# INTERNATIONAL HEALTH NEWS

*William R. Ware, PhD - Editor*

**NUMBER 181** **OCTOBER 2007** **16th YEAR**

*The main topics covered in this issue are scans that directly measure the extent of coronary atherosclerosis, chelation therapy for heart disease, salt intake reduction to reduce cardiovascular risk, the risk of cancer associated with low cholesterol, and finally the cancer risk associated with medical radiation. This selection represents the continuing belief that avoiding cardiovascular disease and cancer are among the very most important issues in preventive medicine.*

*In addition, a number of topics are briefly discussed including risk factors for kidney cancer, the merits of combining coenzyme Q-10 with statin therapy, and the connection between childhood metabolic syndrome and adult cardiovascular disease.*

*Finally, the second part of Hans Larsen's review on the prevention of osteoporosis appears in this issue.*

*Please bear in mind that the cost of publishing this newsletter is solely defrayed by income made from the 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 the 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.

*Wishing you continuing good health,*

***William R. Ware, PhD, Editor***

**Highlights**



## HOW IMPORTANT IS IT TO KNOW YOUR CORONARY CALCIUM SCORE?

The short answer that has emerged from research reported in the last several years appears to be "probably quite important" but with some reservations. The coronary artery calcium score (CACS) results from non-invasive electron-beam tomography of the coronary arteries. Calcified plaque is identified and its extent more or less quantitatively measured. The score is then derived by methods introduced in 1990 by Arthur Agatston, a cardiologist better know to the layman as the inventor of the South Beach Diet. The Agatston score runs from zero to over 1000. Budoff *et al* in a paper just published in the *Journal of the American College of Cardiology* followed a cohort of over 25,000 asymptomatic individuals for a mean of 6.8 years to evaluate the ability of the CACS to predict all-cause mortality. Mean ages varied from 56 to 68 years and the gender of the cohort was close to evenly divided. The risk of all-cause mortality was found to vary strongly with the CACS. For individuals in the CACS ranges 1-10, 11-100, 101-399, 400-699, 700-900 and ≥ 1000, the relative risks for all-cause mortality were 1.13, 1.48, 3.61, 3.84, 5.78, 6,47 and 9.36 when compared to the group with a score of zero, i.e. no observable coronary calcification. In other words, for the lowest category of plaque load, there was a 13% increase in risk, but if atherosclerosis was extensive and advanced as indicated by a score ≥ 1000, the increased risk was over 800%! The authors

calculated that the 10 year survival was 99.4% for a CACS of zero and 87.8% for a score of > 1000. The CACS was an independent predictor of mortality in an analysis of the data which took into account age, gender, ethnicity, and the traditional cardiac risk factors. When the CASC score was added to the traditional risk factors, there was also a significant improvement in predictive power. Also, the calcium score predicted all-cause mortality more accurately than age.

In an accompanying editorial, Alan Guerci, M.D. commented that a large and consistent body of evidence indicates that the CACS is more closely associated with coronary artery disease and associated events than the standard risk factors. He cites 17 studies covering a range of endpoints and outcomes such as sudden death and heart attack to support this assertion. He points out that there are no exceptions to this consistent record of incremental prognostic value of the CACS which now comprises more than 300,000 years of patient observation.

*Budoff, et al. Long-term Prognosis Associated with Coronary Calcification.* ***Journal of the American College of Cardiology****, 2007, Vol. 49, pp. 1860.*
*Guercia, A. D. The Prognostic Accuracy of Coronary Calcification, ibid, pp. 1871.*

**Editor's comments:** The potential importance of measuring coronary artery calcification was highlighted for lay audiences a few years ago by Dr. William R. Davis in the book *Track Your Plaque* (iUniverse, Inc., 2004 paperback). Since Davis' book was published, the incentive for having a coronary artery calcium scan has only increased. The study discussed above adds significantly to the accumulated evidence. As the editorialist points out, the CACS score represents an improvement in predictive power over the conventional risk factors such as total and HDL cholesterol, blood pressure, use of blood pressure medication, age, gender and smoking (the parameters of the famous Framingham Risk Score). What are noteworthy are studies showing that individuals with low risk of coronary heart disease according to the Framingham Risk Score can have very high CACS scores indicating in fact very high risk. For example, in one study 20% of individuals with low-risk Framingham scores (10 year CHD risk < 10%) were in the ≥ 75$^{th}$ percentile of calcium scores (Desai *et al*, Am Heart J. 2004;148:871-7). In the study of Desia *et al* there is presented a graph of the logarithm the CASC (to compress the data due to huge range of the score) vs. the traditional risk factors. While a very modest correlation was found, when one examines the actual plot of the data, it quite closely resembles a shotgun pattern with no visually evident correlation for CACS vs. Framingham Risk %. Other studies have reported similar results. It would seem that there are important risk factors being ignored when one uses the traditional set and if these could be identified, quantified and used the resultant risk estimate would be more in line with that indicated by the extent of coronary atherosclerosis as revealed by the CACS, i.e. there would be a much improved correlation. This failure of the traditional risk factors to predict CACSs results in a significant percentage of those with low traditional risk scores being incorrectly reassured that all is fine when in fact, quite the opposite may be true. The situation is improved considerably by including the presence or absence of diabetes and/or a family history of coronary heart disease, with the former having a large impact on the 10-year risk but it seem quite likely that there are other risk factors that need to be included. Studies also find that for some individuals, there is a very high Framingham risk but a low or even zero CACS, and it has been pointed out several times in the literature that these individuals, and especially those with zero CACS, have in fact a very low risk of CHD related events and may be at risk of over treatment and undue concern. There is now a free online calculator for calculating CHD events based on combining Framingham risk with CACS (J Thorac Imaging, 2006;21:91). This calculator, which also includes diabetes and family history as a risk factors, can be found at www.newportbodyscan.com/cacrisk.htm.

Thus there seems to be strong support for the value of the so-called coronary calcium scan. The downside is the radiation exposure common to CT scans in general, but for some, and perhaps many, the benefits may well outweigh the risks.

Finally, it seems worth noting that when one looks at a large number of studies of the risk factors associated with coronary artery calcification, almost all find that neither total cholesterol nor LDL cholesterol are significantly correlated with the CACS. This is consistent with studies reported a number of years ago which mostly found no correlation between serum cholesterol and the extent of coronary atherosclerosis as observed and measured at autopsy on individuals who died in accidents. Taken together, these results suggest a problem with the hypothesis that circulating cholesterol is related to the initiation and progression of coronary atherosclerosis, a view which nevertheless appears widely held today.

# CHELATION THERAPY FOR SECONDARY PREVENTION IN CORONARY HEART DISEASE

Chelation therapy in this context involves intravenous (IV) infusion of the so-called chelating agent ethylene diamine tetracetic acid (EDTA). Chelation therapy has been used for a number of years in many countries with the goal of treating vascular problems and preventing the recurrence of ischemic cardiac events, but in North America it is approved only for the treatment of lead poisoning. Many physicians using chelation therapy find it to be a valuable addition to their options, but most of the evidence favoring its efficacy is of an anecdotal nature. As readers of this newsletter know, such evidence is dismissed by mainstream medicine as worthless or even dangerous.

In a recent issue of *Alternative Medicine Review* Dr. L. Terry Chappell, M.D. discusses the relative merits of chelation therapy vs. drug therapy to reduce the risks associated with the failure of drug-eluting stents used to treat coronary occlusions. This paper represent an extension using the same data that was the basis of an earlier paper by Chappell *et al* which looked at subsequent cardiac and stroke events in patients with known vascular disease treated with EDTA chelation therapy. This report is being discussed not to direct attention to this clinical application but to note a beneficial effect from this highly controversial therapy.

The earlier study involved 220 consecutive patients (consecutive to eliminate selection bias) with known vascular disease who were given chelation therapy and then followed for 3 years. Primary endpoints were heart attack, stroke and death from any cause. Secondary outcomes were the resolution of symptoms, the need for coronary artery bypass surgery (CABG) or coronary angioplasty. The study, conducted over the period of 1992 to 2001, was a multi-center retrospective trial of IV EDTA chelation therapy. Of the 220 patients in the chelation study, 23 had had angioplasty, mostly with stent placement. To obtain a control, i.e. predicted results in the absence of EDTA chelation, the authors compared the results their follow-up with the pooled results of 7 reported randomized trials of patients treated with medical therapy, or angioplasty with or without stents. They served as the control.

At the start of the study, 84% of the patients had symptoms, 20% a coronary bypass, 26% angioplasty, 5.9% transient ischaemic attacks, and 0.9% an endarterectomy (carotid artery clean-up). After at least 20 IV EDTA treatments and a three-year follow-up, in the cohort of 220 patients, 15 heart attacks were predicted, none observed, 6 deaths were predicted and none observed, 31 repeat angioplasties predicted, and 2 required, and 16 CABG operations predicted with 6 actually required. In connection with the question of the comparison between usual care (including the drug clopidogrel plus aspirin) and EDTA chelation to prevent failure of angioplasty or restenosis at the site of a stent, patients treated primarily with either of these two procedures where examined as a subgroup and their outcomes after EDTA therapy compared to the predicted results from the meta-analysis of 7 studies which generated controls. Repeat angioplasty in the control group was 22.3% and in the EDTA group, 4%. CABG was required by 11.8% of the controls, and 0% of the EDTA group.

Chappell points out that the risk of blood clots from drug eluting stents does not begin until about six months after insertion, and cardiologists use drug intervention such as clopidogrel plus aspirin for at least 12 months in an attempt to prevent this adverse event. However, there is evidence from a large trial that this drug intervention has no impact on reducing the number of patients subsequently needing additional invasive therapy whereas the EDTA therapy appeared to provide significant benefit related to those endpoints in a similar clinical setting.

*Cahppell, L. Terry. Should EDTA Chelation Therapy be Used Instead of Long-Term Clopidogrel plus Aspirin to Treat Patients at Risk from Drug-Eluting Stents?* ***Alternative Medicine Reviews,*** *2007,Vol. 12, pp.152-58.*

*Chappell, L. Terry et al. Subsequent Cardiac and Stroke Events in Patients with Known Vascular Disease with EDTA Chelation Therapy: A Retrospective Study.* ***Evidence-Based Integrative Medicine,*** *2005, Vol. 2, pp.27-35*

**Editor's comments**: EDTA chelation is approved by the FDA and by Health Canada for the treatment of lead poisoning. It is tolerated in some jurisdictions and is indeed practiced where allowed. There is an extensive anecdotal literature favoring the therapy but few satisfactory trials. Scientists that conduct the highly respected Cochrane Database Systematic Reviews concluded in 2002 that there was insufficient evidence of chelation therapy improving clinical outcomes for patients with atherosclerosis or cardiovascular disease and that

randomized trials were necessary. The results of a randomized trial from Alberta, Canada published in *JAMA* (2002; 287:481-486) found that there was no evidence to support a beneficial effect of chelation therapy in patients with ischemic heart disease, stable angina and a positive treadmill test for ischemia. However, this study had only one endpoint, the time on the treadmill to ECG evidence of ischemia. The follow-up which continued for a year was underpowered with regard to adverse cardiovascular events and the results for this endpoint were without statistical significance. The study was immediately criticized for using as a control the same IV solution as for the chelation, but without the EDTA. The problem is that the solution was high in magnesium and vitamin C, both of which could have produced favorable changes in both the placebo and treatment groups, and thus this was not really a test of EDTA chelation. Also, the Alberta trial had a very restricted endpoint based on one exercise-induced ECG feature which was applied to individuals who ranged from asymptomatic to those who had had bypass surgery or angioplasty or heart attacks. A randomized trial has been organized by the U.S. National Institutes of Health with a primary composite endpoint of all-cause mortality, non-fatal heart attack or stroke, coronary revascularization or hospitalization for angina. The plan is to enroll over 1900 patients with prior heart attack and thus it is a secondary prevention trial. Those who are interested in or who believe in chelation therapy eagerly await the results.

Randomized trials involve a placebo group who undergo IV drip lacking the hypothesized active ingredient. The drip requires 3 hours and thus 90 hours for 30 treatments. Recruiting participants for a randomized study may prove difficult! Nevertheless, anecdotal evidence will never satisfy mainstream medicine. Even anecdotal evidence that patients in wheel chairs with blue feet, scheduled for amputation due to diabetic vascular problems resulting in gangrene, leave a chelation clinic after a dozen or more treatments with pink feet, no gangrene, canceled surgery and some go off to play golf. Not good enough. Might be a placebo effect, it is said. This is a good example of the problems created by the now almost universal requirement for placebo controlled studies, something many physicians for example would never dream of demanding in the context of home plumbing interventions or hundreds of remedies for everyday non-medical problems. In fact, an entirely valid and meaningful debate could be organized around the question of when anecdotal results are dramatic enough and reproducible enough to obviate the need for placebo controlled trials. After all, the development and at least the initial use of many surgical procedures follow this latter anecdotal model. But then this is just part of a much larger set of problems associated with medical studies which include the misuse of statistics, invalid placebos, statistical significance promoted in the absence of clinical significance, underpowered endpoints, non-equivalent controls, politics, conflicts of interest and bias in general.

## SALT INTAKE AND CARDIOVASCULAR DISEASE

There appears to be little doubt that reduced sodium (i.e. salt) intake lowers blood pressure and can prevent hypertension, although the extent varies from individual to individual. However, studies concerned with subsequent changes in morbidity and mortality are limited and inconclusive. In the April 20 issue of the British Medical Journal (BMJ), Cook and associates from several American institutions report on an observational follow-up study of the Trials of Hypertension Prevention (TOHP I and II). These randomized intervention trials had cardiovascular events as endpoints (heart attacks, stroke, coronary revascularization and cardiovascular death). Several thousand participants were followed for between 10-15 years. The reductions of sodium intake were approximately 2.6 and 2.0 g/day with the interventions lasting between 18 and 48 months. A 25-30% lower incidence was found in the intervention groups during the follow-up period, benefits that exceed those found in a recent meta-analysis. This is the first study to report beneficial effects from dietary salt reduction on cardiovascular outcomes based on randomized trial data.

In an accompanying editorial, it is pointed out that in Westernized countries, people derive salt mostly from bread and processed food, and only a small fraction comes from discretionary use (estimated at 20%). Thus it is suggested that a population wide policy of salt reduction in developed countries can only be achieved with collaboration of the food industry. But it is pointed out that historical evidence suggests opposition from this industry or at best, slow progress when salt reduction is involved. Also, it is pointed out that advice provided in the primary

care setting has been shown to be ineffective. The remaining option is to legislate salt reduction in processed foods.

Last year the American Medical Association (AMA) also called for a reduction of salt in processed and restaurant foods. This was reinforced by the recent publication of the scientific report behind these recommendations. The AMA also encouraged the US Food and Drug Administration to develop warning labels for high-sodium foods. The report contends that a 1.27 g/day lower lifetime intake of sodium translates into an approximately 5 mm Hg smaller rise in systolic blood pressure as individuals age from 25 to 55 (sodium chloride, i.e. table salt is approximately 39% sodium) This corresponds to a 20% lower prevalence of hypertension and a reduction of mortality associated with CHD of 9%, 14% for stroke and 7% from all causes and would theoretically save 150,000 lives annually. The report however points out that even motivated individuals would find it difficult to reduce sodium intake because most derives from processed and restaurant foods. The report concludes, as did the above mentioned analysis the BMJ, that while an appropriate voluntary food industry response would be helpful, regulatory measures may be required to force the issue both as regards warning labels of high salt content and mandatory salt content reduction in processed foods.

*Cook, N.R. et al. Long Term Effects of Dietary Sodium Reduction on Cardiovascular Disease Outcomes: Observational follow-up of the Trials of Hypertension Prevention (TOHP).* ***BMJ,*** *published online April 20, 2007.*
*Dickenson, B.D. et al. Reducing the Population Burden of Cardiovascular Disease by Reducing Sodium Intake.* ***Archives of Internal Medicine****, 2007, Vol. 167, pp. 1460.*

## LOW CHOLESTEROL, STATINS AND CANCER

In the July 31 issue of the *Journal of the American College of Cardiology,* a study was reported which has stirred up considerable interest, concern, and editorial caution. The study was designed to examine the effect of statin induced lipid lowering on the risk of elevated liver enzymes and rhabdomyolysis (a muscle disorder which can be fatal). The researchers had data on the incidence of cancer which was ultimately analyzed and included in the published report at the suggestion of the journal editors, a very unusual scenario indeed. What Alsheikh-Ali *et al* found was a significant inverse association between cancer incidence and the level of LDL achieved in the lipid lowering therapy. Put in simple terms, the lower the LDL the higher the risk of cancer. In the published account, the authors were careful to refer to the body of older epidemiologic data from a number of studies which also associated low cholesterol levels with increased cancer risk. They also point out that in this older literature the association of low cholesterol and cancer was observed in some studies where the confounding by possible disease-related cholesterol lowering was ruled out by excluding early deaths. However, the results of Alsheika-Ali *et al* were termed "unexpected" by both the researchers and the journal editors, and editorialist comments emphasized the non-definitive and hypothesis generating nature the observed connection between low LDL and cancer. Incidentally, the statin-associated elevated liver enzymes and rhabdomyolysis were not related to the magnitude of the LDL lowering.

*Alsheika-Ali et al. Effect of the Magnitude of Lipid Lowering on Risk of Elevated Liver Enzymes, Rhabdomyolysis and Cancer.* ***Journal of the American College of Cardiology****, 2007, Vol. 50, pp. 409-18.*
*DeMaria, A.N. and Ori Ben-Yehyda. Low-Density Lipoprotein Reduction and Cancer, ibid, pp. 421-2.*
*LaRosa, J.C, Means and Ends of Statins and Low-Density Lipoprotein Cholesterol Lowering. ibid, pp.419-20.*

**Editor's Comments**: Critics of the cholesterol hypothesis in general and aggressive lipid lowering in particular have repeatedly pointed out examples in the literature of the association observed by Alsheikh-Ali *et al* (see for example *The Cholesterol Myths* by Uffe Ravnskov, MD, PhD. New Trends Publishing, Inc., 2000). In fact, low cholesterol has been associated not only with cancer but also with overall mortality in general, which has repeatedly been observed to increase from a minimum (men) or from a constant value (women) as the level of total cholesterol decreases from the somewhere around 150-160 mg/dL. This issue will be discussed in detail in this newsletter in an up-coming Research Report.

# MEDICAL RADIATION AND THE RISK OF CANCER

It has been well know for decades that so-called ionizing radiation such as x-rays, gamma rays, and beta and alpha particle radiation has the potential to initiate cancer. Radiation has even been associated with fatal cancers in famous researchers who experienced heavy exposure. Furthermore, the extensive study of the exposed survivors of the two nuclear blasts in Japan has provided invaluable time and dose-dependent data on this association. Thus it is not surprising that there is interest in the potential cancer risks associated with diagnostic and therapeutic radiation, especially as these techniques become more popular and their use more widespread. Two recent studies address this issue. Both were multicenter, one restricted to the US, the other international.

The first study by Einstein *et al* attempts to estimate the lifetime attributable risk (LAR) of cancer associated with computed tomography coronary angiography (CTCA). CTCA is a non-invasive approach to visualizing the coronary arteries using a contrast medium and a sophisticated x-ray scanning system. This scan technique has consistently shown the ability to detect significant narrowing of the major coronary arteries and as well can detect "soft plaque" or fatty matter in artery wall that may lead to future problems. It obviously avoids the low but finite morbidity and mortality associated with the conventional but highly invasive cardiac catheterization which yields the angiogram. Einstein *et al* use data on radiation intensities encountered in the CTCA procedure and the most recent risk estimates for cancer from exposure to low-level ionizing radiation, data which incidentally supports the linear, no-threshold model which they regard as applicable to the x-rays used in CTCA, a model which assumes that the risk of cancer increases in a linear fashion with no lower threshold. They conclude that the use of modern CTCA is associated with a non-negligible LAR for cancer, a risk that varies markedly but is consistently greater for women, younger individuals, and for combined cardiac and aortic scans. To quote the worst example, a combined scan of the heart and aorta had LAR of 1 in 114 for a 20 year-old woman. The highest LARs were for lung cancer and in younger women, cancer of the breast.

In the second study, one of case-control design, John *et al* compared 2254 breast cancer cases with 3431 controls. Data were collected regarding low-dose chest x-rays. The authors claim that to their knowledge this is the largest population-based case-control study to date. It was found that there were increased risks for breast cancer (250%) in women who had radiotherapy for a previous cancer. In addition, they found approximately a 150% increase in risk associated with diagnostic chest x-rays for tuberculosis and 120% for pneumonia. All were statistically significant. Risks were highest in women exposed at a young age. The researchers found no evidence for increased risk associated with other diagnostic chest x-rays, and this was true for women with and without indications of increased genetic risk. The authors conclude that women exposed to diagnostic or therapeutic radiation should seek continuing surveillance for breast cancer.

*Einstein, A.J. et al. Estimating Risk of Cancer Associated with Radiation Exposure form 64-Slice Computed Tomography Coronary Angiography. JAMA, 2007, Vol. 298, pp. 317-23.*

*John, E.M. et al. Medical Radiation Exposure and Breast Cancer Risk: Findings from the Breast Cancer Family Registry.* ***International Journal of Cancer****, 2007, Vol. 121, 386-94.*

**Editor's comments:** These studies present the classical risk-benefit dilemma. When an x-ray scan or chest x-ray appears justified, in most cases the risk of subsequent cancer may well be a secondary consideration. Thus the take-home message from these to studies should be an awareness of a potential problem and thus increased attention to early detection. When alternatives to x-rays such as MRI are available and may provide equally satisfactory answers, perhaps patients should push harder for this alternative. Finally, the risks vs. benefits of routine x-ray screening need to be weighed both by patients and their physicians. This is particularly relevant to those seeking what they consider to be the ultimate in preventive medicine, the whole-body scans done purely for screening purposes.

# NEWS BRIEFS

## COENZYME Q-10 AND STATIN DRUG USE

A small but randomized double-blind study has examined the efficacy of either coenzyme Q-10 (Co Q-10) or vitamin E with regard to relieving the symptoms of muscle pain and other muscle problems associated with the use of statin drugs. In the group assigned to 100 mg/day of Co Q-10 for 30 days, pain severity was found to be decreased by 40% and pain interference with daily activity decreased by 38%. No significant benefits were found for the vitamin E group. The authors conclude that Co Q-10 supplementation may offer an alternative to stopping treatment with this class of drug. .

*Caso, G. et al. Effect of Coenzyme Q-10 on Myopathic Symptoms in Patients Treated with Statins.* ***American Journal of Cardiology****, 2007, Vol. 99, pp. 1409.*

**Editor's comments**: It is well known that statin drugs can reduce the levels of Co Q-10, a vital enzyme especially in the cellular mitochondria. It is of interest that Merck, a producer of a popular statin, holds patents on the combination of a statin and Co Q-10 but have never formulated or marketed the combination. The conventional wisdom still holds that the routine use of Co Q-10 cannot be recommended in statin-treated patients (J Am Coll Cardiol 2007;49:2231-7). Q-10 supplementation is nevertheless widely suggested by physicians practicing integrative medicine and also by some cardiologists, and is used in some countries as a prescription drug for congestive heart failure.

## MEAT AND KIDNEY CANCER

Kidney cancer accounts for almost 2% of all cancers worldwide with an annual death toll of about 78,000. A recent meta-analysis of studies regarding the connection between meat consumption and kidney cancer has revealed significant risks associated with all meat, red meat, poultry and processed meat. The increased risks which all achieved statistical significance ranged from 18 to 30%. The authors comment that this study supports the reduction of meat consumption as an important approach to decreasing the incidence of kidney cancer in the general population.

*Mohammed, F. et al. Consumption of Different Types of Meat and the Risk of Renal Cancer: Meta-analysis of Case-Control Studies.* ***Cancer Causes Control****, 2007, Vol. 18, pp 125-33.*

## ALCOHOL AND KIDNEY CANCER

Lee *et al* have reported an analysis of 12 prospective studies which address the question of the role of alcohol in the etiology of kidney cancer. Participants totaled over 530,000 women and 220,000 men and follow-up times ranged from 7 to 20 years. Compared with non-drinking, alcohol consumption (≥ 15 g/day or one drink) was associated with a decrease of 28% in the risk of kidney cancer, a result that achieved statistical significance. In addition, statistically significant trends with increased intake were seen in both men and women, but there were no differences across alcoholic beverage type (beer vs. wine). The authors point out that alcohol drinking (presumably heavy) is associated with increased risks of the oral cavity, larynx, pharynx, esophagus, liver and breast, other approaches to reducing the risk of kidney cancer such as maintaining a healthy weight and avoiding smoking should be encouraged.

*Lee et al. Alcohol Intake and Renal Cell Cancer in a Pooled Analysis of 12 Prospective Studies.* ***Journal of the National Cancer Institute****, 2007, Vol. 99, pp. 801-10.*

**Editor's comment:** The cancers mentioned by the authors carry dose-dependent risks and significant risk appears typically with a threshold of 2-3 drinks per day. Breast cancer is an exception where the threshold is one drink per day.

## HEAD AND NECK CANCER RELATED TO SMOKING AND ALCOHOL

In a pooled analysis of 15 case-control studies, Hashibe *et al* found that smoking was strongly associated with cancers of the head and neck with ever vs. never smoking approximately doubling the risk. Alcohol when combined with smoking was found to increase the risk only when consumption exceeded two drinks per day vs. never drinking, and this result was limited to cancers of the pharynx and larynx. The authors comment that these are to two main risk factors for these cancer sites.

*Hashibe, M. et al. Alcohol Drinking in Never Users of Tobacco, Cigarette Smoking in Never Drinkers, and the Risk of Head and Neck Cancer.* ***Journal of the National Cancer Institute****, 2007, Vol. 99, pp. 777-89*.

## CHILDHOOD METABOLIC SYNDROME AND ADULT CARDIOVASCULAR DISEASE

A recently published study in the journal *Pediatrics* examined the probability of cardiovascular disease in adults who had been diagnosed with the

metabolic syndrome as children 25 years earlier. The children ranged in age from 6-19 and as adults from 30-48 years. Both the presence of pediatric metabolic syndrome and changes in age-specific body mass index from childhood to adulthood were significant predictors of adult metabolic syndrome and thus adult cardiovascular disease risk. The authors suggest that these finding should provide incentives for targeted interventions.

*Morrison, J.A. et al. Metabolic Syndrome in Childhood Predicts Adult Cardiovascular Disease 25 Years Later: The Princeton Lipid Research Clinics follow-up Study.* ***Pediatrics****, 2007, Vol. 120, pp. 340-5.*

## MEDICARE PROVIDES A POWERFUL INCENTIVE FOR HOSPITALS TO CLEAN UP THEIR ACT

In an attempt to encourage US hospitals to improve the quality of their services, Medicare will no longer pay expenses incurred for the results of the following conditions or events occurring during hospitalization: falls, infection after heart surgery, urinary tract infections from using catheters, pressure ulcers or bed sores, and vascular infections from using catheters. Medicare regards these as preventable incidents. And the Centers for Medicare and Medicaid Services said that it would also work to add three more conditions next year. Hospitals will be required to pick up the expenses associated with the above problems, and the rules state that the hospitals cannot pass on to the beneficiary any charges associated with the designated hospital-acquired complications. Medicare provides coverage for about 43 million elderly and disabled individuals in the US.

*Associated Press story carried by Yahoo, August 18, 2007.*

**Editor's comments:** This news bit is presented only because it reflects the state of what one might call the deteriorating care-giving culture in some hospitals that is viewed as requiring a negative financial incentive as a remedy, in this case, on a national basis in the US.

## LOW-GLYCEMIC-INDEX OR GLYCEMIC LOAD DIETS BETTER FOR WEIGHT LOSS

The highly respected Cochrane Collaboration organization has just published an analysis of six randomized studies comparing low-glycemic-index (GI) or low-glycemic-load (GL) diets with higher GI or GL diets and conventional weight loss diets. Those on the low-GI diets lost on average 2.2 pounds more than those on the comparison diets and obese individuals had results also favoring the low-GI diet with a loss on average about 9.2 pounds compared to 2.2 pounds for the comparison diets. However, one expert, Dr. Lawrence Cheskin from Johns Hopkins, quoted by *The Heart.org,* commented that the differences in weight loss, while statistically significant, were of a rather tiny magnitude.

*Thomas, D.E. et al. Low Glycemic Index or Low Glycemic load Diets for overweight and obesity.* ***Cochrane Database System Reviews****, 2007, 3:CD005105.*

**Editor's comments:** Small average weight losses that are not sustained seem to be the norm with diet studies, in sharp contrast to the dramatic results promoted daily on TV by the commercial weight-loss industry. If one is overweight, say weighing 220 pounds, changes of a few pounds or even 10 pounds does not seem to be clinically that meaningful even if such changes are statistically significant in a study. The time has come to scientifically investigate the programs that claim large sustained and continuing weight loss that will take the overweight and obese into or near the normal weight ranges. Also, one of the central questions seems to be why some individuals find it impossible to lose significant weight, even with severe calorie restriction and perhaps increased physical activity. While there are theories that invoke the action of leptin and insulin, this seems to be an area obviously deserving intensive study.

# RESEARCH REPORT

## Osteoporosis – Risk Factors, Prevention, and Treatment: Part II

**by Hans R. Larsen, MSc ChE**

### Diet and Lifestyle

There are several diet and lifestyle factors, which can have a profound effect on the risk of developing osteoporosis.

**Protein Intake**
Italian researchers have linked excess protein consumption to the creation of an acid environment in the body and possible subsequent disease and bodily deterioration. In a clinical study involving 100 patients the researchers found that a high protein intake (>30 grams/day) produces an acidic urine. They also found that the body, in its attempt to neutralize the acid environment created by the protein, first depleted sodium reserves. It then used ammonia as a neutralizing agent followed by calcium, presumably pulled from the bones. Other studies have shown that omnivorous women lost 35 per cent of their bone mass over a 15-year period following menopause as compared to lacto-ovo vegetarians who only lost 18 per cent. The researchers point out that vegetables and fruits usually produce an alkaline body environment because of their high content of calcium, magnesium, sodium, and potassium. Meats, fish, grains and eggs, on the other hand, acidify the body because they leave an acid ash of nitrogen, phosphorus, chloride and sulfur. The researchers conclude that a diet high in animal protein causes acidosis and stress to the body resulting in cellular congestion and a general slowdown in body functions. They recommend a daily protein intake of no more than 20 grams/day (3 oz beef sirloin steak) with 30 grams/day being the maximum acceptable intake.[72]

Researchers at the University of California believe that the explosive growth in osteoporosis and hip fractures is caused by an over-acidic diet. They point out that the modern western diet contains lots of grains, cheese, bread, and meat which all produce acid in the body. In order to neutralize this acid overload the body, if necessary, pulls carbonates, phosphates, and ammonia out of the bones, eventually leaving them fragile and porous. The researchers point out that countries with a diet high in meat, cheese, and fish have 40 times as many hip fractures as some Asian countries where fruits and vegetables are the mainstay and cheese and meat are seldom eaten. A recent study involving American women found that those who ate the most acid-producing diet had four times as many hip fractures as those on the least acid-producing diets. Another study found that potassium bicarbonate is very effective in neutralizing the effects of high-acid diets. The researchers recommend that people go easy on cheese (very acid forming), meat and grains and instead increase their intake of fruits and vegetables. They also suggest that avoiding an acid-forming diet may actually be more important than ensuring an adequate calcium intake.[73]

Researchers at Tufts University have discovered that the effect of protein intake on bone mass is highly dependent on the concurrent intake of calcium and vitamin D. Their study involved 342 healthy men and women aged 65 years or older who participated in a three-year, randomized, placebo-controlled trial of calcium and vitamin D supplementation. The calcium group received 500 mg of calcium citrate maleate and 700 IU (17.5 micrograms) of vitamin-D daily in the form of supplements. The average total daily calcium intake in the supplement group was 1346 mg/day as compared to 871 mg/day in the control group. The average total protein intake was 79 grams/day varying between 14 and 20 per cent of total energy intake. Plant protein intake was about 5 per cent of energy. Bone mineral density (BMD) was measured every six months at the femoral neck, spine and total body. At the end of the three-year supplementation period the researchers observed that the BMD for total body and femoral neck had increased significantly amongst those in the calcium/vitamin D supplement group who had the highest intake of protein (greater than 20 per cent of total energy on average). BMD in total body and femoral neck decreased in the placebo group irrespective of protein intake. The researchers conclude that a high protein intake is associated with an increase in BMD provided it is accompanied by supplementation with calcium citrate maleate and vitamin D.[74,75]

Thus, it would seem that a moderate to high protein diet is not detrimental if accompanied by supplementation with calcium, vitamin D, and potassium bicarbonate.

**Smoking**
Researchers at the University of Melbourne have discovered that women who smoke have a significantly higher risk of developing osteoporosis. Their study involved 41 pairs of female twins, one of whom was a heavy smoker, while the other was a light smoker, or did not smoke at all. The researchers conclude that women who smoke a pack of cigarettes a day through adulthood will, by the time of menopause, have a 5 to 10 % lower bone density than non-smokers. It is estimated that a 10% decrease in bone density corresponds to a 44% increase in the risk of a hip fracture.[76]

**Coffee**
American researchers report that postmenopausal women with a high caffeine intake tend to lose bone mass much more extensively than do women with a lower consumption. Their study involved 489 women between the ages of 65 and 77 years. Women with an intake of more than 300 mg/day of caffeine (18 oz of brewed coffee) were found to have a significantly greater loss of bone mass at the spine than did women who consumed less than 300 mg/day. A subgroup of the women was found to have a genetic abnormality that further increased their caffeine-induced bone loss. Other research has shown that caffeine-induced bone loss can be partially offset by an adequate calcium intake.[77]

**Cola Drinks**
Tufts University researchers have found that consumption of cola drinks is associated with a considerably lower BMD at the hip and Ward's triangle in women, but not in men. BMD at the spine does not appear to be affected by cola drinks.[78]

**Salt Intake**
There is increasing evidence that a high salt (sodium) intake is associated with accelerated bone loss. An Australian study involving 124 postmenopausal women found that those with a high salt intake had significantly more bone loss at the hip than did women with a lower intake. The conclude that halving salt consumption from 3450 mg/day to 1725 mg/day would have the same beneficial effect on BMD as increasing dietary calcium intake by 891 mg/day.[79]

**Elevated Resting Heart Rate**
There is some evidence that older women with an elevated heart rate are at increased risk for osteoporotic fractures. A 2002 study involving almost 10,000 women aged 65 years or older found that those with a resting pulse rate of 80 bpm or higher had a 1.6-fold increased risk of osteoporotic fractures of the hip, pelvis or ribs, and a almost 2-fold increase in the risk of vertebral fractures. It is not quite clear why this association exists, but the University of California researchers involved in the study speculate that a high resting pulse rate may be an indication of generally poor health, lack of exercise, or long-standing cumulative stress.[4]

## Associated Diseases and Disorders

**Hyperhomocysteinemia**
Hyperhomocysteinemia is characterized by elevated blood levels of the amino acid homocysteine. High homocysteine levels have been implicated as a risk factor for atherosclerosis and stroke. The "official" normal blood level range for homocysteine is 5 – 15 micromol/L. However, there is increasing evidence that this upper level may be too high and that a maximum level of 7 micromol/L for people under 60 years of age and a maximum level of 12 micromol/L for those over the age of 60 years may be more appropriate. There is evidence that a high homocysteine level is associated with increased osteoclast activity (loss of bone minerals.[80] It is also becoming clear that high homocysteine levels are associated with an increased risk of osteoporosis and osteoporotic fractures.[81]

It has long been established that homocysteine levels and status of folic acid, vitamin B6 and vitamin B12 are closely linked. A study of 1550 men and women participating in the National Health Nutrition Examination

Survey (NHANES) found that participants with a homocysteine level of 20 micromol/L or higher had significantly lower BMD (measured at the hip with DEXA scan) than did those with a serum level less than 10 micromol/L. NHANES researchers conclude that a low serum vitamin B12 level, a high level of homocysteine, and a high level of methylmalonic acid are all independent risk factors for osteoporosis. They found no association between folate levels (serum and red blood cell) and BMD or osteoporosis risk.[82]

In contrast, Norwegian researchers found a correlation between low folate levels and low BMD (in women only) and also confirmed a strong correlation between high homocysteine levels and low BMD in women only. The Norwegian researchers found no association with vitamin B12 levels.[83]

British researchers have also concluded that a low serum folate level is a significant risk factor for osteoporosis with vitamin B6 and vitamin B12 having a lesser effect.[84] Korean researchers believe that homocysteine activates osteoclast formation through the generation of reactive oxygen species (free radicals) and that this activation and its resulting loss of bone mass can be prevented by supplementation with antioxidants such as N-acetylcysteine.[85]

It is clear that a high homocysteine level is a significant risk factor for low BMD, osteopenia, and osteoporosis. There is also evidence that low levels of folic acid and vitamin B12 (correlates with high levels of methylmalonic acid) are associated with an increased risk. Fortunately, oral supplementation with folic acid (400-800 micrograms/day), vitamin B6 (50 mg/day), and vitamin B12 (1000 micrograms/day as sublingual methylcobalamin) will not only raise the levels of these vitamins, but will also result in a substantial reduction in homocysteine level.

**Celiac Disease**

Celiac disease (gluten-sensitive enteropathy or GSE) causes malabsorption and consequent deficiencies of many important nutrients including vitamin D, folic acid, vitamin B12, vitamin K, calcium, and iron.[86-88] As all these nutrients are involved in bone formation, it is not surprising that celiac disease is strongly associated with osteoporosis and fractures.

A very large Swedish study involving more than 13,000 individuals with celiac disease (and 65,000 controls) found that celiacs experienced twice the risk of hip fracture and a 40% greater risk of any fracture when compared to normal controls.[89] Fortunately, at least two major studies have shown that adhering to a gluten-free diet can halt and even reverse celiac-associated bone loss. Argentinean researchers reported in 1997 that 3 years on a gluten-free diet results in an average one standard deviation increase in bone mass. Their study involved 25 celiac patients with osteopenia at the lumbar spine (72%) and other locations. The increase in bone mass was greater in premenopausal women than in postmenopausal women.[90] Italian researchers carried out a study involving 86 newly-diagnosed celiac patients. At baseline, 34% of participants had normal BMD, 40% had osteopenia, and 26% had osteoporosis. After one year on a gluten-free diet, BMD had improved substantially.[91] Another Italian study involving 40 newly-diagnosed celiac patients found that 20% of them had excessively high homocysteine levels as compared to an incidence of 6% in the non-celiac control group. Celiacs also exhibited folate deficiency more often than did control (42.5% vs. 8.3%). The Italian researchers also observed a strong correlation between high homocysteine levels and low levels of vitamin B12 and folic acid. A gluten-free diet normalized folate, vitamin B12, and homocysteine levels.[92] This finding would tend to indicate that celiac disease can cause hyperhomocysteinemia.

**Hyperparathyroidism**

Hyperparathyroidism involves an excessive blood serum level of the parathyroid hormone (PTH). PTH promotes the release of calcium from the bones (demineralization) and a high level is associated with an increased risk of osteopenia and osteoporosis. Hyperparathyroidism can be **primary,** ie. caused by one or more benign tumours on the parathyroid glands, or it can be **secondary.** Renal failure and long-term vitamin D deficiency are major causes of secondary hyperparathyroidism. The normal serum level of PTH is 10 – 65 pg/mL (10 – 65 ng/L).

## Drug-Related Osteoporosis

Thyroid medications, prednisone, and warfarin have all been linked to an increased risk of osteoporosis.

**Thyroid Medications**

Researchers at the University of California discovered that women who have been taking relatively large doses of thyroid hormone such as levothyroxine sodium for many years tend to have a lower bone mineral density in arms, hip, and spine. Their study involved 991 whit women aged 50 to 98 years. A total of 196 of the women had been taking thyroid hormone for an average of 20.4 years (range of 1 to 68 years); 67% were taking it for hypothyroidism, 10% after treatment for hyperthyroidism, and 23% had no idea why they were taking it. The effect of the thyroid hormone therapy was found to be dose-dependent with women taking more than 200 micrograms/day (1.6 microgram/kg of body weight) having from 3.2 to 3.8% less bone mass in arms, hip, and spine. The researchers conclude that women taking higher doses of thyroid hormone are at risk for accelerated osteoporosis. They recommend that a blood test be used to ensure that patients get no more thyroid hormone than absolutely necessary.[93]

French researchers report that a significant proportion of osteoporosis cases may be caused by the inappropriate use of thyroid hormones. Thyroid hormones are widely prescribed for older people and are among the drugs most prescribed to women in both Germany and the United States. The drugs can be used to either suppress an overactive thyroid gland or to bolster a failing one. The researchers evaluated the results of 33 clinical studies involving 1266 women and 95 men. They concluded that suppressive thyroid hormone therapy is associated with increased bone loss in postmenopausal women, but not in premenopausal women. Replacement therapy, on the other hand, was found to be associated with bone loss (spine and hip) in premenopausal women, but not in postmenopausal women. The researchers point out the over-treatment with thyroid hormones is common and that careful titration of the medication dose and close monitoring of blood levels of the hormones are required in order to avoid detrimental effects. They specifically caution against ”overzealous or irrelevant” prescription of thyroid hormones.[94]

**Corticosteroid Medications**

Corticosteroids (prednisone) are often used in the treatment of rheumatoid arthritis, polymyalgia rheumatica, lupus erythematosus, and other autoimmune diseases and allergies. Most physicians agree that osteoporosis is a serious side effect of glucocorticoid therapy. Several studies have shown that patients undergoing long-term treatment with corticosteroids increase their risk of experiencing osteoporotic hip fractures and vertebral deformities and may experience substantial bone loss (4-10% a year). The risk is particularly significant for patients taking more than 7.5 mg/day of prednisone for 6 months or longer.

There are several viable approaches to lessening this risk, but unfortunately these measures are not widely applied – at least not in the UK. A survey showed that only 14% of patients taking prednisone were given supplements or medications to avoid osteoporosis. Dr. Johannes Bijlsma, MD of the Utrecht University Hospital points out that supplementation with calcium and vitamin D can be quite effective in preventing osteoporosis. He recommends the following guidelines for corticosteroid treatment:

- Use the lowest possible dose for the shortest possible time;
- Encourage physical activity and prevent falls;
- Supplement with calcium, if necessary, to achieve a daily intake of at least 1000 mg;
- Supplement with vitamin D (400 IU/day at least) if patients are housebound.

Postmenopausal women with very low bone density may also need to be treated with hormone replacement therapy or bisphosphonates, but Dr. Bijlsma is reluctant to recommend this option to all patients.[95]

Researchers at the Medical College of Virginia have confirmed that supplementation with calcium and vitamin D can, to a large extent, counteract the negative effects of prednisone on BMD. Their randomized, double-blind, placebo-controlled trial involved 96 patients with rheumatoid arthritis, 65 of whom were receiving an average of 5.6 mg/day of prednisone. Half of the participants were given 1000 mg of elemental calcium (in the form of calcium carbonate) plus 500 IU of vitamin D daily in two divided doses – at breakfast and dinner. The other half was given placebo tablets. Calcium intake from food was about 900 mg/day for both groups. At then end of the two-year study the patients in the prednisone-treated placebo group had lost bone density in the lumbar spine and femur (thigh bone) at a rate of 2.0% and 0.9% per year respectively. In contrast, the patients taking the supplements had gained 0.75% and 0.85% per year respectively. No statistically significant changes in bone density were seen in patients not taking prednisone whether or not they took calcium and vitamin D. The

researchers conclude that supplementing with 1000 mg/day of calcium (elemental) and 500 IU of vitamin D will prevent bone mineral loss in patients being treated with low doses of prednisone.[96,97]

**Warfarin**
A team of researchers from Washington University School of Medicine and the NYU Medical Center investigated the association between osteoporotic fractures and warfarin usage in over 14,000 Medicare beneficiaries who were hospitalized with atrial fibrillation. Most of the study participants (70%) had hypertension, 48% had heart failure, and 35% had a history of stroke. A total of 1005 of the study participants (6.9%) experienced an osteoporotic fracture during the 3-year study period. The researchers found that men who had been taking warfarin for a year or more had a 63% higher relative risk of experiencing an osteoporotic fracture when compared to men not taking warfarin. Hip fractures were most common (65% of all fractures) and were associated with a 30-day mortality of 39%. Men using warfarin for less than a year did not have an increased risk of osteoporotic fractures. Osteoporosis risk was not increased in women irrespective of duration of warfarin usage.[98]

Although this study did not find an increased risk of osteoporosis among female warfarin users, it is possible that an association still exists, but is masked by other, more important, risk factors such as loss of estrogen production after menopause. This hypothesis is supported by the recent finding by Australian researchers that children on long-term warfarin therapy also experience a marked reduction in bone density.[99]

## Treatment with Pharmaceutical Drugs

Conventional medical treatment of osteopenia and osteoporosis involves one or more of the following treatment protocols:

- Hormone replacement therapy;
- Calcitonin infusions;
- Bisphosphonate therapy;
- Treatment with selective estrogen receptor modulators;
- Treatment with strontium ranelate.

**Hormone Replacement Therapy**
If started soon after menopause, estrogen therapy prevents the early phase of bone loss and decreases the incidence of subsequent osteoporosis-related fractures by about 50%.[100,101] Unfortunately, long-term hormone replacement therapy has been linked to increased risk for cardiovascular disease, breast cancer, venous thromboembolism, ischemic stroke, gallbladder disease, and dry eye syndrome.[102-107] Thus, hormone replacement therapy (HRT) is rarely used nowadays for the prevention or treatment of osteoporosis.

**Calcitonin**
Calcitonin is a hormone produced by the thyroid gland. It suppresses demineralization (bone loss) by inhibiting the activity of osteoclasts and increases bone formation by osteoblasts. Calcitonin is available in two forms – human calcitonin (*Cibacalcin*) and calcitonin derived from salmon (*Calcimar, Miacalcin*). It can be given by injection or through the use of a nasal spray. Salmon-calcitonin is generally considered to be more effective than human-calcitonin, but tends to have more side effects. Calcitonin is particularly effective in reducing vertebral fractures and also helps relieve pain associated with osteoporosis.[108]

**Bisphosphonate Therapy**
Bisphosphonates are potent inhibitors of bone resorption; they bind tightly to hydroxyapatite crystals and thus are retained in bone for many years. The fact that bisphosphonates interfere with the normal bone remodeling process basically means that their use results in “old bones”. The long-term effects of this impaired remodeling process are not known.

The first bisphosphonate to be marketed was etidronate (*Didronel, Didrocal*), which is given in cycles of two weeks interspersed with 11 weeks of calcium carbonate supplementation. Etidronate is effective in increasing BMD in the spine (1% increase per year), but less effective in doing so at the hip.[109]

Second generation bisphosphonates include alendronate (*Fosamax)*, risedronate (*Actonel)*, and zoledronate (*Zometa*). These newer drugs are taken continuously on a daily basis and should preferably be accompanied by supplementation with calcium and vitamin D.

Alendronate is significantly more effective than etidronate.[110] A clinical trial involving medication with 10 mg/day of alendronate plus 500 mg of calcium found that the BMD in the lumbar spine increased by slightly more than 4% a year in the first and second years of treatment. This corresponds to an improvement of about 0.4 standard deviations.[111] Alendronate is usually only prescribed for postmenopausal women whose BMD is more than 2.5 standard deviations below the young healthy norm and who have already suffered one or more fractures. It is not cost-effective for women with osteopenia. A recent study found that treating women with osteopenia with alendronate for 5 years would cost between $70,000 and $332,000 per quality-adjusted life-years gained.[112] This essentially is saying that alendronate is not any more effective than no drug therapy in women with osteopenia.

Bisphosphonates have, as do all pharmaceutical drugs, the potential for serious side effects, among them necrosis (rotting) of the jaw bone.[113] Merck & Co, the manufacturer of *Fosamax* is currently facing several class action suits launched by *Fosamax* users who developed severe necrosis after undergoing dental work.[114]

It is well known that both alendronate and naproxen, a popular non-steroidal anti-inflammatory drug (NSAID), can cause damage to the stomach lining including the actual development of stomach ulcers. Researchers at the Baylor College of Medicine have found that a combination of alendronate and naproxen is considerably more dangerous than either drug on its own. Their clinical trial involved 26 healthy volunteers (18 women and 8 men) between the ages of 30 and 50 years. The study participants were randomized to receive either 10 mg of alendronate once a day, 500 mg of naproxen twice a day or a combination of the two for a 14-day period. The presence of stomach lining damage was measured using videoendoscopy at the beginning and end of the test periods. The first test period was followed by a one-week wash-out period after which the participants were assigned to another regimen and so on until all the participants had tried all three regimens.

The researchers found that 10 mg/day of alendronate produced ulcers in 8 per cent of the participants, 500 mg of naproxen twice a day produced ulcers in 12 per cent, and 10 mg/day of alendronate plus 500 mg of naproxen twice a day produced ulcers in 38 per cent of the volunteers and significant side effects in 69 per cent. It is clear that alendronate and naproxen act synergistically in inducing stomach ulcers. The researchers conclude "it would appear prudent not to prescribe anti-inflammatory doses of traditional NSAIDs to patients receiving alendronate (and vice versa)."[115]

It is possible that the gastrointestinal side effects of alendronate can be somewhat lessened by always taking the medication with a full glass of water and remaining in the upright position for at least an hour after taking it.

**Selective Estrogen Receptor Modulators**

Selective estrogen receptor modulators (SERMs) act like estrogen at specific sites in the body. Tamoxifen, for example, acts to prevent breast cancer, while raloxifene (*Evista*) acts to prevent bone loss and may also have some effect in breast cancer prevention and reduction in low-density cholesterol. A clinical trial involving 34 postmenopausal women with low BMD taking 60 mg of raloxifene daily for 12 months found that BMD increased by 2.9% at the spine and by 3.0% at the femur. LDL cholesterol showed a drop of 22.6%.[116] Another clinical trial involving 129 postmenopausal women with osteoporosis found that treatment with 60 mg/day of raloxifene + 1000 mg/day calcium + 300 IU/day vitamin D3 for 2 years resulted in an increase in BMD of 3.2% at the lumbar spine and 2.1% at the femoral neck.[117] A large multinational trial involving 7705 women in 25 countries concluded that 60 mg/day of raloxifene reduced the risk of vertebral fractures by 30%.[118]

As in the case of alendronate, raloxifene is not cost-effective in the treatment of osteopenia. A recent study concluded that 70-year-old women with osteopenia would gain 19 days of quality-adjusted life if treated with

raloxifene for 5 years as compared to women treated with calcium/vitamin D plus weight-bearing exercise. This corresponds to a cost of $69,000 per quality-adjusted life year gained. Alendronate therapy resulted in a gain of 11 days of quality-adjusted life after treatment for 5 years.[119]

Hot flushes and leg cramps are common side effects associated with raloxifene therapy, but the most serious adverse effect is a 3-fold increased risk of venous thromboembolism.[118,120] The best way of preventing venous thromboembolism is by daily supplementation with nattokinase (2000 – 4000 FU/day) and by wearing flight socks when travelling by air.

**Strontium Ranelate**

Strontium ranelate (Protelos) is highly effective in both preventing and treating osteoporosis and is also effective in preventing osteoporosis-related fractures. It has a dual action in that it both slows bone resorption (demineralization) and increases bone formation. It does this by destroying excess osteoclasts (the cells that promote bone demineralization) and, at the same time, promoting the creation of osteoblasts (the cells responsible for the formation of new bone). Studies have also shown that strontium ranelate significantly improves the micro-architecture of trabecular bone, thus leading to greater strength and toughness.[121]

A major study published in the *New England Journal of Medicine* in 2004 concluded that supplementing with 2 grams/day of oral strontium ranelate reduced the risk of vertebral fractures by 50% in a group of 1649 postmenopausal women with low BMD.[122]

In another study involving 5091 postmenopausal women with osteoporosis, hip fracture was reduced by 36% and vertebral fracture by 39%. This trial also clearly demonstrated the beneficial effect of strontium on BMD. Increases of 8.2% at the femoral neck and 9.8% at total hip were observed in women treated for 3 years.[123] A recent Cochrane review concluded that strontium ranelate is effective in both prevention and treatment of osteoporosis. Doses used in the trials ranged from 125 to 1000 mg/day for prevention to 500 to 2000 mg/day for treatment of existing osteoporosis. A 37% reduction in vertebral fractures and a 14% reduction in non-vertebral fractures were demonstrated over a 2-year period with 2 grams/day of strontium ranelate (containing 700 mg of elemental strontium).[124]

In addition to its many advantages in the treatment of osteopenia and osteoporosis, strontium ranelate is also remarkable in its lack of undesirable side effects. It does not, as may the bisphosphonates, cause rotting of the jaw bone or stomach ulcers, especially if used in combination with naproxen and perhaps other non-steroidal anti-inflammatory drugs (NSAIDs).

Although recent studies have focused on the use of strontium ranelate, previous studies have found the following forms of organically-bound strontium to be equally effective – strontium gluconate, strontium carbonate, strontium lactate, and strontium chloride.[125]

Strontium ranelate was developed in France and, unfortunately, it not available in North America.

## Treatment with Natural Remedies

Essentially, all the natural remedies effective for prevention of osteopenia and osteoporosis are also effective in the treatment of these conditions. Thus, a natural treatment program would include several or all of the following supplements in the amounts indicated (NOTE: These dosages include amounts obtained from the diet and a daily multivitamin):

- Vitamin D 2000 – 4000 IU/day
- Calcium 1200 mg/day (elemental)
- Magnesium 3 x 200 mg/day (elemental)
- Strontium 600 mg/day (elemental)
- Zinc 15 mg/day
- Boron 3 mg/day

- Potassium 4500 mg/day (elemental, max 1500 mg/day from supplements) *
- Vitamin B12 1000 mg/day (sublingual tablet)
- Lycopene 15 mg/day
- Vitamin C 3 x 500 mg/day
- Vitamin K2 100 micrograms/day
- Folic acid 400 – 600 micrograms/day
- Vitamin B6 50 mg/day
- Fish oil 1 – 2 g/day of EPA + DHA(1)

(1) Although clinical data on the effect of fish oils on the prevention and treatment of osteoporosis is scarce, there is now some indication that fish oil supplementation may increase BMD at the spine, at least in young men.[126,127] There is also some evidence that a low grade systemic inflammation may be involved in osteoporosis, in which case fish oils again would be highly beneficial.

* Assuming normal kidney function

The Allergy Research Group (Nutricology) has developed an excellent product that contains most of the above-mentioned supplements.

### *Allergy Research Strontium Osteo Complex Formulation (6 tablets)*

| | |
|---|---|
| Vitamin D3 | 600 IU |
| Calcium | 1100 mg |
| Magnesium | 400 mg |
| Strontium carbonate | 1000 mg (600 mg of elemental strontium) |
| Zinc | 10 mg |
| Boron | 3 mg |
| Lycopene | 5 mg |
| Vitamin C | 500 mg |
| Vitamin K2 | 100 mcg |

Thus, adding extra vitamin D, vitamin C, magnesium, and lycopene as well as potassium, folic acid, vitamin B6, vitamin B12, and fish oil would result in a superior, natural prevention and treatment therapy for osteopenia and osteoporosis.

To the best of my knowledge there is no indication that this supplementation program would interfere with the concomitant use of alendronate or raloxifene.

Before embarking on the supplementation program it would be desirable to establish a baseline with a DEXA scan and the following blood tests:

- Vitamin D3 (25-hydroxy vitamin D)
- PTH
- Electrolytes (calcium, magnesium, potassium)
- Homocysteine
- Folic acid (in red blood cells)
- Vitamin B12 or methylmalonic acid
- Alkaline phosphatase (ALP)
- High sensitivity C-reactive protein

The results of these tests may help to pinpoint the reason for any excessive bone loss as well as gauging the effectiveness of the supplementation program.

***Please see Part I published in the September issue for complete references***

**References**


72. Morter, Jr., M.T. and Panfili, Adolfo. The body's negative response to excess dietary protein consumption. Journal of Orthomolecular Medicine, Vol. 13, No. 2, Second Quarter 1998, pp. 89-94
73. Fox, Douglas. Hard cheese. New Scientist, December 15, 2001, pp. 42-45
74. Dawson-Hughes, Bess and Susan S. Harris. Calcium intake influences the association of protein intake with rates of bone loss in elderly men and women. American Journal of Clinical Nutrition, Vol. 75, April 2002, pp. 773-79
75. Heaney, Robert P. Protein and calcium: antagonists or synergists? American Journal of Clinical Nutrition, Vol. 75, April 2002, pp. 609-10 [editorial]
76. Hopper, JL and Seeman, E. The bone density of female twins discordant for tobacco use. New England Journal of Medicine, Vol. 330, February 10, 1994, pp. 387-92
77. Rapuri, PB, et al. Caffeine intake increases the rate od bone loss in elderly women and interacts with vitamin D receptor genotypes. American Journal of Clinical Nutrition, Vol. 74, November 2001, pp. 694-700, 569-70
78. Tucker, KL, et al. Colas, but not other carbonated beverages, are associated with low bone mineral density in older women. American Journal of Clinical Nutrition, Vol. 84, October 2006, pp. 936-42
79. Devine, A, et al. A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. American Journal of Clinical Nutrition, Vol. 62, October 1995, pp. 740-45
80. Herrmann, M, et al. Increased osteoclast activity in the presence of increased homocysteine concentrations. Clinical Chemistry, Vol. 51, No. 12, 2005, pp. 2348-53
81. Herrmann, M, et al. Homocysteine: A newly recognized risk factor for osteoporosis. Clin. Chem. Lab. Med., Vol. 43, No. 10, 2005, pp. 1111-17
82. Morris, MS, et al. Relation between homocysteine and B-vitamin status indicators and bone mineral density in older Americans. Bone, Vol. 37, 2005, pp. 234-42
83. Gjesdal, CG, et al. Plasma total homocysteine level and bone mineral density. Archives of Internal Medicine, Vol. 166, January 9, 2006, pp. 88-94
84. Baines, M, et al. The association of homocysteine and its determinants MTHFR genotype, folate, vitamin B12 and vitamin B6 with bone mineral density in postmenopausal British women. Bone, Vol. 40, March 2007, pp. 730-36
85. Koh, JM, et al. Homocysteine enhances bone resorption by stimulation of osteoclast formation and activity through increased intracellular ROS generation. Journal of Bone and Mineral Research, Vol. 21, July 2006, pp. 1003-11
86. Scharla, S. Causes of osteoporosis: Don't forget celiac disease. Dtsch. Med. Wochenschr., Vol. 128, No. 17, April 25, 2003. [article in German – English abstract only]
87. Stazi, AV and Trinti, B. Reproductive aspects of celiac disease. Ann. Ital. Med. Int., Vol. 20, No. 3, July-September 2005, pp. 143-57 [article in Italian – English abstract only]]
88. Stazi, AV and Trinti, B. Reproduction, endocrine disorders and celiac disease: Risk factors of osteoporosis. Minerva Med, Vol. 97, No. 2, April 2006, pp. 191-203 [article in Italian – English abstract only]]
89. Ludvigsson, JF, et al. Coeliac disease and the risk of fractures. Aliment. Pharmacol. Ther., Vol. 25, No. 3, February 1, 2007, pp. 273-85
90. Bai, JC, et al. Long-term effect of gluten restriction on bone mineral density of patients with celiac disease. Aliment. Pharmacol. Ther., Vol. 11, No. 1, February 1997, pp. 157-64
91. Sategna-Guidetti, C, et al. The effects of 1-year gluten withdrawal on bone mass, bone metabolism and nutritional status in newly-diagnosed adult celiac disease patients. Aliment. Pharmacol. Ther., Vol. 14, No. 1, January 2000, pp. 35-43
92. Saibeni, S, et al. Prevalence of hyperhomocysteinemia in adult gluten-sensitive enteropathy at diagnosis: Role of B12, folate, and genetics. Clinical Gastroenterology, Vol. 3, June 2005, pp. 574-80
93. Schneider, DL, et al. Thyroid hormone use and bone mineral density in elderly women. JAMA, Vol. 271, April 27, 1994, pp. 1245-49
94. Uzzan, B, et al. Effects on bone mass of long term treatment with thyroid hormones. Journal of Clinical Endocrinology and Metabolism, Vol. 81, December 1996, pp. 4278-89
95. Bijlsma, JWJ. Prevention of glucocorticoid induced osteoporosis. Annals of the Rheumatic Diseases, Vol. 56, September 1997, pp. 507-09
96. Buckley, LM, et al. Calcium and vitamin D-3 supplementation prevents bone loss in spine secondary to low-dose corticosteroids in patients with rheumatoid arthritis. Annals of Internal Medicine, Vol. 125, December 15, 1996, pp. 961-68
97. Birdsall, TC. Prevention of corticosteroid-induced osteoporosis. Annals of Internal Medicine, Vol. 127, July 1, 1997, p. 90
98. Gage, BF, et al. Risk of osteoporotic fracture in elderly patients taking warfarin. Archives of Internal Medicine, Vol. 166, January 23, 2006, pp. 241-46

99. Barnes, C, et al. Reduced bone density in children on long-term warfarin. Pediatric Research, Vol. 57, No. 4, 2005, pp. 578-81
100. Ettinger, B, et al. Long-term estrogen replacement therapy prevents bone loss and fractures. Annals of Internal Medicine, Vol. 102, March 1985, pp. 319-24
101. Cauley, JA, et al. Estrogen replacement therapy and fractures in older women. Annals of Internal Medicine, Vol. 122, January 1995, pp. 9-16
102. Blakely, JA. The Heart and Estrogen/Progestin Replacement Study revisited. Archives of Internal Medicine, Vol. 160, October 23, 2000, pp. 2897-2900
103. Colditz, GA. Relationship between estrogen levels, use of hormone replacement therapy, and breast cancer, Journal of the National Cancer Institute, Vol. 90, June 3, 1998, pp. 814-23
104. Grady, D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease. Annals of Internal Medicine, Vol. 132, May 2, 2000, pp. 689-96
105. Bath, PMW and Gray, LJ. Association between hormone replacement therapy and subsequent stroke. British Medical Journal, Vol. 330, February 2005, pp. 342-45
106. Cirillo, DJ, et al. Effect of estrogen therapy on gallbladder disease. JAMA, Vol. 293, January 2005, pp. 330-39
107. Schaumberg, DA, et al. Hormone replacement therapy and dry eye syndrome. JAMA, Vol. 286, November 7, 2001, pp. 2114-19
108. Mehta, NM, et al. Calcitonin for osteoporosis and bone pain. Curr. Pharm. Des., Vol. 9, No. 32, 2003, pp. 2659-76
109. Greenspan, SL, et al. Bisphosphonates: Safety and efficacy in the treatment and prevention of osteoporosis. American Family Physician, Vol. 61, No. 9, May 1, 2000, pp. 2731-36
110. Iwamoto, J, et al. Comparison of effect of treatment with etidronate and alendronate on lumbar bone mineral density in elderly women with osteoporosis. Yonsei Medical Journal, Vol. 46, No. 6, 2005, pp. 750-58
111. Rozkydal, Z and Janicek, P. The effect of alendronate in the treatment of postmenopausal osteoporosis. Bratisl. Lek. Listy, Vol. 104, No. 10, 2003, pp. 309-13
112. Schousboe, JT, et al. Cost-effectiveness of alendronate therapy for osteopenic postmenopausal women. Annals of Internal Medicine, Vol. 142, No. 9, May 3, 2005, pp. 734-41
113. Farrugia, MC, et al. Osteonecrosis of the mandible or maxilla associated with the use of new generation bisphosphonates. Laryngoscopy, Vol. 116, January 2006, pp. 115-20
114. http://www.yourlawyer.com/topics/overview/Fosamax
115. Graham, David Y. and Malaty, Hoda M. Alendronate and naproxen are synergistic for development of gastric ulcers. Archives of Internal Medicine, Vol. 161, January 8, 2001, pp. 107-10
116. Song, EK, et al. Effectiveness of raloxifene on bone mineral density and serum lipid levels in post-menopausal women with low BMD after discontinuation of hormone replacement therapy. J. Clin. Pharm. Ther., Vol. 31, No. 5, October 2006, pp. 421-27
117. Meunier, PJ, et al. Treatment of postmenopausal women with osteoporosis or low bone density with raloxifene. Osteoporosis International, Vol. 10, No. 4, 1999, pp. 330-36
118. Ettinger, B, et al. Reduction of vertebral fracture risk on postmenopausal women with osteoporosis treated with raloxifene. JAMA, Vol. 282, No. 7, August 18, 1999, pp. 637-45
119. Meadows, ES, et al. Cost-effectiveness of preventative therapies for postmenopausal women with osteopenia. BMC Women's Health, Vol. 7, 2007 www.biomedcentral.com/1472-6874/7/6
120. Grady, D, et al. Safety and adverse effects associated with raloxifene. Obstetrics and Gynecology, Vol. 104, No. 4, October 2004, pp. 837-44
121. http://www.servier.com/pro/osteoporose/congres/ECTS2007/ects2007_video.asp
122. Meunier, PJ, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. New England Journal of Medicine, Vol. 350, January 29, 2004, pp. 459-68
123. Reginster, JY, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis. Journal of Clinical Endocrinology & Metabolism, Vol. 90, No. 5, 2005, pp. 2816-22
124. O'Donnell, S, et al. Strontium ranelate for preventing and treating postmenopausal osteoporosis. Cochrane Database System Review, Vol. 18, No. 4, October 2006, CD005326
125. Genuis, SJ and Schwalfenberg. Picking a bone with contemporary osteoporosis management: Nutrient strategies to enhance skeletal integrity. Clinical Nutrition, Vol. 26, 2007, pp. 193-207
126. Hogstrom, M, et al. N-3 fatty acids are positively associated with peak bone mineral density and bone accrual in healthy men. American Journal of Clinical Nutrition, Vol. 85, No. 3, March 2007, pp. 803-07
127. Vanek, C and Connor, WE. Do n-3 fatty acids prevent osteoporosis? American Journal of Clinical Nutrition, Vol. 85, No. 3, March 2007, pp. 647-48

# The Prostate Monitor
## Editor: William R. Ware, PhD

***Reviews of recent studies from the peer-reviewed literature***

**NUMBER 7** **October 2007** **1st Year**

*Under- and over-diagnosis of prostate cancer are contentious issues constantly debated in the literature. The pros and cons are sufficiently numerous and compelling that consensus appears impossible. This presents a huge challenge to the layman who can easily be presented with strong views on either side during discussion of something as seemingly simple as deciding whether or not to have a PSA test. In this issue of The Prostate Monitor we discuss some recent relevant results, although it would be a mistake to pretend that they resolve the debate or the issues involved. Nevertheless, they provide "food for thought" for all men who have never had a PSA test and most surely will eventually be offered or even pressured strongly to have one.*

*Other topics discussed include the influence of the hair growth stimulant Propecia on serum PSA levels and the merits of eating cruciferous vegetables such as broccoli for the purpose of primary prevention of prostate cancer.*

*Wishing you continuing good health,*

***William R. Ware, PhD, Editor***



## UNDER- AND OVER-DIAGNOSIS OF PROSTATE CANCER

This became an unresolved issue with the advent of widespread PSA screening. Elevated PSA only indicates probabilities of the presence of prostate cancer simply because there are other causes of values considered high in comparison to age adjusted population averages. In addition, while many studies have been directed at the merits of various PSA cut-off values above which concern and perhaps a biopsy are indicated, there is also no general agreement on the best cut-off. Concern that an elevated value can provide a false positive indication which can lead to over diagnosis and perhaps unnecessary treatment has been voiced repeatedly over the years. Screening leads to the discovery of some low-grade tumors which may be indolent and never cause a problem and yet are frequently treated in order to "play it safe" or satisfy the demands of patients for treatment independent of the indications present. However, proponents of PSA screening point out that screening detected cancers tend to have favorable stage distribution in the sense that they are mostly localized and very frequently curable with low morbidity, whereas prostate cancers detected in the pre-PSA era tended to be much more advanced, frequently not organ-confined and much less successfully treated with either surgery or radiation. In fact, since the introduction of widespread PSA testing there has been a 75% decrease in the

proportion of patients presenting with metastatic disease and prostate cancer-specific mortality rates have decreased dramatically. It is worth pointing out in passing that it appears generally agreed that if one really wants to know whether or not they have prostate cancer, a 10-12-needle biopsy is needed, and even this procedure has a small by significant false negative rate. The point is that the PSA test is not really a prostate cancer-specific test, but nevertheless, the probability of having cancer goes up with the PSA level. However, after surgical removal of the prostate or primary radiation therapy, PSA becomes a sensitive and highly useful marker of recurrence and progression. Several studies have recently appeared that address the issue of over- and under-diagnosis.

The first study by Graif *et al* (1) which was based in the U.S. involved a total of 2126 men treated with radical prostatectomy in one of three periods (1989-95, 1995-2001, and 2001-05). The criteria for over-diagnosis was a tumor of 0.5 $cm^3$ or less, confined to the prostate with clear surgical margins and no Gleason pattern of 4 or 5 (see our book for a discussion of Gleason patterns). Under-diagnosis was defined as non-organ confined tumors or positive surgical margins. The results indicated that the proportion of men over-diagnosed was 1.3% to 7.1%. The proportion under-diagnosed was 25% to 30%. It was also found that reducing the PSA threshold for biopsy from 4.0 to 2.5 ng/mL resulted in a lower rate of under-diagnosis from 30% to 26% and a higher rate of over-diagnosis from 1.3% to 7.1% and a 5-year progression-free survival rate which went from 85% to 92%. It was also found that men 55 years of age or younger were significantly more likely to meet the criteria for over-diagnosis. Thus in this study under-diagnosis occurred more frequently than over-diagnosis and the rate associated with the latter was small. The authors conclude that their results suggest that PSA screening does more good than harm.

The second study by Pelzer *et al* (2) evaluated the possible over- and under-diagnosis in a group of 680 patients recruited from an Austrian screening project. Two groups of patients who underwent radical prostatectomy were evaluated, one with PSA in the range of 2.0 to 3.9 (lower range) and the other 4.0 to 10.0 ng/mL (higher range). Criteria for over- and under-diagnosis were similar to those used by Graif *et al*, i.e. the presence or absence of organ-confined disease, although Pelzer *et al* had a higher limit on the Gleason score (<7) than Graif *et al*. Over-diagnosis was found in 19.7% in the lower PSA group and 16.5% in the higher PSA group. Comparable numbers for under-diagnosis were 18.9% and 36.7%. For the entire cohort the researchers found 17.6% and 30.3% over- and under-diagnosis respectively. In addition, 8.7% of the tumors for the entire group were insignificant by the Epstein criteria (Jonathan Epstein MD, Johns Hopkins School of Medicine). Thus this study also shows that under-diagnosis occurs more frequently than over-diagnosis for individuals in a screened population with PSA in the range of 4.0 to 10 ng/mL.

The much lower incidence of over-diagnosis observed by Graif *et al* compared to Pelzer *et al* may be due to the much lower limit on Gleason Score employed to identify this category. (no scores of 4 or 5 compared to < 7). Also, Graif *et al* used tumor volume ascertained during pathological study of the removed prostates as part of the criteria for over-diagnosis. In an associated editorial, H. Ballentine Carter, a well known urologist and prostate cancer specialist at Johns Hopkins, makes the following observations: (a) In a cohort of men older than 65 years with prostate cancer where 95% were not screen detected and more than half had a PSA above 10 ng/mL, 333 would need to undergo surgery to prevent one prostate cancer death in 10 years. Another study of a similar group found that 200 men would need to be treated to prevent one prostate cancer death during 12 years; (b) most men in the US today (> 85%) have low to intermediate risk prostate cancer which is diagnosed at a median age of 68 years and more than 90% of them undergo active treatment rather than watchful waiting. Therefore, there is no gain in years of life for most men diagnosed and treated for prostate cancer in the US today; (c) this may not be the case for younger men where comorbidities and competing causes of death are much lower; (d) while it can be argued, as do Pelzer *et al*, that over diagnosis can be balanced by high quality treatment with minimal impact of quality of life, most men do not have access to high quality treatment.

Thus it appears clear that the two studies reviewed do not resolve the ongoing debate regarding the merits of screening, especially in older individuals. However, it is hard to argue with the widely held belief regarding the benefits of establishing a PSA baseline for all men in their early 40s and subsequently screening for the rate of change of the PSA level or the PSA velocity as an alternative approach to using PSA thresholds and proceeding to biopsy when one is exceeded. This subject, and in particular the use of PSA velocity and doubling times in this context is discussed in our book. This is an important issue for all men over 40 years of age and knowledge of the details is obviously of benefit in decision-making and in evaluating advice during physical exams.

Rather than looking at the pathological features in removed prostates that help distinguish indolent prostate cancer from more aggressive forms of the disease, Roehl *et al* (3) accumulated data on two populations, one screened by conventional means including PSA, the other derived from patients referred by physicians who did not rely on screening. All were treated with a radical prostatectomy by one surgeon (William J. Catalona, Northwestern Feinberg School of Medicine, Chicago, IL). At issue were the benefits of screening, if any, associated with 7-year post surgical progression-free probabilities. The results were 83% for the screened patients and 77% for the referred patients. The difference was statistically significant. These results were not surprising when the preoperative PSA, Gleason score, clinical stage and pathologic stage (based on examining the removed gland) were compared for the two groups. These features were more unfavorable in the referred group. When the results were submitted to a so-called multivariate analysis, screening status was a significant independent predictor of treatment failure. It can be argued that all this really demonstrates is that screening produces a group of patients with less advanced cancer with a better post-treatment prognosis. But this does appear to strengthen the argument for screening although some would regard the difference between 77% and 83% as not that compelling.

## PSA LEVELS, PROSTATIC INTRAEPITHELIAL NEOPLASIA AND FINASTERIDE

It is now well known that finasteride (Proscar), a 5-alpha reductase enzyme inhibitor used to treat enlarged prostate, also reduces PSA levels by about 50%. Thus when PSA readings are being judged in the context of the likelihood of prostate cancer, the values have to be adjusted based on the length of time finasteride has been used. But finasteride is also used to treat what is called androgenic alopecia, which is a fancy term for male pattern baldness. However, the dose is 1/5 that used to treat prostate enlargement. Thus the obvious question—does 1 mg/day of finasteride influence PSA levels? The answer is yes. In a recent study by D'Amico and Roehrborn (4), it was found that for men aged 40-49, treatment for 48 weeks reduced PSA levels by 40% whereas for those aged 50—60, the decrease was 50%, the same as the 5 mg/day dose. Thus men taking Propecia need to be aware of this fact and inform their doctor if no correction is made to their PSA results. This very recent study is interesting in that it would have been natural to assume that most doctors already know about this effect. After all, it is mentioned even in older editions of the Physician's Desk Reference, a standard reference book that most physicians have on their bookshelf or on their computer. The fact that Propecia has roughly the same effect on PSA levels as the 5 mg dose of Proscar points to an interesting question—does the low dose of finasteride also confer protection against prostate cancer and does it also slightly increase the risk of advanced disease? This latter aspect, which was associated with the 5 mg/day dose of Proscar, is incidentally still being debated and may be an artifact.

In addition to the effect of finasteride on male pattern baldness, action of this enzyme inhibitor in preventing a potentially serious precancerous condition has just been reported (5). The condition is prostatic intraepithelial neoplasia (PIN) which is classified in terms of high and low grades. The high grade form (HGPIN) is currently thought to be associated with increased risk of prostate cancer but whether HGPIN actually involves lesions which are precursors to this disease is still being debated. This subject is discussed in our book. The study in question was part of the now famous Prostate Cancer Prevention Trial (PCPT) which examined the connection between PSA levels during a 7 year follow-up and biopsy detected cancer either when indicated or at the end of the study. One arm of the study involved examining the impact of 5 mg/day of finasteride on the incidence of prostate cancer, the results of which were briefly mentioned above. In addition the impact of this dose of finasteride on the incidence of HGPIN was determined from biopsy samples. It was found that finasteride reduced the incidence of HGPIN from 4.6% in the placebo group to 3.2% in the treatment group. HGPIN accompanied by prostate cancer was found in 3.2% of the finasteride group and 4.6% in the placebo group. This study demonstrated that finasteride decreased the risk of HGPIN by 21% overall (alone or with cancer), a similar reduction as was found for prostate cancer in the PCPT trial. The authors suggest that this observation may explain how finasteride accomplishes the cancer incidence reduction and supports the hypothesis that HGPIB is a pre-malignant lesion in the prostate.

Reducing the incidence of HGPIN is obviously desirable. Just like the diagnosis of prostate cancer, the detection of HGPIN in biopsy samples leads to a series of undesirable events including repeat biopsies and

anxiety regarding the implied risk of prostate cancer, either as a coexisting condition which was missed or a threat for the future.

## FRUIT AND VEGETABLE INTAKE AND RISK OF PROSTATE CANCER

Epidemiologic evidence indicates an association between high vegetable and fruit intake and a reduced risk for many cancers. However, prospective studies of this association for prostate cancer have either shown non-statistically significant inverse associations or no associations, although there have been indications of potential benefit for cruciferous vegetables. A study has just been reported that examined the relationship between fruit and vegetable intake and the risk of prostate cancer among approximately 30,000 men during an average 4.2 years follow-up (6). A particular strength of this study, according to the authors, was the ability to control for confounding due to screening. All participants underwent screening according to the same prescribed regimen and only participants who had the same number of screening examinations were compared. It was found that high intakes of cruciferous vegetables, including broccoli and cauliflower may be associated with reduced risk of aggressive prostate cancer, particularly extras-prostatic disease. No associations with vegetables in general or fruit achieved statistical significance. The significant inverse associations for broccoli and cauliflower were seen only for intakes of > 1 serving/week, which represented the top quartile of intake.

Cruciferous vegetables in general and broccoli in particular seem to come up rather frequently in studies of diet and disease. Neither are probably top choices in North America for the vegetable portion of meals. However, this study found benefit for only on serving per week, which is not really an overkill in broccoli consumption. There is another option, albeit unproven by proper studies, and that is the cruciferous vegetable concentrate available in capsule form. But of course, there is no assurance that this extract contains the ingredients that are actually active in cancer prevention. Studies that will settle that question will probably never be conducted, given that vegetable extracts are not patentable. A compromise is to eat that one serving of broccoli or cauliflower or both per week and to play it safe take extract capsules as well. For those who do not like broccoli or cauliflower, experimenting with sauces such as cheese sauces or a rich Hollandaise sauce is suggested as a way of enhancing the palatability of these vegetables.

**REFERENCES**


1. Graif T et al., 2007. Under diagnosis and over diagnosis of prostate cancer. J Urol. 178(1):88-92.
2. Pelzer AE et al., 2007. Under diagnosis and over diagnosis of prostate cancer in a screening population with serum PSA 2 to 10 ng/ml. J Urol. 178(1):93-97.
3. Roehl KA et al., 2006. Survival results in patients with screen-detected prostate cancer versus physician-referred patients treated with radical prostatectomy: early results. Urol Oncol. 24(6):465-471.
4. D'amico AV, Roehrborn CG, 2007. Effect of 1 mg/day finasteride on concentrations of serum prostate-specific antigen in men with androgenic alopecia: a randomised controlled trial. Lancet Oncol. 8(1):21-25.
5. Thompson IM et al., 2007. Finasteride decreases the risk of prostatic intraepithelial neoplasia. J Urol. 178(1):107-109.
6. Kirsh VA et al., 2007. Prospective study of fruit and vegetable intake and risk of prostate cancer. JNCI Cancer Spectrum. 99(15):1200-1209.



**Editor: William R. Ware, PhD**
INTERNATIONAL HEALTH NEWS is published 10 times a year by
Hans R. Larsen MSc ChE, 1320 Point Street, Victoria, BC, Canada, V8S 1A5
E-mail: editor@yourhealthbase.com World Wide Web: http://www.yourhealthbase.com
ISSN 1203-1933

The Prostate Monitor is published 10 times a year by
International Health News, 1320 Point Street, Victoria, BC, Canada, V8s 1A5
Editor: William R. Ware, PhD
e-mail: editor@yourhealthbase.com
The Prostate Monitor does not provide medical advice.
Do not attempt self-diagnosis or self-medication based on our reports.