INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

NUMBER 177 **MAY 2007** **16th YEAR**

Trying to prove that taking vitamins is either a waste of money because they don't work or that they are actually dangerous appears to currently be a popular focus of epidemiology. Papers now appear frequently, and in respected and high profile journals. These studies are immediately attacked as flawed, confounded, biased or deceptive by defenders of supplementation. A study design such as was used in one of the reports discussed below makes one wonder what is really going on. This study involved a placebo-controlled trial of a supplement but the design allowed both the intervention and placebo groups to take unknown but significant amounts of the supplement used in the intervention. In this issue the latest volley from the anti-supplement camp is discussed, partly because it received significant media coverage.

Vitamin D continues to be featured almost monthly because, in the opinion of the editor, it has become one of the major issues in preventive medicine in the past year. This month's "vitamin D topic" involves the prevention of colorectal cancer. Three papers are discussed, but the highlight is the just published meta-analysis by Gorham et al.

Two studies examined this month relate to a topic discussed last month, i.e. the metabolic syndrome. Also last month the risks vs. benefits of fish consumption were discussed. In the present Newsletter, an important addition to the subject is presented, namely fish consumption during pregnancy and its impact on the neurodevelopment of the child. The results will probably surprise some readers.

Finally, the use of non-steroidal anti-inflammatory drugs is examined in the context of both pain relief and the primary prevention of colorectal cancer. The discussion is based on recently released guidelines from the American Heart Association and the U.S. Preventive Services Task Force and focuses on risk vs. benefit

This issue also features a Perspective on absolute vs. relative risk and how the "spin" of the presentation of clinical trial results can have a profound effect on patient reaction to the proposed intervention. Also this issue contains the latest Prostate Monitor.

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Wishing you continuing good health,

William R. Ware, PhD, Editor

Highlights

THE LATEST ANTI-VITAMIN VOLLEY

The *National Post,* one of Canada's two national newspapers, carried the headline "Vitamins may increase the risk of death" (February 28). This was to alert the reader to the results of a study published in the January 28 issue of the *Journal of The American Medical Association* which described a multicenter review and meta-analysis (reevaluation of combined studies) of antioxidants used for the primary and secondary prevention of various diseases. The investigators divided 68 studies into two groups according to their judgment as to the presence of low- or high-risk of bias. Of the 47 studies in the low-risk category, only 13 concerned primary prevention and the remainder were studies involving individuals with a variety of illnesses. When all 68 studies were considered together, there was no significant effect on mortality. When the dose dependence of individual supplements was considered, the relative risks (RRs) were 1.004, 1.000006 and 0.998 for beta-carotene, vitamin A and selenium, respectively, RRs the authors appear to regard as statistically and significantly different from 1.00, the null or no effect result. No dose-dependent risk was found for vitamins C or E, the duration of supplementation, or whether the study in question was for primary or secondary prevention.

For the low-bias risk studies (47) the overall relative risk of mortality was 1.05, i.e. a 5% increased risk, a result which achieved statistical significance. When the mortality risk for individual supplements was examined, the only significant results that were found, aside from beta-carotene (RR 1.06) were when the high-risk bias studies and studies involving selenium were excluded from the analysis. This occurred for vitamin A (RR 1.16), and Vitamin E (RR 1.04). For selenium, statistically significant protective effect was found.

Bjelakovic, G, et al. Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention. ***Journal of the American Medical Association****. 2007, Vol. 297, No. 8, pp. 842-5.7*

Editor's comment: Of the 21 so-called high-risk of bias studies, 7 were for primary prevention. In the low-risk of bias studies, 13 out of 47 were for primary prevention. These low-bias risk studies were considered the best for the analysis. Thus this meta-analysis concerns mainly the influence of antioxidant supplements on individuals who had one or more diseases. Some who favor supplements generally suggest that benefits are mostly seen in the primary prevention setting, not when they are used in an attempt to decrease mortality in sick people. In the low-risk of bias studies analyzed, only 4 out of 47, when judged individually, generated statistically significant results. Thus 43 of the 47 studies that formed the main basis of the analysis would have been disregarded when judged individually, according to modern standards of significance, in the context of the effect of a supplement or supplements on mortality. By combining all 47, the relative risk was pushed slightly above the null result of 1.00 to 1.05, a relative risk many would consider too small to make much of a fuss over, especially considering the large variation in subject characteristics, supplement doses and protocol that are involved in this mix of studies. One of the studies included in the low-risk of bias group was a single dose study using 200,000 IU of vitamin A with a follow-up of 3 months—hardly representative of usual supplement practice. Also, Faloon *et al* list 16 large studies of significant duration showing benefit of antioxidants which were excluded (www.lef.org, online statement, March 6, 2007)

In addition, what importance is the reader is to attach to the statement "…analysis revealed significant influence" of bias-risk of 16% on mortality"? It seems bias-risk is not risk associated with the supplement intervention but with the design and execution of the studies. Yet, when one reads the abstract of this paper, the impression is that supplements increase the risk of mortality by 16%, but this number 16% is not found, aside from one very restricted result for vitamin A mentioned above, in any of the data presented which relates to the main issue, do antioxidants increase mortality. That the overall result from the 68 studies found there was no evidence of increased mortality suggests that the headline in the *National Post* is somewhat of an exaggeration. In fact, this study appears to be a fishing expedition in which very small fish were landed—the size that could be used for bait. The *National Post* quotes Mary Charlson, Chief of the Center for Complementary and Alternative Medicine at Weill Cornell Medical College in New York, who pointed out that the researchers omitted from their analysis almost 750 studies that found no deaths, and that this would skew the results. She commented, "They are significantly overreaching the data, and I think it's going to cause people a lot of concern." Also, Meir Stampfer, Professor of Nutrition and Epidemiology at the Harvard School of Public Health was quoted as saying, "This study does not advance our understanding, and could

easily lead to misinterpretation of the data." http://www.newsvine.com/_news/2007/02/27/58960

8-antioxidants-dont-help-you-live-longer

VITAMIN D AND COLORECTAL CANCER

This is an important question given that worldwide there are about a million new cases and a half-million deaths annually attributed to colorectal cancer (CRC). The U.S. figures are also dismal. It was the second leading cause of death from cancer with 145,300 cases and 56,300 deaths in 2005. The observation of higher age-adjusted mortality rates of colorectal cancer in the northern and northeastern U.S. when compared to Hawaii, Florida and the southwest suggests the possibility that Vitamin D status is implicated in the etiology of this disease. When viewed together, the following studies underscore the importance of determining vitamin D status with serum 25-hydroxyvitamin D determinations, both in studies and for individual assessment.

THE WOMAN'S HEALTH INITIATIVE STUDY REPORTS ON VITAMIN D AND COLORECTAL CANCER

In early 2006, the Woman's Health Initiative investigators reported on a study of supplementation with calcium plus vitamin D and the risk of colorectal cancer. The results for calcium plus vitamin D showed no effect. The study received considerable media attention and many physicians who read the abstract or heard about it on the news probably concluded that this was another study to add to their list where supplements failed the test of modern evidence-based medicine. Also, medial attention may have discouraged women from taking the supplements. It was quickly pointed out by two experts in this field, Michael Holick from Boston University and Edward Giovannucci from Harvard, in separate letters to the editor of the *New England Journal of Medicine* that the vitamin D intervention dose used was inadequate (400 IU), and the duration of the follow-up too short. It was also pointed out that at the start of the study the subjects in the placebo and intervention groups had an intake of about 400 IU per day, half of which was from supplements, and throughout the study both groups were allowed to continue taking any amounts of vitamin D they wanted, but the treatment group got an extra 400 IU. However, buried in the text was a small sub-group analysis where serum levels of 25-hydroxyvitamin D, a vitamin D status marker, were found to be inversely related to the risk of CRC. When serum levels of < 12 ng/L were compared with ≥ 23 ng/L, the risk of CRC was increased by a factor of 2.5. This statistically significant result was not mentioned in the abstract. As will become clear from what follows, this result was important.

Wactawski-WendeJ. et al. Calcium Plus Vitamin D Supplementation and the Risk of Colorectal Cancer. ***New England Journal of Medicine,*** *2006, Vol. 354, No. 7,pp. 684-96.*

Holick, M. ***New England Journal of Medicine****, 2007, Vol 354, No 21, pp. 2287.*

Giovannucci, E. ibid pp. 2287

VITAMIN D AND COLORECTAL CANCER PREVENTION—A POOLED ANALYSIS

The above study suffered from a design where a supplement was tested by adding it to the normal intake of both the placebo and intervention groups, and only a minute fraction of the participants had their serum 25-hydroxyvitam D levels measured. Gorham *et al* have just published a study where they pooled five studies, all of which were based on 25-hydroxyvitamin D levels rather than merely estimates of oral intake. When they compared the risk of CRC for serum levels of ≤ 12 ng/mL with levels ≥ 33 ng/mL, they found a 50% lower risk of colorectal cancer, and in addition, there was a highly significant trend of decreasing risk with increasing level of this vitamin D marker. The authors conclude their paper with a brief discussion of vitamin D intake and 25-hydroxyvitamin D levels. Based on a median population level of 20 ng/mL, they estimate that it would require supplementation of 1000 IU/day to raise the levels to 33 ng/mL, but this would be less than optimal because half the population would still be below this level. If instead, the intake was 2000 IU/day, they estimate levels of 46 ng/mL, a level that should produce substantial protection from colorectal cancer. The studies in this pooled analysis were all done on white-skinned individuals. Persons with dark skin are much more susceptible to vitamin D deficiency and the authors point out that for these individuals, higher levels might be required. They cite a number of studies that demonstrate that 2000 IU/day is safe and is well below the intakes where adverse effects might begin to appear. The authors also discuss the potential synergistic action of vitamin D and calcium in the context of CRC prevention. Finally, the authors comment that the time period required for

an increase in vitamin D status to reduce the risk of CRC is unknown, but could require ≥ 10 years.

Gorham, E. D. et al. Optimal Vitamin D Status for Colorectal Cancer Prevention. A Quantitative Meta Analysis. ***American Journal of Preventive Medicine****, 2007, Vol. 33, No. 3, pp. 210-16.*

Editor's comment: A blood test for 25-hydroxy vitamin D is available from most diagnostic labs and can be ordered by a physician. For residents in the temperate zone, the result will vary from summer to winter and will also depend on the amount of sun exposure in the summer and during winter vacations "in the sun" and of course on the level of supplementation. The result should be compared with the recent literature, not with the range given on the laboratory printout. Optimum levels, as discussed above and in recent issues of this Newsletter, appear to be in the range of 40-50 ng/mL (approximately 100-125 nmol/L).

VITAMIN D AND COLORECTAL CANCER—A MULTIETHNIC STUDY

A prospective cohort study (follow-up study) conducted by researchers at the University of Southern California and the University of Hawaii examined the relationship between vitamin D intake and colorectal cancer (CRC) in five ethnic groups: African Americans, Native Hawaiians, Japanese Americans, Latinos, and Whites. Vitamin D intake was ascertained from a food and supplement questionnaire and follow-up was for an average of 7.3 years. Vitamin D intake ranged from< 85 to ≥ 600 IU/day for men and < 70 to ≥ 500 IU/day for women when the intake was stratified into quintiles (five groups). For men with the highest total intake (≥ 600 IU/day compared to the lowest intake, the risk of CRC was approximately cut in half. While this result was statistically significant, for women the smaller protective effect was not. For calcium intake, a significant protective effect was observed for both men and women.

Park, S-Y. et al. Calcium and Vitamin D intake and the Risk of Colorectal Cancer: The Multiethnic Cohort Study. ***American Journal of Epidemiology****, 2007, electronically published ahead of print, Jan. 10.*

Editor's Comment: This study did not measure serum 25-hyderoxyvitamin D levels nor was any attempt made to examine potential confounding from sun exposure, which in the areas in question is an important source of vitamin D all year. Thus the intake from food and supplements is on top of that generated by the sun, which confound the results. The need to correlate CRC incidence and actual vitamin D status obtained from 25-hydroxyvitamin D levels seems obvious. It also seems clear that once this is done, vitamin D emerges as very significant for primary protection against CRC, but only if the total intake from food, supplements and sunlight results in levels of the metabolite 25-hydroxyvitamin D well in excess of 30 ng/mL and that supplementation of 1000-2000 IU/day is thus indicated. When the study of Gorham *et al* is compared with the studies that found no or small benefit, of which only two of the most recent are discussed, it is clear that there is a strong dose dependence and that intake from food, a poor source, and from low levels of supplementation such as is recommended by various guidelines (e.g. 400 IU/day) does not for most individuals raise their vitamin D status to a protective level in this context. For those who wish to make a case for the position that vitamin D does not reduce the risk of CRC, there are ample studies published in high-profile journals and the opportunity for citation bias is great. However, it appears that now enough is known to allow one to dismiss these negative studies on the grounds that the intake of vitamin D was insufficient, the results confounded, or the study design flawed. When overall vitamin D status is examined rather than estimated from food and supplement intake, a quite different picture emerges—one of dramatic benefit. Thus Gorham and colleagues are to be commended for their meta analysis which brought together five such studies and provided the statistical power to yield convincing evidence and as well, guidance as to indicated supplement levels.

FISH CONSUMPTION DURING PREGNANCY—INTELLECTUAL AND SOCIAL DEVELOPMENTAL BENEFITS FOR THE CHILD

In 2004 the U.S. government issued guidelines regarding fish consumption for pregnant women. The advice was to limit the consumption of seafood to 340 g per week, the objective being to limit the intake of neurotoxins that might adversely affect the fetus. But optimum fetal neurodevelopment depends on specific nutrients derived from dietary sources and the essential omega-3 fatty acid docosahexaenoic acid (DHA) is not only one of the most critical, but seafood is the major source. A

study has just appeared in the journal *Lancet,* which examines an important question, i.e. is the limitation of seafood intake to less than 340 g/week during pregnancy potentially detrimental to fetal neurodevelopment? In this study, Hibbein *et al* report on the results of follow-up study based in Bristol, UK. Over 14,500 pregnancies were involved and 13,988 children survived for at least 12 months. Questionnaires were used during pregnancy and the children were followed for 6 months to 8 years. The object was to assess developmental, behavioral and cognitive outcomes as they related to the level of seafood consumption during pregnancy. About 85% of the eligible expectant mothers participated. Questionnaires were used periodically to determine development and behavioral characteristics; the intelligence quotient (IQ) at age 8 was determined for 5449 children.

After adjustments for confounding, maternal seafood intake during pregnancy of less that 340 g/week was associated with increased risk of the children in question being in the lowest fifth for verbal IQ and in addition there was a significant trend to greater risk as the seafood consumption declined to zero. Low maternal seafood intake was also associated with increased risk of suboptimal outcomes for development in the areas of social behavior, as well as motor, communication and social development, and for each outcome the lower the fish intake the higher the risk for suboptimal development. The authors conclude that maternal seafood consumption of less than 340 g/week did not protect children from adverse neural development, and that in fact intake exceeding 340 g/week (12 oz or 3/4 lb) resulted in beneficial effects on child development. Thus the authors conclude that following the guidelines could actually be detrimental, and that the results suggest that the benefits from eating more than 340 g of seafood per week outweighed the risk of harm from exposure to trace contaminants.

Hibbein, J. R. et al. Maternal Seafood Consumption in Pregnancy and Neurodevelopmental Outcomes in Childhood (ALSPAS study): An Observational Cohort Study. ***Lancet,*** *2007, Vol. 369, Feb 17, pp. 579-84.*

Editor's comments: The guideline of 340 g/week of fish can be traced back to a study published in 2003 (*Risk Analysis,* 2003; 23:107) which examined the neuropsychological consequence of *in utero* exposure to organic mercury (methyl mercury), the form found in fish. The study was based on data collected in the Faroe Islands, Seychelles Islands and New Zealand. The analysis was complicated, but the bottom line was a finding that the safe upper limit for mercury was estimated to be 0.1 micrograms per kg of body weight per day. If we assume a 70 kg woman (154 pounds) then this translates into 7 micrograms /day of mercury from fish. In the paper on fish consumption and risks discussed in the last Newsletter, one can find data on the mercury content of fish, and the recommended ones such as salmon have levels below 0.05 micrograms per gram whereas trout comes in at 0.07. Taking 0.05 micrograms per gram of fish as an assumed level, 340 grams of fish per week would be equivalent to an intake of 17 micrograms of mercury per week or 2.4 micrograms per day. This is about a third of the allowable 7 micrograms per day, and in addition the guideline number appears, from the data in the 2003 study, may be conservative. Thus the finding by Hibbein *et al* that fish consumption above this guideline limit appeared to carry no significant risks in the context of neurological development is understandable. One can also question the applicability of the 2003 study to North American and European populations, based as it was for the most part in underdeveloped areas with the associated potential for unrecognized confounding. The Government of Canada has just set an upper limit of 1 part per million of mercury for fish sold over the counter. Species, which may exceed this limit, are shark, swordfish, fresh and frozen tuna, marlin and orange roughy. This list includes fish frequently offered in restaurants. The level of 0.05 micrograms/g is only 5% of this level. Restricting fish consumption to species low in mercury and high in omega-3 fatty acids involves eating, for example, salmon, herring, sardines or trout. A compromise is of course available—purified fish oil capsules. Someday governments may require mercury content to be given on the label of all canned fish, a move which would be helpful in selecting canned tuna. In this context it is also of interest that selenium appears to some extent to neutralize the adverse effects of mercury. While fish also contains selenium, some may wish to consider supplementation. For men, there is the added incentive provided by a large trial of selenium and vitamin E for the primary prevention of prostate cancer. That study is using 200 micrograms of selenomethionine per day.

LATEST GUIDELINES FOR NONSTEROIDAL ANTI-INFLAMMATORY DRUGS – NSAIDS FOR PAIN RELIEF

After Merck announced the worldwide withdrawal of Vioxx in 2004, there has been a steady erosion of confidence in the safety of both the specific COX-2 inhibitors such as Celebrex (Celecoxib), the only coxib on the market in the U.S. at present, and the prescription and over-the-counter nonsteroidal anti-inflammatories such as diclofenac, ibuprofen (Advil) and naproxen (Aleve). At issue are not the well known gastrointestinal problems that are associated with these inhibitors but the increase in risk of cardiovascular (CV) events. The American Heart Association has just released an update of guidelines for the use of these painkillers. The paper first summarizes what is currently known about CV risks. For Celebrex vs. a placebo, the risk of a heart attack is reported to be about 5 events per 1000 person years compared to about 2 events per 1000 person years. For the nonselective NSAIDs, the results are expressed as relative CV risks. When comparison was with a placebo or no treatment, Diclofenac exhibited statistically significant relative risks from 1.40 to 2.40 (40% and 140% increase in risk) depending on the type of trial and the event, but in all cases the number of trials was large. For ibuprofen the only risk found was for individuals who had already experienced an acute heart attack (MI), where significant relative risks of 1.25 and 1.50 were found for recurrent MI or actual mortality. When naproxen was compared with a selective COX-2 inhibitor, a significant protective effect was reported from a meta-analysis of randomized controlled trials (relative risk, 0.64 or a 36% reduction).

The basic philosophy of the guidelines is that for patients whose pain is not controlled by non-pharmacological approaches one starts with the lowest dose of the least risky analgesic and then progresses to more risky solutions if symptoms are not adequately controlled. Thus the first choice includes acetaminophen, ASA (aspirin), so-called non-acetylated salicylates (e.g. magnesium or sodium salicylate) or prescription narcotic analgesics such as tramadol with the qualification that the narcotic based painkillers should be considered only for short-term use. At the next level are the non COX-2 selective NSAIDs. Based on the data mentioned above, naproxen appears to be the preferred choice according to the guidelines if the concern is CV events. However, there is the ever-present risk of gastrointestinal bleeding with long-term or high dose therapy using aspirin or other NSAIDs. As regards the possibility of using a COX-2 inhibitor if nonselective NSAIDs fail to provide adequate relief, the guidelines emphasize that the risk associated with these analgesics is greatest in patients with prior history of or at high risk for CV disease, and that for these individuals, the use of COX-2 inhibitors should be limited to those for whom there is no appropriate alternative and then only at the lowest dose and for the shortest duration necessary. The paper also points out that more data are needed on the CV safety of conventional NSAIDs and until such data is available, the use of any COX inhibitor (selective or non-selective), including those available over the counter, for long periods of time should only be considered in consultation with a physician.

Antman, E. M. et al. Use of Nonsteroidal Antiinflammatory Drugs. An Update for Clinicians. ***Circulation****, 2007, Vol. 115, electronically published ahead of print.*

Editor's comment: It is becoming clear that for someone with a severe pain problem such as is associated with rheumatoid or osteoarthritis or severe back pain has no completely safe solution within the framework of pharmacologic treatment and must seek professional help in maximizing the benefit and minimizing the risk. However, there are other potential solutions such as the long-chain omega-3 fatty acids (e.g. from fish oil) which are natural antiinflammatory substances and also the natural substance turmeric (curcumin). The reader is referred to the October, December-January and February issues of the Newsletter for recent studies concerning the analgesic use of these substances, which incidentally appear to be essentially free from adverse side effects. Given the gastrointestinal and cardiovascular side effects of non-narcotic pharmacological pain relief, the bottom line appears to be—you can't win.

NSAIDS FOR PRIMARY PREVENTION OF COLORECTAL CANCER

Evidence has accumulated over the years suggesting that aspirin and nonsteroidal anti-inflammatory drugs provide some protection against the development of colorectal cancer, and this has been described as an added advantage when these drugs are used for analgesic purposes. However, there is the question of whether or not these drugs, many of which are available over-the-counter, should be taken for primary prevention when there are no other indications for their use. The U.S. Preventive Services Task Force has just issued recommendations concerning this matter. This is an important question since colorectal cancer is the third most common type of cancer in both men and women and, as mentioned above, the second leading cause of cancer-related deaths in the U.S.

The vast majority of colorectal cancers arise from adenomatous polyps (ordinarily initially benign growths of abnormal cells on the inner wall of the colon). These are frequently removed during colonoscopy. The USPSTF recognizes (a) that there is fair to good evidence that aspirin and NSAIDs when taken at higher doses and for longer periods reduce the risk of polyp formation; (b) that there is good evidence that low-dose aspirin does not lead to a reduction of CRC; (c) that there is fair evidence that aspirin at higher doses than recommended for prevention of CVD and as well NSAIDs are associated with a reduction in the incidence of CRC: (d) that there is fair evidence that aspirin use over longer periods may result in a reduction in the incidence of CRC; (f) that there is poor quality evidence that aspirin and NSAID use reduces CRC mortality. On the other side of the ledger, aspirin increases the incidence of gastrointestinal bleeding in a dose-related manner and may increase the risk of hemorrhagic (bleeding) stroke. NSAIDs also increase the risk of gastrointestinal bleeding and in addition, renal impairment, especially in the elderly. Overall, the USPSTF concluded that the harms outweigh the benefits of aspirin and NSAID use for the primary prevention of CRC. Their report also points out that the American Cancer Society currently does not recommend aspirin or NSAIDs for the prevention of CRC because of potential side effects, especially gastrointestinal bleeding. Other high profile organizations offer no recommendations.

U.S. Preventive Services Task Force. Routine Aspirin or Nonsteroidal Anti-inflammatory Drugs for the Primary Prevention of Colorectal Cancer. Recommendation statement. ***Annals of Internal Medicine****, 2007, Vol. 146, No. 5, pp. 361-5.*

Editor's Comment: The USPSTF is, in the opinion of the Editor, very conservative, but in this case it seems that their recommendation should be seriously considered. In sharp contrast to aspirin and NSAIDs, the protective aspect of high serum levels of 25-hydroxyvitamin D discussed above is apparently accompanied by no significant side effects and appears to offer a much safer alternative to aspirin and NSAIDs for someone concerned about primary prevention of CRC. Supplements or dietary interventions frequently seen suggested include fiber, calcium, curcumin and multivitamins.

NEWS BRIEFS

THE METABOLIC SYNDROME AND ERECTILE DYSFUNCTION

A recent study from Austria has examined the relationship between the metabolic syndrome (MBS) and erectile dysfunction (ED) in men aged 30-69. The International Diabetes Foundation definition of MBS described in the April Newsletter was used. It was found that the waist-to-hip ratio and MBS itself were both independently associated with a decrease (unfavorable direction) in an international index score used to judge the severity of ED. When the results were stratified by age, moderate to severe ED was correlated with MBS only in men 50 years of age or older. The authors compared their results with earlier studies which found a correlation with younger men as well and attribute this to the use of a different definition of MBS (NCEP definition). They also suggest that the relationship between MBS and ED involves vascular problems, which are a common characteristic of individuals with MBS. Such a view is also consistent with the observation that ED shares major risk factors with atherosclerosis, hypertension, diabetes and elevated blood lipids.

Heidler, S. Is the Metabolic Syndrome an Independent Risk Factor or Erectile Dysfunction? ***Journal of Urology****, 2007, Vol. 177, pp. 651-654.*

METABOLIC SYNDROME AND ALZHEIMER'S DISEASE

The metabolic syndrome is characterized by a clustering of abdominal obesity, hypertension, high fasting glucose and high blood levels of triglycerides coupled with low levels of HDL cholesterol. The syndrome is associated with increased risk of cardiovascular disease and type 2 diabetes. Since it has been hypothesized that the development of Alzheimer's disease has a significant vascular component, a link between the metabolic syndrome and this disease seems likely but has not been established. This issue has now been addressed by Razay *et al* in a case-control study published recently in the *Archives of Neurology*. Fifty consecutive patients diagnosed with Alzheimer's disease in memory disorder clinics in Australia and England were matched with 75 cognitively normal controls. The NCEP definition of the metabolic syndrome was used (See the April Newsletter for a discussion of definitions of this syndrome). The metabolic syndrome was associated with over a 3-fold increase in risk of Alzheimer's disease and if the hypertension component of the definition was excluded, the risk was instead 7-fold higher. Both results were statistically significant and were adjusted for age, gender and location. Compared with controls, the patients with Alzheimer's disease had significantly larger mean waist circumference, higher mean blood levels of triglycerides and glucose, and lower levels of HDL, but they had lower mean systolic blood pressure. The authors comment that the increasing prevalence of the metabolic syndrome coupled with the ever-increasing number of elderly individuals will have serious implications for health care, and that steps to reduce the risk of the metabolic syndrome could have a role in the prevention and treatment of Alzheimer's disease.

Razay, G. et al. The Metabolic Syndrome and Alzheimer Disease. ***Archives of Neurology****, 2007, Vol 64, January, pp.93-96.*

ANALGESICS AND HYPERTENSION

A study has just been reported which adds considerable to the evidence that the use of non-narcotic analgesics such as acetaminophen, aspirin and NSAIDs such as ibuprofen is related to the risk of developing hypertension. This study by Forman *et al* from Harvard utilized data from the male health professionals enrolled in the ongoing Health Professionals Follow-up Study. Men with prevalent hypertension or those using blood-pressure lowering drugs were excluded. The final study sample included over 16,000 men. When compared to non-users, acetaminophen use 6-7 days per week resulted in a 34% increase in risk of hypertension. The same comparison for NSAIDs and aspirin yielded increases of 35% and 14%, respectively. These results are quite similar to those found for women in the Nurses' Health study, and in addition, higher risks were found in the Nurses' Health Study II which enrolled considerably younger women. The authors discuss various mechanisms they regard as plausible for explaining these results even though there were differences in the mode of action of the analgesics studied. The conclude that given the widespread use of these pain killers, their ability to increase the risk of hypertension may have important public health implications

Forman, J. P. Frequency of Analgesic Use and Risk of Hypertension Among Men. ***Archives of Internal Medicine****, 2007, Vol 167, Feb 26, pp. 394-99.*

SOME FINAL THOUGHTS

A theme that has and probably always will be present in this Newsletter is statistical significance, which in rough terms means that there is less than a 5% chance of a result in fact being the null result, i.e. no effect. Researchers achieving results of statistical significance are able to publish their work with a positive spin in the title, and frequently in a higher status journal than if the entire study showed no effect. Publications are the feedstock that generate research grants, promotions, fame, and as well, research funds and other financial support from Big Pharma. The war on vitamins is somewhat different, where null results confirm and reinforce in the minds of some what they have come to believe and appear to merit publication in journals of the highest profile. But there will always be a number of nagging questions. First, are the statistically significant results also clinically significant? That is, is the effect large enough to really matter in clinical practice or is it merely a scientific curiosity which helps to get a paper published and perhaps generates a hypothesis, but is irrelevant to the patients who might be concerned. Second, have confounding factors been overlooked, omitted, or was the data necessary for adjusting results simply lacking. In other words, if a more realistic and comprehensive adjustment was performed for factors that might distort the results, would the statistically significant results persist? The classical example of correcting for confounding is adjusting results of the influence of alcohol consumption on lung cancer by taking into account smoking. Finally, in the type of study where cases are compared with selected controls (the case-control study), there will always be questions about the controls not being strictly comparable to the cases, That is, were there factors not considered in selecting controls that ultimately distorted the data? This is just a short list. There are always many questions that can be raised, and authors generally discuss them in the almost mandatory section of their papers which deals with "the weaknesses and limitations of this study." Thus the results of studies which can influence clinical practice arise from what might be described as a rather imperfect and inexact science, a science that not infrequently produces confidence shaking flip-flops with much media attention where flawed but universally accepted studies are overthrown by better, larger, and more carefully adjusted studies. But even these will have their nagging questions. Confidence grows, however, when many studies are consistent, although consistency between a set of flawed studies does not resolve the problem that they are flawed! And it helps if the effect is so large that any adjustment the authors make and as well all the weaknesses they can think of have little impact. It is into this jungle that the patient is being led, mostly out of necessity, by both the medical profession and the pharmaceutical industry. The subject of the following *Perspective* relates to one aspect of navigating this jungle.

ABSOLUTE VS. RELATIVE RISK

Informed Decision-Making With Special Reference To Chemotherapy Associated With Breast Cancer

While many individuals with serious health problems are confronted with options and must make decisions, accepting or rejecting cancer treatment almost seems to be in a class by itself, mainly because accepting treatment puts one at risk of side effects that can have a profound impact on the quality of life. On the other hand, accepting treatment may result in a considerable disease free period or even what amounts to a cure. The decision making process is thus of great interest, as is the question of what data the patient should receive or request and how it is to be interpreted. At one extreme, the patient places himself or herself completely in the hands of the treating physician, and merely accepts without questioning the advice and the justification. Some would consider this realistic given that the physician is the expert and the patient may know little or nothing about the natural history of the disease in question or the factors involved in prognosis if treatment is accepted or rejected. At the opposite extreme is the patient who taken the trouble to become self-educated and is to some extent capable of understanding the options and the underlying clinical data, at least to the extent that an informed decision is theoretically possible. For the former case, the physician may attempt to provide a basis for the patient's decision-making process by taking the time to provide background information and by helping the patient understand the options and where they come from. At the opposite extreme, the patient may find that unless some care is used in how the discussion proceeds, antagonism may develop as the physician becomes frustrated with the patients attitude and insistence on probing deeply into risk-benefit analysis. Of course, in

some situations there are essentially no options, but in some types of cancer there are points in time reached where options exist which offer quite different avenues of treatment. This perspective concerns this latter situation.

Central to this whole process is how the risk-benefit picture is presented, i.e. the spin attached to the presentation of clinical trial results. For example, if chemotherapy is being discussed in the context of post surgical cancer recurrence, i.e. recurrence-free survival for say 10 years, then the benefits of chemotherapy can be presented in terms of the percentage change in the percent surviving without recurrence due to chemotherapy, or the actual absolute change in this percentage, or the absolute survival benefit. Another way of looking at such data is to calculate the number of patients needed to be treated in order to achieve the survival target in one patient. Many patients may have trouble relating to data presented in terms of "numbers needed to treat." Another issue is the patient's comfort level with clinical results presented as numbers, since there are some who do not relate well to probabilities or even percentages. Some physicians use graphical means to overcome this obstacle, e.g. pie charts or other visual aids. Judging by the recent flurry of papers on "communication" in this context, it appears well known in the medical community that different ways of presenting the same data can have a huge impact on the patient's perception of benefit. In what follows we will assume that arguments based on numbers and percentages are appropriate.

Let's examine an example based on an article by Dr. G. Sonpavde which was recently published in the *Journal of Clinical Oncology* [1]. A hypothetical patient has had a modified mastectomy for the removal of a 2-cm tumor which was estrogen-progesterone positive on pathological examination. She was older than 50 years, and there was no evidence of lymph node involvement. By using a computer program developed at the Mayo Clinic, her doctor would have been able to determine that if no additional treatment was given she would have an 81% chance of recurrence-free survival (19% chance of recurrence of the cancer) over the next 10 years. If Tamoxifen was given for 5 years, the risk would decease to 85% recurrence free survival (15% chance of recurrence) whereas chemotherapy would further reduce the risk to 13% chance of recurrence for an 87% chance of recurrence-free survival. This data can be presented to the patient in several ways. Dr. Sonpavde does not use the term "spin" but the following seems to capture the essence of his discussion of this hypothetical case history.

Spin A. Tamoxifen will reduce the 10-year risk of recurrence by 21% (i.e. 100X4/19) whereas chemotherapy will reduce the risk by 32% (i.e. 100X6/19). No mention is made of the 19% vs. 15% vs. 13% numbers, which were the source of the 4 and 6% changes used to get the 21% and 32%. The benefit of 32% reduction in the risk looks very attractive indeed.

Spin B. Tamoxifen will reduce the 10-year risk of recurrence by 4 percentage points (19% to 15%) and chemotherapy by an additional 2 percentage points (15% to 13%).

Spin C: The absolute recurrence survival benefit associated with tamoxifen vs. no post-surgical treatment increases by 4 percentage points from 81% to 85% whereas chemotherapy increases this benefit by another two percentage points to a probability of 87%, i.e. a positive way of putting the data by emphasizing survival, but still based on absolute numbers.

Spin A uses the percent change in the relative risk where Spin B and C describe the benefit in absolute terms. There can be a huge difference in the patient reaction to these two points of view, especially when there are severe side effects associated with treatment and an attempt is being made to sort out the risk vs. benefit. Some women would decide that a gain of 2 percentage points in recurrence-free survival offered in this case by chemotherapy over tamoxifen therapy is not enough to make chemotherapy worthwhile, and others might decide that 4 percentage points was not enough gain to justify tamoxifen treatment over doing nothing. But a 32% reduction in the risk—that can be compelling, *and yet we are taking about the same data!* In addition, there are in fact also some interesting studies where it was demonstrated that drug company representatives frequently use Spin A when presenting clinical trial outcomes while promoting their products to physicians and that when the use of only Spin A was compared with other ways of presenting clinical trial results, the latter resulted in much less enthusiasm for the intervention [2].

There are other aspects to this problem. It takes time for the doctor to explain the different viewpoints associated with Spin A, B and C, and in some health care systems, there is very little financial gain from this endeavor. The physician also runs the risk of not being able to provide therapy in which he or she believes. It also may not be fully appreciated by patients that the numbers used to generate these risk estimates are themselves average or mean values with an associated uncertainty. Some will obtain greater benefit, some will obtain lesser benefit from an intervention than indicated by the median or average outcomes, and when the benefit is small, as measured in absolute terms, for those unlucky enough to obtain lesser benefit than the average this can mean no significant benefit at all but still exposure to the spectrum of potential side effects.

In the case of Dr. Sonpavde's hypothetical patient, she had already had half the planned chemotherapy, had been hospitalized for pneumonia, perhaps because of an impaired immune system due to the chemotherapy, and decided not to complete the treatment after hearing, *for the first time*, spins different than Spin A. She decided just to take tamoxifen—a gain of two additional percentage points predicted for chemotherapy was for her insignificant justification. When her original decision was made she was unaware of Spin B and C. Dr. Sonpavde points out that this scenario, while hypothetical, has occurred several times in the clinic with which he is associated.

There are actually studies that attempt to determine reactions to the spin given clinical trial results. In a recent study the surrogate "patients" were pre-clinical medical students who were presented with vignettes related to a hypothetical cancer diagnosed in their mothers and asked to decide whether or not to endorse chemotherapy based on risks and benefits and then to indicate their preferences for the methods of communicating benefits based on the above spins. Participants preferred the absolute survival benefit method (Spin C) over relative risk reductions (Spin A) or negatively framed methods such as relative or absolutes risk reductions [3].

Another example can be developed from data derived from trials of tamoxifen for the primary prevention of breast cancer in individuals judged to be at high risk [4]. In one often quoted large randomized, placebo controlled trial [5], 6599 women received a placebo and 6576 received tamoxifen for 5 years. In the placebo group, 175 (0.68%) cases of breast cancer were observed, whereas in the tamoxifen group, the number was 89 (0.34%). The percentage change in these relative risks was thus about 50%, an impressive risk reduction. But the absolute risk reduction was 0.34% i.e. 0.68 minus 0.34 or about 1/3 of a percentage point, a far cry from 50% that one sees quoted in the literature [6]. But judging from the number of cases in the placebo group compared to the size of the group 175 vs. 6599, the intervention was in fact undertaken with a cohort where the disease risk was extremely small, and in fact in the intervention group only 86 cases (175-89) were prevented whereas 6576 women were put at risk of the side effects of the drug.

This is a nice example where if only the change in relative risk, in this case 50% is provided to a patient for justification of treatment and what is actually a very small absolute beneficial effect is not discussed, the persuasive aspect of this spin can be very strong indeed. But this drug intervention increases the risk of endometrial cancer, stroke and pulmonary embolism. Bergh [7] sums the matter nicely: tamoxifen therapy used on over 14,000 women, when the treated vs. the untreated were compared, resulted in 53 vs. 22 endometrial cancers, 118 vs. 62 thromboembolic events, and 59 vs. 39 strokes. While again, these are small effects, and they could be magnified greatly by expressing them as percent changes in relative risk, nevertheless, they represent morbidity and perhaps mortality which must be balanced against the very small absolute decrease in risk of developing breast cancer. Thus a women considering tamoxifen intervention as primary prevention due to high risk (family history, gene mutations, etc) might want to consider asking for the latest results of risk reduction as they apply to her clinical presentation, and as well the most recent data on side effects, *both expressed in absolute terms*.

It is also interesting that both this study and other similar studies found that the so-called high-risk populations in fact had what seems to be a rather low 5-year or even 10-year incidence of about 1%. But in a study recently reported [8] where the cohort was estimated to be at a four-fold increased risk based on family history, the rate of cases in the placebo group was only 1.5%. Incidentally, in this study there was no effect of tamoxifen.

The purpose here is certainly not to discuss the pros and cons of tamoxifen or chemotherapy, but rather to alert readers to the difference between relative and absolute benefit and the potential for clinical trial results being presented in a manner that perhaps exaggerates the benefits of an intervention that carries heavy side effects.

Another perspective is overall survival (as compared to recurrence-free survival), which is an appropriate and frequently used endpoint in studies related to metastatic cancer. This turns out to be an interesting way of examining the effectiveness of chemotherapy for adult malignancies. In a recent paper by Morgan *et al* [9] it was reported that cytotoxic chemotherapy for adult malignancies contributed only on average a 2.1% survival advantage in the U.S. [9]. For breast cancer only 1.4% of 5-year survivors could attribute their survival to chemotherapy. Thus patients need to inquire as to the most recent data when attempting to access the risk-benefit associated with chemotherapy vs. no treatment when confronted with metastatic breast cancer where the only option generally offered is cytotoxic systemic therapy.

Cholesterol-lowering drug trial results present a similar situation with regard to spin. An interesting analysis appeared in *The American Journal of Cardiology* in 1998 and examined three ways of presenting the results of three large cholesterol-lowering drug trials. Relative risk reductions for various cardiovascular endpoints ranged from 43% to 19%, but for many endpoints the absolute reduction was less than 10 percentage points. Two studies found large and impressive relative risk reductions for cerebrovascular attacks of 37% and 32%, but the corresponding absolute risk reductions were 1.6 and 1.2% respectively [10]. Several examples of this can be found in the March issue of the Newsletter where the use of cholesterol lowering drugs was examined.

Finally, there is the so-called “Number Needed To Treat” way of presenting the results of a clinical trial. It is not obvious, but the NNT is simply the reciprocal of the absolute relative risk, i.e. the number 1 divided by the difference in the percentages experiencing an endpoint event in the placebo and treatment groups. For example, consider a trial where 200 are given a placebo and 200 get a drug. The endpoint is a heart attack. In the placebo group, there are 40 events (20%), in the treatment group 32 events (16%), i.e. 4 percentage points difference. Thus by treating 200 individuals, 8 events were prevented. By a simple proportion argument, 8/200 = 1/25, or the NNT is 25, which is also the reciprocal of the absolute percentage difference, i.e. 1/(4/100). The problem with the NNT is that some will have difficulty relating to such numbers as 25, 50, 75 or, say 150. The conventional wisdom seems to be that 75 or 150 are large numbers that should cause one to question the wisdom of intervention, but this is of necessity arbitrary.

While the above perspective may appear to be anti-chemotherapy, it is merely an attempt to encourage rational analysis based on the best evidence available. There is no doubt that for some cancers, chemotherapy offers very significant survival advantages. However, as suggested by Morgan *et al*, in adult solid tumors the benefits may be marginal, and individuals with cancer need to consider acquiring detailed information from their physicians about absolute benefits predicted for their particular clinical presentation and proposed therapy. The objective of this perspective has been to alert readers to the importance of absolute risks vs. relative risks, and to inform as to the importance of the spin associated with the presentation of clinical trial data during the discussion of risk vs. benefit.

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The Prostate Monitor
Editor: William R. Ware, PhD

Reviews of recent studies from the peer-reviewed literature

NUMBER 3	May 2007	1st Year

Most men will have at least some issues during their lifetime relating to urinary problems that herald prostate enlargement. Today, one of the most common events calling attention to the prostate is when a man is offered a PSA test during a physical check-up. In many cases, it will be very strongly recommended. It is safe to say that almost all men have no understanding as to what this really entails in terms of cancer diagnosis, false positives, false negatives, unnecessary biopsies, or even what the number means that comes back from the lab. Then there is the man who has been diagnosed with prostate cancer. Unless he has prepared himself with fairly extensive reading, he is not in a good position to digest and evaluate the information his doctor will present concerning the validity of his diagnosis, the seriousness of the disease, or his treatment options, and yet the decision he makes can have an important impact on his future quality of life. Then there is the man who has had what is quaintly called definitive treatment, generally involving surgery or radiation. But not infrequently evidence develops that the cancer has come back, or to put it another way, it was never entirely destroyed. Again, there are options and again the decision as to what to do can impact a man's quality of life. For the intelligent, educated patient, comfort and satisfaction with decisions concerning these and other aspects of prostate health and disease will depend on knowledge about the actual details of the pros and cons of the options that permeate the treatment of prostate disorders. In fact, prostate cancer may well be unique among the solid adult tumors as regards the number of options that exist at any stage in the whole saga from diagnosis to cure or palliation.

*The Prostate Monitor attempts to keep men up to date concerning developments in the various areas of great concern. This section of the Newsletter also supplements our book**, The Prostate and Its Problems**. Our intention in writing this book was that a man could pull it off his bookshelf as prostate problems arise or a diagnostic result is presented to him as positive and obtain a quick education in whatever aspects confront him, and at the same time the book was intended to provide a valuable resource for wives who sooner or later are going to become involved in discussions about a prostate problem or are going to have to live with the consequences of a decision regarding therapy. However, we believe this book is unique in the extent to which it also discusses prevention and the impact of supplements, diet and lifestyle in the context of prostate problems. For the man who as yet has no symptoms of these problems, he should nevertheless be aware of the importance and potential of prevention, given the serious and even devastating impact that prostate enlargement or prostate cancer can have on his life and the high probability that one or both of these disorders will afflict him. The Prostate Monitor will also attempt to keep readers up to date on matters regarding prevention, but we refer them to the chapters on prevention for comprehensive information.*

In this issue we concentrate on what happens after treatment failure, i.e. recurrence or evidence that the primary treatment failed to eradicate the cancer. In particular the problem of an increasing PSA with no symptoms or indications of metastasis is discussed. This is a situation in which many men will find themselves and we discuss recent guidelines and various aspects of hormone treatment, the next step after exhausting both surgical and

radiation treatment options. Hormone therapy is also used as primary treatment when surgery or radiation is judged unwise. This is discussed in some detail in Chapter 7 of our book.

Wishing you continuing good health,

William R. Ware, PhD, Editor

You can order *The Prostate and Its Problems* at http://www.yourhealthbase.com/prostate/book.htm

HORMONE TREATMENT OF PSA-ONLY RECURRENCE AFTER PRIMARY THERAPY OR SALVAGE RADIATION THERAPY

This is an area that suffers from a lack of studies that apply directly to PSA-only recurrence in the PSA era and have the design to successfully address the relevant and important questions. Thus management is controversial. It is also an area of great interest and concern to many prostate cancer patients faced with a rising PSA who have exhausted their surgical and radiation options. Typical scenarios that bring an individual to the point in question are PSA failure after radical prostatectomy or radiation therapy or after the failure of salvage radiation therapy for PSA failure following surgery. Recurrence in this context is evident only from a rising PSA, i.e. there are no clinical manifestations of metastatic disease. Worldwide, the number of individuals who find themselves in this situation is huge. Ryan and Small have just summarized recommendations for therapy under these circumstances [1]. These recommendations are based on extrapolations from existing studies and represent the consensus derived from a panel at a recent meeting (Innovations and Challenges in Prostate Cancer: Recommendations for Defining and Treating High Risk Disease) [2] The only clinical parameter claimed to be significant in this context is the PSA doubling time (PSADT). The treatment recommendations are as follows.

PSADT less than 6 months

Prognosis: Median 4.5 years to bone metastasis.
Recommended therapy: Androgen deprivation therapy. Other possibilities—intermittent androgen blockage, combined (total) androgen blockage with an antiandrogen plus LHRH agonist (preferred). LHRH monotherapy acceptable. Consider salvage radiation therapy if appropriate.

PSADT between 6 and 12 months

Prognosis: A 70% 5-year metastasis-free survival probability.
Recommended therapy: Intermittent androgen deprivation therapy or an antiandrogen plus 5α-reductase inhibitor, e.g. flutamide plus finasteride (Proscar). Consider salvage radiation therapy if appropriate.

PSADT greater than 12 months

Prognosis: Greater than 80% probability of being metastasis-free at 5 years and 90% probability of 5-year prostate cancer specific survival.
Recommended therapy: No immediate therapy indicated. Lifestyle modifications may be appropriate and androgen deprivation therapy can be considered for highly anxious patients. Consider salvage radiation therapy if appropriate.

These consensus guidelines apply to cases of PSA-only failure after surgery or radiation therapy. Thus to apply them to the case of failure of salvage radiation therapy after recurrence post radical prostatectomy represents an extrapolation. This is due to the lack of PSA-era studies that address this particular population. Also, the cut-offs

of 6 and 12 months for doubling times appear to be educated estimates given that various studies have use different cut-offs, including ≤ 3 months, to identify aggressive cancer including aggressive systemic cancer that many experts regard is benefiting from immediate hormone therapy [3]. A constant PSA doubling time implies an exponential increase which means that a graph of PSA vs. time curves upward. Those inexperienced with the mathematics involved can obtain a calculated doubling time from the Memorial Slone-Kettering prostate website (Google: Memorial Slone Kettering prediction tools, select prostate sidebar link, click "open calculator", and select PSA doubling from additional tools on the nomogram page.). However, in many cases, an approximate estimate made simply by looking at the numbers may be adequate. In the case of recurrence after radiation therapy, the rise will be from the minimum PSA reached some time after treatment, but patients having had radiation therapy may experience a "bounce" in PSA months after an apparent minimum has been reached, but this is temporary. However, it can cause anxiety but the repeated measurements of PSA employed to establish a valid doubling time will generally be sufficient to differentiate the bounce from a true recurrence.

The term "androgen deprivation therapy" is in this context being used to describe surgical castration or the use of LHRH agonists (e.g. leuprolide or goserelin) or complete androgen blockage which involves adding an antiandrogen (e.g. flutamide, bicalutamide or nilutamide) i.e. combined therapy. Antiandrogen therapy used alone is also termed peripheral androgen blockage and has the advantage of avoiding a decrease in testosterone to the castrate level and associated side effects which occur with the LHRH agonists, but antiandrogen therapy has its own set of sides effects. The addition of a 5α-reductase inhibitor is a relatively new use of a drug traditionally employed to treat benign prostatic hyperplasia. See Chapter 7 of our book for a discussion of the use of 5ARIs in this context. The suggestion of salvage radiation therapy is of course for men who have had surgery and have suffered recurrence. If salvage radiation fails, then the above recommendations are probably relevant.

The paper of Ryan and Small [1] also discusses the issue of immediate vs. delayed androgen deprivation therapy. Again, there is a lack of adequate studies that directly address this issue in the context of PSA-only recurrence, but the authors cite several studies that suggest that patients at high risk (i.e. short doubling times) with no clinical manifestations of metastasis may benefit from early rather than delayed androgen deprivation therapy regardless of the prior local-treatment modality. Again, this conclusion represents an extrapolation, and it appears that the matter of delayed vs. immediate hormone therapy, and as well, intermittent vs. continuous therapy remain areas where the urologic community is divided. For those with PSA doubling times between 6 and 12 months, the Consensus Panel recommendation is for intermittent androgen deprivation therapy or using peripheral androgen blockage (antiandrogen therapy) with a 5α-reductase inhibitor, those in the lowest risk group with a PSADT of greater than 12 months may, in the panel's opinion, be appropriate candidates for observation only.

For those with PSADT between 6 and 12 months, these guidelines leave open the question of which hormone therapy to use, androgen blockage with an LHRH agonist with or without an antiandrogen, or just antiandrogen therapy with or without a 5α-reductase inhibitor. The LHRH agonists and the antiandrogens have different sets of side effects, and these are more or less additive when combined therapy is used. Thus this is not a simple matter. The decision is also made more complicated by the suggestion that the therapy be intermittent, which can relegate side effects to a less important position in the decision making process, since most will decrease or disappear during the off-treatment phase. The reader is referred to Chapter 7 of our book where the side effects are discussed in detail.

It is noteworthy that the actual PSA level reached during recurrence but before intervention, either immediate or delayed, is not included in this consensus guideline, no doubt because this is also a controversial area with limited relevant studies. In fact, one prominent expert claims to start hormone therapy only after the PSA level reaches 20 ng/mL or "there are other signs of impending trouble" ([4], pp. 412) and one study of deferred treatment which apparently is yet to provide a full report used both 1 and 10 ng/mL as trigger points for abandoning deferral [1]. As discussed in our book, individuals with advanced cancer rarely have positive scans indicating bone metastasis before their PSA reaches 40-50 ng/mL. Some perspective can be gained by considering that if one has a value of 0.5 ng/mL and the data so far indicate a doubling time of 12 months, it would take over 5 years to reach 20ng/mL and over 6 years to reach 40 ng/mL.

A very recent study from Memorial Slone-Kettering Cancer Center also highlights the importance of the PSADT prior to the diagnosis of metastasis in connection with the outcome after this diagnosis in men treated only with radical prostatectomy who have PSA-only recurrence [5]. Some patients included in the study also had salvage radiation therapy, the results of which suggested micro metastases were present prior to the salvage treatment. The study involved only 95 patients, presumably because most men with rising PSA received hormone therapy before metastasis was clinically manifest. In this study the diagnosis of metastatic disease was considered a definitive indication for starting androgen deprivation therapy. Median prostate-cancer specific survival after diagnosis was 6.6 years. The probability of 5-year survival after diagnosis of metastasis was 78% if the pre-diagnosis (of metastasis) PSADT was > 3 months and 42% if it was ≤ 3 months. [3]. Primary sites for metastases were bone (63%) and lymph nodes (36%). The mean PSA level at first documented metastasis was 46.4 ng/mL with a huge range of 2.2 to 108.5. This large range suggests that using the PSA level as a trigger of starting androgen deprivation therapy when the treatment has been delayed is not very clear-cut. The pathologic features of the primary tumor, the PSA level at diagnosis of metastasis, time to biochemical recurrence, and time from surgery to metastasis had no apparent association with survival after metastasis was diagnosed. This however should not be interpreted as meaning that post-operative factors are unimportant in predicting how aggressive and "high-grade" a cancer is. Also, D'Amico *et al* found a preoperative PSA velocity of more than 2.0 ng/mL/year was associated with a post-surgical PSADT of < 3 months, which was their criterion for high-grade disease with poor prognosis [3]. It should be noted that in the above discussion of PSA-only recurrence, the rising PSA is not being equated to the actual presence of metastatic disease.

POMEGRANATE JUICE FOR A RISING PSA

For individuals with PSA doubling times > 12 months who are on "observation" only, recent results from the University of California at Los Angeles may be of considerable interest [6]. This paper was briefly mentioned in the February Newsletter. In this study participants who had been treated for prostate cancer with either surgery or radiation had rising post-treatment PSA with a level > 0.2 but < 5 ng/mL and a Gleason Score of ≤ 7. Participants had to have enough PSA data to calculate a doubling time, no hormonal treatment prior to entering the study and no evidence of metastatic disease. In what the authors claim is the first clinical trial of pomegranate juice therapy for patients with recurrent prostate cancer; the protocol consisted of 8 ounces of pure juice daily until disease progression endpoints were reached. Data from 46 patients were used in the analysis. The study used the brand *POM Wonderful Variety* which is widely available, both pure and diluted with other juices, in North American grocery stores. After 33 months of follow-up, the mean PSA doubling time significantly increased from 15 months at baseline to 54 months. In addition, 35% of the 46 patients involved actually achieved a decrease in PSA (apparent arrested progression) during the intervention and 4 achieved a PSA decline of > 50%. The authors point out that the PSA doubling time is increasingly being seen as an important surrogate biomarker for prostate cancer mortality, and men with greater doubling times can expect longer survival. While the mechanism of action of pomegranate juice is unknown, the authors discuss possibilities such as antioxidant and prostaglandin-inhibitory actions of the polyphenols present in the juice and the ability of these polyphenols to promote tumor cell death and inhibit proliferation and invasion.

While one might think that pomegranate juice, being natural, would be totally benign, it nevertheless may present a potential risk to individuals taking various medications. Preliminary research indicates that the juice of this fruit may have similar but probably weaker effects as seen with grapefruit juice and it can also interfere with drug metabolism [7,8]. Anyone considering trying pomegranate juice who is taking any medication should check with their physician or pharmacist (or both!) to see if grapefruit juice is contraindicated and if so, consider this to apply to pomegranate juice as well. It may still be possible to try pomegranate juice if the potential drug interference is monitored since the potential benefits suggested by the above study could be very significant indeed and the drug interference minor or nonexistent.

A preliminary report on this study is discussed (page 298-9) in our book *The Prostate and Its Problems,* where a detailed discussion of PSA doubling times and recurrence after primary treatment can also be found The results of the study reported above are even more impressive than those provided in the meeting abstract quoted in the book. These results should also stimulate research into the use of this fruit juice for primary prevention and prevention of recurrence. If a pharmaceutical company had a patentable drug that could produce the above improvement in PSA doubling times there would no doubt be great excitement in the boardroom. But this study employs a nutrient available at the grocery store! Critics will of course demand large randomized placebo

controlled studies. It must also be pointed out that a decrease in PSADT may not translate into longer time to metastasis. While this has apparently never been studied, it nevertheless is a reasonable working hypothesis. Pomegranate juice has a number of other apparent health benefits. This is an interesting topic and will be covered in a future mini-review.

HORMONE THERAPY FOR METASTATIC PROSTATE CANCER

Once metastasis has been diagnosed, an obvious question concerns the benefits of hormone treatment as opposed to waiting until palliative treatment is required. Worldwide, opinions and practice regarding the use of hormone therapy (HT) under these circumstances are variable, partly because of uncertainty concerning the impact of HT on overall survival. The only randomized study was limited by interpretation problems that arose when placebo patients "crossed over" to HT and confounded the survival analysis and results. A recent study by Lu-Yao *et al* based on a U.S. cohort has attempted to address the question of both prostate cancer specific survival and overall survival with or without HT [9]. At the time this study was initiated a randomized design was not possible on ethical grounds, and instead a population cohort design was used. Only patients over 65 were included and the medical history, treatments and outcomes were obtained from Medicare and the Surveillance, Epidemiology and End Results databases. Essentially all those receiving HT were given a LHRH agonist or surgical castration. The final cohort consisted of 6098 patients diagnosed with metastatic cancer between 1991 and 1999. More than half were 75 years or older and most had aggressive disease (Gleason 8-10) and most did not have significant comorbidity. The most important result was that modern HT was associated with a 34.1% decrease in overall mortality and an approximately 13-month increase in overall survival as compared to those who were untreated until palliation was required. Median overall survival for those who received HT was 26 months. The much shorter survival times in this study as compared to those found in the Memorial Slone Kettering study discussed above may be due to the much older population, the high proportion of aggressive disease, and a time of diagnosis that was considerably further into the course of the metastatic disease due to a range of definitions of metastasis in the large databases used vs. closely following a group of patients in a single institution. Thus the most important conclusion appears to relate to the improvement of overall survival and cancer specific survival attributable to HT rather than the actual survival times.

The investigators also examined the impact of cancer grade on the response to HT. The best outcomes were with poorly differentiated disease (Gleason 8-10), with intermediate outcomes for moderately differentiated disease (Gleason 5-7) and interestingly enough, the worst outcomes for well differentiated disease (Gleason 2-4). In this latter group, treated patients were almost twice a likely to die of prostate cancer compared to untreated patients, although this result, which was not anticipated, lacked statistical significance and should be viewed with caution.

PROGNOSIS FOR HORMONE REFRACTORY PROSTATE CANCER

An unfortunate aspect of hormone therapy is that for many men it eventually stops working. This is termed *hormone-refractory* prostate cancer (HRPC). A recent study examined the PSA doubling time in the context of overall survival from the time of diagnosis of HRPC [10]. The median survival for the entire group was 15.1 months (range 0.5 to 90.5) Those with PSA doubling time of 70 days or less survived 11 months compared to 19 months for those with doubling times of more than 70 days. The authors suggest that inclusion of the PSADT in the clinical assessment might provide guidance as to those who might benefit from aggressive treatment such as chemotherapy, or be considered for experimental drug trials. Chemotherapy will be updated in the next Prostate Monitor.

Readers interested in acquiring a background in the subject of hormone therapy including how it works and what are the many issues associated with this therapy are directed to Chapter 7 of *The Prostate and Its Problems.* It will probably be a number of years before guidelines based on directly relevant clinical studies are available, especially since the impact of various hormone treatment options and protocols on overall survival is also an issue, and such studies not only need to be long-term but must also involve only patients from the PSA era, and to be really useful, need to address a multiplicity of issues of concern for those with PSA-only recurrence.

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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

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