasing risk (RRs = 1.28, 1.37, 1.54, 1.33, $P_{\text{TREND}} = 0.002$). An analysis of food groups revealed that animal fat, red meat and high-fat dairy foods were each associated with increased risk. The connection with animal fat may relate to cooking practices which may introduce carcinogens, and high-fat dairy foods contain fat-soluble hormones and/or growth factors, which may be related to breast cancer risk. Thus the connection with fat may be indirect. These interesting results apply only to premenopausal women, a factor that may explain the discrepancies between these results and all other studies, where the subject populations were mostly or entirely composed of postmenopausal women.

SPECIFIC FATS

Fat can be classified according to saturated, monounsaturated, polyunsaturated, and trans-fat types. Many studies lump all of these together and simply examine risks relative to total fat. Saturated fats have been traditionally one of the subtypes highlighted for disapproval in the context of breast cancer. However, as Hanf

and Gonder [26] point out, nine of ten prospective cohort studies failed to find a connection and one found a reduced, not elevated risk. Monounsaturated fats such as found in olive oil have traditionally been regarded as protective, but 6 of 9 studies found no protective effect, two detected elevated risk, and one showed the expected lowering. Polyunsaturated fats (omega-3 and omega-6 fats) such as those found in plant oils and oily fish were examined in 8 studies with all results of no statistical significance.

Japan is a special case due to the low risk of breast cancer in the general population. In a recent large prospective cohort study [32] of women 40-79 years of age with a mean follow up of almost 8 years, a significant decrease in risk was found for the highest vs. the lowest quartile for fish and long-chain omega-3 fatty acid intake (RR = 0.56, 95% CI 0.33-0.94 and 0.50, CI 0.30-0.85 respectively). Among postmenopausal Japanese women at baseline, the highest quartile of vegetable fat intake was associated with a 2.08-fold increase in risk (95% CI 1.05-4.13). Consistent with this study, the Singapore Chinese Health Study reported significant reduced risk of breast cancer associated with dietary omega-3 fatty acids from fish and shellfish. Relative to the lowest quartile of intake, individuals in the highest three quartiles exhibited a 26% reduction in risk. While omega-6 fats were not in general implicated in risk, for subjects who consumed low levels of marine omega-3 fatty acids, a comparison between those in the lowest vs. highest quartiles of omega-6 fats had almost double the risk of breast cancer. Consistent with other prospective studies, no risk was associated with either total or saturated fat. A recently reported prospective study from Sweden also identified vegetable oil-based dietary fats, which are high in omega-6 fatty acids, as presenting a statistically significant risk for breast cancer (Odds Ratio = 1.74, 95% CI 1.12-2.72). Thus studies that lump omega-3 and omega-6 fats together and simply look at total polyunsaturated fats may be uninformative.

These results suggest the importance of the omega-3/omega-6 dietary ratio on breast cancer risk. Simopoulos [33] has reviewed the relevant literature concerning this ratio and cancer risk. While much more research is needed to clarify the role of the polyunsaturated fatty acids and in particular the omega-3 to omega-6 ratio in the context of breast cancer, the above results are very suggestive. It is interesting in this context that the typical North American and European diets result in a very low ratio of omega-3 to omega-6, both in the diet and in the cellular phospholipids (in blood cells) [34]. This is due to both a very high consumption of omega-6 fats and low consumption of omega-3 fats. Thus attempts to associate omega-3 or fish intake and breast cancer risk in countries in these areas may be doomed from the start because of the overwhelming influence of the omega-6 intake. This may be why conflicting results have been reported concerning risk and fish intake in North America and Europe [26]. It would be interesting to study the long-term intervention with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplementation on breast cancer risk where the omega 3/omega 6 ratio in serum cellular phospholipids was monitored. This ratio (actually the EPA/arachidonic acid ratio or its inverse) can now be measured with a blood test available from commercial laboratories and there is significant evidence concerning the optimum range of this ratio in connection with a number of important health issues. The ratio is easily modified simply by consuming fish oil or the purified omega-3 fatty acids EPA and DHA [34]. The reader is referred to the *International Health News* newsletter (March-May 2005) for a research report that provides a detailed discussion of the role of polyunsaturated fatty acids in inflammation, immunity and a number of other health issues.

DIETARY PATTERNS

Humans obviously do not generally eat individual foods in isolation but rather consume complex mixtures of nutrients at most meals. Thus in recent years there has been growing interest in attempting to identify favorable and unfavorable so-called dietary patterns based on epidemiologic studies aimed at establishing a connection with the risk of various diseases and disorders. Analysis actually involves recovering patterns *a priori* from large databases of food consumption where information exists concerning the presence of various diseases in the cohort in question. Dietary patterns are particularly interesting because breast cancer shows strong variations with location of residence and changes in risk take place that are associated with migration from low- to high-risk areas. This suggests that a component of risk involves lifestyle issues including diet.

In this context there have been five recently reported prospective cohort studies that examined the connection between dietary patterns and the risk of breast cancer [35-39]. Large cohorts from North America, Italy and northern Europe were involved. The results seem quite disappointing, with only a salad and vegetable pattern yielding significant results in the Italian study and a so-called Southern pattern showing reduced risk in a large US study. In the salad—vegetable pattern, the prominent components were raw vegetables and olive oil. The

foods most strongly implicated in the Southern pattern were cabbage, and legumes. The southern pattern was associated with a group having a lower level of education and more manual labor type work. The authors suggest that for this particular group, the southern pattern may also have been the diet experienced during the developmental years, and this may play a role in its protective effect. Diet patterns such as the Prudent Pattern (higher intake of fruits, vegetables, whole grains, low-fat dairy products, fish and poultry) or the Western Pattern (higher intakes of red and processed meats, refined grains, sweets and desserts and high-fat dairy products) were not found to have any significant association with breast cancer risk. In addition, in the Italian study, a different Western Pattern (potatoes, red meat, eggs and butter), the Canteen Pattern (pasta and tomato sauce) and a different Prudent Pattern (cooked vegetables, pulses and fish) all were found not to be associated with increased or decreased risk. As Männistö *et al* comment [37], the results of dietary pattern analysis support “the suggestion derived from traditional epidemiology that relatively recent dietary habits may not have an important role in the etiology of breast cancer.”

A recent study by Fung *et al* [40] relates to this failure of diet pattern analysis. Instead of patterns, they looked at the closely related “quality score” of several diets. While no risk or benefit was found in the context of breast cancer prevention for postmenopausal women in general, stratification by tumor type found on prospective follow-up of a Nurses’ Health Study cohort that scoring high on the items in certain diets correlated with risk reduction for estrogen receptor negative tumors. Since this tumor type is in the minority, these results would explain why pattern analysis studies and diet studies which did not or were unable to stratify for tumor estrogen receptor type typically yielded null results. The diets found to be potentially protective were heavy in fruits and vegetables, fish, whole grains, had a high monosaturated to saturated fat ratio, a low percentage of energy from fat or saturated fat, and one diet approximated the traditional Mediterranean diet. The traditional Mediterranean diet has in a number of studies been associated with reduced risk of cancer [41].

FRUITS, VEGETABLES AND FIBER

Hanf and Gonder [26] have recently reviewed the evidence for a connection between fruit and vegetable consumption and the risks of breast cancer. Prospective cohort studies have uniformly failed to reveal a risk reduction. Riboli and Norat [42] in a review and meta-analysis published in 2003 identified 15 case-control studies and 10 prospective cohort studies. When all studies were analyzed together, no significant effect was seen for either fruits or vegetables. The same conclusion was reached by Smith-Werner *et al* in a pooled analysis of 8 prospective cohort studies—consumption of fruits and vegetables was not significantly associated with reduced breast cancer risk. Likewise, a recently reported prospective study involving over 285,000 women with a follow-up mean of 5.4 years found no association with either total or specific vegetable and fruit intake and breast cancer [43]. These null results may also reflect the estrogen receptor problem discussed above.

Hanf and Gonder [26] have also reviewed five prospective cohort studies regarding the association of dietary fiber and breast cancer. Four of five found no association and to this can be added a study which was not included and which also gave a null result.

DAIRY PRODUCTS

Moorman and Terry [44] have reviewed the literature regarding the consumption of dairy products and the risk of breast cancer. They found that the available epidemiologic evidence failed to support a strong association between either milk or other dairy products and the risk of this disease. A pooled analysis of cohort studies by Missmer *et al* [45] also found no associations with dairy products. The related issue of vitamin D and calcium contained in dairy products will be discussed later.

CARBOHYDRATES, DIETS WITH HIGH GLYCEMIC LOAD, AND THE INTAKE OF HIGH GLYCEMIC INDEX FOODS

The widespread reaction to the notion that dietary fat was bad and at the root of many ailments resulted in a significant change in dietary habits in North America and an increase in carbohydrate consumption to compensate for the loss of calories from fat. Much of the carbohydrate involved was of high glycemic index, a measure of the impact of the carbohydrate on blood sugar levels. As discussed above, evidence currently available suggests that the condemnation of fat was supported by improperly conducted studies, was simplistic and ignored the multiplicity of fat types. It may take some time before this is generally appreciated. Hyperinsulinemia (high circulating insulin levels), which can result from prolonged consumption of high glycemic index carbohydrates, has been shown to be associated with increased breast cancer risk. Thus the interest in a

potential association with diets having a high glycemic load (glycemic index times the amount consumed) from large amounts of rapidly digested carbohydrates. While retrospective and case-control studies have suggested a positive association between high glycemic index or high glycemic load diets, seven prospective cohort studies reported over the last three years and involving a total of 368,272 women provide little support for this association [46-52]. In the face of massive null results, the few significant associations that have been reported [29,53,54] may possibly be merely due to chance in spite of statistics that suggest otherwise.

DIET AND NUTRITION IN EARLY LIFE

Studies looking back into childhood not only have the serious problem of distant-time recall, but also the nature of the foods involved has changed, making it difficult to apply the results from studies that look back into the past. For example, the trans-fat content of many processed and so-called fast foods is currently decreasing dramatically due to pressure from governments and the public and the unfavorable publicity being given to fast-food vendors who have not as yet addressed this problem. Also, drinking whole milk is now uncommon, and the “unnatural” constituents of milk (hormones, antibiotics, growth factors, various pesticides, etc.) have changed over the years. The contemporary practice of shortening the interval between pregnancies in cows has altered the endogenous bovine estrogen content of milk. Long-term recall is also highly problematic for both mothers who may be quite old when surveyed regarding the diets of their now adult female children during early childhood through adolescence, and women themselves may have paid little attention to what they ate during this period except to recall the foods they disliked. The sort of detailed quantitative recall necessary for a potentially informative study may in fact be impossible. The few studies that have been reported will not be reviewed. Any positive or negative judgments concerning the impact of current childhood diets on breast cancer risk 20-50 years from now seems too theoretical.

CONCLUSIONS--PART I

Risk factors that were described as non-modifiable appear to offer little opportunity for risk reduction. It would seem highly unlikely that a woman would base the decision as to when to have a first pregnancy on its impact on the risk of breast cancer, and the nature of modern society in fact frequently encourages delaying this event until after the completion of education and the establishment of a career have taken place, and intentionally childless marriages are not uncommon even though this increases the risk of breast cancer. Nutrition and lifestyle changes that might delay menarche do not appear to have been seriously investigated. Women considering breastfeeding their children should consider the benefits of prolonged breastfeeding on the risk of breast cancer in later life, but again many aspects of life in modern societies work against the practicality of such action, although it is certainly not impossible. Benign breast disease and conditions classified as fibrocystic disease which may evolve into cancer may be reversible. This is discussed later.

While there have been a large number of studies concerning breast cancer and diet, it has become clear that a number of important issues remain unresolved. In particular, insufficient attention has been directed toward premenopausal women who appear to be more sensitive to dietary content than the postmenopausal women who make up the majority of subjects in studies. Thus premenopausal women should perhaps worry about high intakes of animal fat, red meat and high-fat dairy products. Also, fruits, vegetables, fish, whole grains and a diet with a high monosaturated (e.g. olive oil) to saturated fat ratio may be protective even if there is no evidence for this from studies that fail or are unable to stratify by tumor estrogen receptor status. The same can be said for the Mediterranean diet. The diets found by Fung *et al* to be advantageous for premenopausal women are generally regarded as healthy diets.

Attention should perhaps be paid to the balance between omega-3 and omega-6 fatty acids. One school of thought maintains that some if not many of the health problems associated with modern industrialized societies involve excessive consumption of omega-6 fatty acids from such sources as vegetable oils which overwhelm the beneficial effects associated with the modest consumption of omega-3 fatty acids from, for example fish. Achieving a better balance of these two classes of polyunsaturated fats may be beneficial in the context of this review, and readers are encouraged to investigate this potentially important subject by referring to the sources mentioned above.

Finally, studies on individual dietary components such as fat and dietary patterns are generally corrected for the influence of energy balance and weight gain. Thus there are dietary issues that involve both fats and carbohydrates, which concern just the impact on weight and body fat distribution. The relationship between breast cancer risk and body fat distribution, weight, and weight gain at various stages in life will be discussed in Part II, as will beverages, which some would include among dietary factors. Also, for postmenopausal women, the absence of clear dietary directions for breast cancer risk reduction should not discourage interest in a healthy diet aimed at reducing the risk of heart disease, other cancers, diabetes, and elevated weight or obesity. The reader is referred to Dr. Walter C. Willett's book, *Eat, Drink and Be Healthy, The Harvard Medical School Guide to Healthy Eating* for evidence-based information concerning healthy diets [55].

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