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The feature of this issue involves the conflict between relative vs. absolute benefit or harm from interventions or actions or aspects of lifestyle. Patients need to be told if a treatment which is widely promoted as resulting in a 30-40% risk reduction in fact only benefits one patient out of several hundred treated, especially if the treatment has side effects that can potentially profoundly alter the quality of life. This subject has been a contentious issue for decades. Traditionally, readers of the reports of clinical or observational studies had to work through the tables and calculate the absolute values themselves. Those familiar with statistics could then decide if the associated number needed to treat or harm could also be correctly estimated from the data—something that required a fairly good understanding of this metric. There are signs that this situation is changing for the better, but there is a long way to go and studies suggest that some physicians are uncomfortable with carrying out detailed analysis of studies because they lack the background in epidemiology and its associated statistical basis. For the pharmaceutical industry, the relative risk reduction or benefit is an excellent marketing tool. Statistical significance should also be viewed with suspicion since the clinical significance may be negligible but the result still passes the test which itself carries a number of assumptions which may or may not be true. The highway of medical progress as well as academic advancement appears paved with odds ratios and the related relative risks or benefits and so-called confidence limits which indicate the probability of a result being due to pure chance. To some extent, experience-based judgement and wisdom have been replaced by a statistical calculation package that comes on a CD.

This issue also returns to the topic of psychiatric drugs for children. First, the new evidence of the alarming increase in ADHD is discussed. Also, when data now suggests that 50% of all children up to 18 years of age will have been diagnosed with mental disease sometime during their lifetime, why is this not considered a crisis of profound importance? Also discussed is the potential threat of the new (fifth) addition of the famous or infamous Diagnostic and Statistical Manual of Mental Disorders, the bible of psychiatric diagnosis, also called the DSM, to create a whole new definition of normal which lead to a vastly over-diagnosed and over-treated population.

The other major topic in this issue involves the latest attack on vitamin and mineral supplements. The study has been widely covered by the TV and print media. The results of a detailed analysis of the tables in the published report leads your editor to the conclusion that the study should be ignored and that it is surprising that it was even published, especially in a high-profile journal.

Recent studies regarding lifestyle and diabetes, radiation hormesis, grape seed extract, white vegetables and finally the impact of screen time on brain development are also briefly reviewed.

This issue also contains the latest Prostate Monitor.

Finally, 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 the publication of IHN. You can find the store at http://www.yourhealthbase.com/vitamins.htm.

Wishing you and your family good health,

William R. Ware, PhD, Editor

ABSOLUTE VS. RELATIVE RISK. WHY PATIENTS SHOULD DEMAND THE ABSOLUTE NUMBERS

As will become clear from the following discussion, expressing clinical trial results as relative risk reduction represents one of the greatest marketing tools in the pharmaceutical industry play book. The same applies to screening, although in a somewhat different context and as well to the manner in which results from follow-up studies are presented.

First consider an example from the famous MRFIT follow-up study of the risk associated with elevated cholesterol.[1] The results of MRFIT were presented as definitive by pointing to the result that the risk of dying from a heart attack (MI) with total cholesterol (TC) above 265 mg/dL was an impressive 413% higher than if it was below 170 mg/dL (a comparison between the first and tenth deciles). That should be enough to convince anyone! However, the percentage difference between the number of deaths from heart attack when these two groups were compared was only 1% (1.3% vs. 0.3%). Thus cholesterol as a risk factor did not seem to make any difference as regards CHD mortality to about 99% of the subjects with either very elevated cholesterol or very low cholesterol during 6 years of follow-up. Furthermore, almost all those in the high cholesterol group had familial hypercholesterolemia, a rare inherited disease known to impact CHD mortality in a number of ways independent of blood lipids. Nevertheless, cholesterol was quickly accepted as a major risk factor for heart disease and even cardiovascular disease in general, and dietary cholesterol, while having a significant influence on serum levels in only a very small fraction of individuals, was demonized and this became a significant food marketing tool. This is an example where relative risk can be very misleading, but the practice of emphasizing relative risk continues to this day.

In a perspective published in 2008, Schwartz and Meslin provided two examples drawn from screening data.[2] For mammography, they use data indicating that performing mammography regularly for 20 years yields a mortality rate of 9.1 per 1000 (0.91%) vs. 14 per 1000 (1.4%) if no screening is done. The difference is 4.9 per 1000 or 0.49%, the absolute risk reduction (ARR). However, the relative risk reduction is 4.9 per 1000 divided by 14 per 1000, which is 35%. However, if one calculates the number of women that would have to be screened to prevent one breast cancer death over 20 years, it is 204 (i.e. 1/0.0049, the reciprocal of the probability difference). For colon cancer screening using the occult stool blood test, 217 patients must undergo annual screening for 18 years to prevent one death from colon cancer, but the relative risk reduction associated with 18 years of annual screening is an impressive 31%. These examples illustrate the how large relative benefit can actually represent very small absolute benefits.

An associated consideration in the context of screening involves the adverse impact of false positives which can result in invasive procedures with small but not insignificant morbidity and even mortality, and as well, the potential for temporary elevated levels of stress and worry. There is also the problem of overtreatment or aggressive treatment for a cancer, which poses a doubtful or insignificant threat during the anticipated lifetime of the individual. But if one ignores the alleged risks of radiation in mammography, something those who believe in radiation hormesis would encourage, then mammography screening is not associated with the risk of adverse results directly resulting from the procedure. But if the colon cancer screening was done with colonoscopy, this would not be the case, with the worst case scenario being accidental perforation followed by emergency surgery and perhaps peritonitis. One of the worst-case scenarios associated with screening involves an unnecessary invasive diagnostic procedure prompted by a false positive, which results in lifelong disability, stress, bitterness and a significant burden on others.

Or consider the hypothetical example of an analgesic drug. If a randomized controlled trial found that the absolute benefit was only 1.5%, this would mean that 67 individuals would need to take the drug for one to obtain immediate pain relief. For the other 66, there would be no significant effect. Probably, such a drug would never be marketed for this indication, especially if much more effective drugs were available

The same picture emerges in lipid-lowering trials with statin drugs. In 11 primary prevention trials with major CHD events as the endpoint, a meta-analysis (combined weighted result for the set of studies) found there was a 26% relative risk reduction, but the absolute risk reduction was only 1%. This means that 100 patients needed to be treated, in this case over roughly 4-5 years, to prevent one major CHD event.[3] In the Cholesterol Treatment Trialists' Collaborators meta-analysis of 14 studies that involved a mixture of primary and secondary prevention and included diabetic patients, the relative risk reduction for a major coronary event was 23% but the absolute risk reduction only 2.4%.[4] Secondary prevention, or mixed primary and secondary prevention trials generally have slightly higher absolute risk reduction than pure primary prevention trials. In the CARDS study of statin treatment of diabetics, the relative risk reduction for acute coronary events was 36% but the absolute risk reduction only 1.9%, which translates into needing to treat 53 patients to prevent one event over about 4 years. Two other similar studies (ASCOT and ASPEN) found absolute risk reductions of 0.7% and 0.6% with NNT of 143 and 167 respectively.

The statin trials involve a class of drug that has serious side effects such as liver damage and muscle disorders including those, while rare, that can be life threatening. Statin use also increases the risk of cataract formation, temporary total amnesia, and mild cognitive impairment. The numbers needed to treat to cause one harmful event are generally larger than the numbers needed to treat to prevent one adverse coronary event, but the risks are nevertheless there, perhaps seriously underreported, and must be considered when a patient tries to decide if the one out of a 100 chance that the drug will provide benefit makes the risk of side effects worth taking.

The matter of relative vs. absolute risk came up several times in the recent annual meeting of the European Association for the Study of Diabetes, a very large meeting just held in Lisbon, Portugal. The risk of cardiovascular disease is considerably enhanced in individuals with diabetes (most diabetics are of type 2, incidentally) and is a subject of considerable concern among physicians and researchers involved in diabetes. The American Diabetes Association is a strong advocate of the use of lipid-lowering with statin drugs as part of both prevention and treatment programs. Dr. Peter Sawicki, MD, PhD, from the Institute for Healthcare Economics and Clinical Epidemiology in Köln made a strong point that when diabetic patients are informed about their risk and the effects of statins on the risk reduction for cardiovascular and cerebrovascular events, physicians should use absolute risk reduction numbers. This assertion was justified with a detailed review of the relevant randomized clinical trials where the absolute risk reductions were small in spite of misleading large relative risk reductions.

What is at issue here is informed consent based on knowledge and understanding of risks and benefits. This subject has been discussed repeatedly in the literature. In 2002 in a paper in the JAMA, scientists from the University of California at Davis examined 359 randomized controlled trials published in 5 major journals.[5] They focused on 1989, 1992, 1995 and 1998 and looked for studies that reported absolute risk reduction and numbers needed to treat to prevent one event over the course of the study. Absolute risk reduction was reported in only 18 articles and NNT in only 8. While this practice is slowly changing, the data still generally has to be extracted from tables or figures and the desired numbers calculated. Most readers do not have the time, interest or in some cases capability to do this. Frequently the data needed is absent even though the article was vetted by editors and peer reviewers. Articles that address issues concerning guidelines and standards of practice frequently focus on relative benefit, sometimes totally ignoring tiny absolute benefits and touting results as compelling or robust, indicating large and conclusive benefits and clearly justifying the use of the drug or drug class in question. The information presented in abstracts frequently provides only the relative benefit. Most clinical

trials are sponsored by the pharmaceutical industry and some of the participating scientists have financial ties to the industry (some studies suggest about 50%). They clearly wish to present the most favourable picture and thus emphasize relative over absolute benefits, and the same approach no doubt exists when drug representatives visit physician's offices. Physicians probably never take the time to study tables and figures and calculate absolute benefits and NNT. Without full-text access to many journals, they also are isolated from the actual data, editorials and commentary and letters to the editor.

While calculated results for absolute risk reduction or benefit are now more frequently reported in journals, we appear to have a long way to go. For example, a recent letter to the editor of the *Canadian Medical Association Journal* complained about two recent articles which failed to provide absolute risk reduction.[6] With regard to one of the articles, which concerned cardiac imaging, the author comments "How can I counsel patients on the hazards of cardiac imaging without this crucial information?" The editor admitted "We should have made this easier for readers to find…"

There is of course a certain arbitrariness associated with this problem. What is an appropriate threshold where the NNT becomes clinically significant? Researchers calculating the impact of a drug on large populations of course come up with impressive number of lives saved if mortality is the issue, but how does this apply to a given patient trying to decide about taking a drug or to agree to screening. Unfortunately, there is no answer and conservative clinicians will have quite different thresholds compared to those who believe in aggressive use of pharmaceuticals. Furthermore, the NNT is in some cases a dangerous oversimplification because it may derive from studies that are not particularly applicable to the patient involved in making a decision. Finally, knowledge of the risk of harm is frequently hard to acquire, unavailable or can not be trusted.

A final example. Since statins do not appear to have any influence on the progression of coronary atherosclerosis,[7] the number needed to treat to prevent one case of plaque progression is infinite, the result of dividing by zero when taking the reciprocal of the absolute risk reduction.

Schwartz and Medslin [2] add perspective to this discussion by citing a number of studies which indicate a wide variation in the ability of patients to understand numeric or probabilistic arguments in general and absolute risk reduction and numbers needed to treat in particular. They describe a well known aspect of human cognition that may lead people to assign excessive importance to events that are quite unlikely or overestimate the importance associated with such events because of an optimistic bias. While these problems can theoretically be overcome by physicians taking considerable time and effort to help patients come to an informed decision regarding accepting or rejecting a suggested therapy or undergoing screening, the financial and reimbursement milieu in which modern medicine works is not suited to this approach. This suggests a degree of hopelessness in the context of informed consent.

STIMULANT USE IN CHILDREN UP STRONGLY

A recent study looked at the trends in stimulant medication in children over a period of 12 years ending in 2008. Normally the indication is for attention deficit hyperactivity disorder (ADHD).[8] Among those 6-12 and 13-18 years of age, the prevalence of use increased by 6.5% annually to reach about 5% use by 2008. This rate of increase doubles approximately every 11 years. These results were based on periodic household surveys and a follow-back of pharmacy records. The prevalence of use in 2008 for boys was 4 times that of girls. The authors make the interesting observation that most children diagnosed with ADHD are not treated with stimulants. This is based on another survey published in 2010.[9] Actually, for boys about 40 % were treated and for girls 26%. The authors point out that about half those diagnosed show only mild symptoms and other treatments and non-stimulant medications are available. Thus, for example, with boys the actual prevalence

of ADHD in the 13-18 age group is about 13%, i.e. those who meet the DSM-IV (the current diagnostic bible) definition and have been diagnosed sometime in their lifetime. If, however, one includes all the diagnoses available to practitioners via the DSM, then excluding eating disorders, 48% of boys and 51% of girls in this age-range have sometime during their lifetime been diagnosed with a mental disorder. Some would regard these figures as supporting the position of Dr. Alan Francis, head of the DSM-IV writing project that DSM-IV caused a false and unnecessary epidemic of childhood mental disorders which resulted in vast and potentially harmful overtreatment, unfortunate and perhaps permanent labelling and potential problems in later life associated with health insurance.

Even the 5% of a population of children ages 13-18 judged to have mental disease warranting a prescription for a stimulant is disturbing. Typically, that amounts to one or two in every classroom. The survey cited above found a population prevalence in this age group of about 4% for what they termed severe impairment, which is consistent with the suggestion that only the more severe cases were actually treated with stimulants. What is wrong with children, society and the environment that produces these remarkably high rates of mental problems, or does the prevalence even for severe impairment still represent overdiagnosis or even the actual effect of drug treatment as has been discussed several times in this Newsletter? This would appear to be an urgent challenge for researchers, especially if the 6% annual rate of prevalence increase is correct. While working on that, researchers need to explain why the rates are highest in the Northwest US and lowest in Southwest by a factor of about 3. Race or ethnicity also shows smaller but still large variation, in this case between white and Hispanic and white and non-African American or Hispanic.

As has been discussed a number of times in this Newsletter (see Research Reviews in the February and March 2011 issues available online in our archives), the wisdom of the use of stimulants by children is highly debatable and the serious adverse side effects experienced are variable but include reduction to a zombie state, suicide, violent actions, and addiction to the medication and substance abuse in general. Note that these stimulants used for ADHD are all classed in the US as so-called Schedule II drugs. Thus the nature of these stimulant drugs can be discerned by the company they keep, which includes cocaine, opium, morphine, codeine, methadone, oxycodone, and hydromorphone! Drug addicts “snort” stimulant drugs just as they snort other Schedule II drugs in the process of achieving a high. The fact that apparently 5% of teenage children have been prescribed drugs from this class boggles the mind. No one seems to respond with concern when they hear of someone who has put their child on Ritalin, but if told instead that the child was taking amphetamines or Speed, which amounts to the same thing, they might be alarmed.

The good and somewhat surprising news in the stimulant use study is that the prescription prevalence is both low and decreasing in preschoolers (about 0.1%, down from 0.3% in 2002) but they do not break this down to examine toddlers! This low percentage still represents 100,000 users in the U.S. But this is probably about to change. The American Academy of Pediatrics has just issued new clinical practice guideline for ADHD.[10] They have extended the age limit downward to four-year olds and suggest that if non-pharmaceutical therapy does not work, medication is indicated. This recommendation relies heavily on DSM-IV. Recall that the chairman of the DSM-IV writing program, the well known academic psychiatrist Alan Francis, now believes that this bible of diagnosis has caused significant overdiagnosis and overtreatment for ADHD in children which he describes as an epidemic.

POTENTIAL THREAT OF DSM-V TO CHILDREN

According to an articles in the British newspaper *The Telegraph* (September 14) and the *Daily Mail* (online September 15) awareness of the potential problems for

children represented by the changes and additions about to take place in the new edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) is increasing among psychologists in the UK. Kate Fallon, General Secretary of the Association of Educational Psychologists, comments "In 2013 we're expecting new criteria for the definition of mental illness to be adopted in the UK. These criteria will lead to many more children being diagnosed as mentally ill, based on reports of their behaviours. A shy child could be diagnosed with social anxiety; a sad or temporarily withdrawn child could be diagnosed with depression. Behaviors develop over a long period of time, often with a range of complex causes; we can't "cure" the behaviors we don't like with a quick fix of medicine. They usually require careful management by all the adults around the child." Her position is that parents need to take time and energy to help their children deal with their problems and warned it was tempting to opt for a drug, which would be quick to change their behavior.

The British Psychological Society has also expressed similar concerns according to the *Daily Mail* and said pigeonholing problems as "illnesses" ignores the wider causes. The Society does not dispute that some children have emotional and behavioral problems but says that patients and the public are "negatively affected" by the continued "medicalisation" of natural and normal responses to their experiences, and by classifying such problems as illnesses with a medical response is not the best way to help these kids. It appears that according to the view of the writing teams creating DSM-V, the limits of normal behavior are going to shrink significantly. If DSM-IV was a disaster resulting in "epidemics" of overdiagnosis and overtreatment, it would appear that the worst is yet to come.

It appears that indeed a storm is brewing over DSM-V. The number of mental illness is rumoured to increase from around 350 to over 500, each with its list of symptoms and how they rank, and how many factors are needed for a "patient" to qualify for diagnosis of a mental illness. Presumably, for many situations, one could fill out a questionnaire and a computer could spit out a series of diagnosis and the indicated drugs and dosage.

LATEST ATTACK ON SUPPLEMENTS

A paper has just appeared in the *Archives of Internal Medicine* which uses data from the Iowa Woman's Health Study to examine the association of dietary supplements with mortality in older women.[11] The study period was from 1986 to 2008 divided into three unequal periods when data was updated. Multivitamins plus 14 individual vitamins and minerals were included in this observational study. The full multivariate analysis attempted to take into account confounding by age, educational level, place of residence, presence of diabetes, high blood pressure, body mass index, waist to hip ratio, hormone replacement therapy, physical activity, smoking status, energy intake, alcohol, and dietary saturated fat, whole grain products, fruits, and vegetables. The abstract summarizes the results. Positive, significant hazard ratios (HR), essentially odds ratios), i.e. enhanced risk of mortality, were obtained for multivitamins (1.06), B6 (1.10), folic acid (1.15), iron (1.10) magnesium (1.08), zinc (1.08) and copper (1.45). Inverse association was found for calcium (0.91).

This study has received extensive media coverage since the media loves studies that find common alternative practices dangerous. The editorial and invited commentary view the study with considerable enthusiasm. Thus, it is of interest to dig into the tables and see what the broader picture is. The following issues arise:

- If study had been confined to the second and third periods, 1997-2003 or 2004-2008, only iron would have appeared significant for both periods based on the 95% confidence intervals. Folic acid gave a statistically significant HR>1.0 only in the third period. Thus an 11 year study, which would have been more relevant to modern times, would not have produced the same results and in particular a condemnation of the multivitamin. It might

not even have been published. The results appear strongly dependent on the contribution of data from 1986 to 1996.

- For multivitamin use, the fully adjusted results have HR values of 0.97 and 0.94 (benefit) for the second and third periods, respectively, and probably if the results had been combined and adjusted this lack of risk would have persisted with simply tighter confidence limits. Thus it is hard to believe that combining data giving adjusted HR values of 0.97 and 0.94 into to a new set covering both periods would change the results to yield a significant risk for mortality from multivitamins. The data presented naturally does not allow the reader to perform the multivariate adjusted analysis.
- In one or both of the later two periods, only iron, magnesium and folic acid had HR > 1.0 with the potential for achieving statistical significant risk by combining the results to obtain a large number of cases.
- Over 22 years, huge changes occurred in medical practice that might have interacted with the use of specific substances. Folic acid is a good example where high doses have been implicated in increased mortality, and its recommendation at very high doses by cardiologists increased in the 2004-2008 period as did the HR, reaching statistical significance in the last period.
- Null results for such supplements as vitamin D can easily be explained by the traditional low doses used and the interference of A with D, which was common in cod liver oil users.
- The results for multivitamin use are not corrected for the increase in dose over the 22 years for many of the components in this supplement, in some cases to quite high levels in “super” products. The HR values decline from the earliest period (1.02) to the last period (0.94) but none were statistically significant. Was the risk in the first period, if real, due to not enough rather than too much?
- When dealing with data where most results are non-significant at some point in the analysis and HRs that are statistically significant are only slightly larger than 1.00 (the null result), one can wonder as to the validity of the assumptions and weighting involved in adjusting for a large number of confounders in order to produce a few statistically significant results.
- For CVD and cancer mortality, multivitamin intake over the entire period did not present a significant risk. For all other causes of mortality, a HR of 1.17 was obtained for multivitamins, but the only other supplement in the 14 studied that presented a significant risk for this subgroup analysis was vitamin C. A bizarre result which undermines confidence in the statistical analysis.
- The cohort at baseline in 1986 consisted of 37,772 individuals. Users of iron, magnesium, selenium and copper numbered, 2738, 1410, 1251, 229 respectively with resultant very low event numbers (deaths). The same applies to beta-carotene and folic acid where the user numbers were 378 and 509.
- If one distrusts the multivariate analysis to correct for confounding, then it is of interest to examine just the results adjusted only for age and energy intake over the full 22 years. In this case, copper is the only supplement with risk, and vitamin B complex, C D and E and calcium appearing statistically significantly *protective* against overall mortality for the entire period.
- For multivitamins, the data adjusted for age and energy over the entire study yielded event rates for users vs. non-users which gave an absolute risk *reduction* of 0.98 % with 95% confidence limits indicating a non-significant result (95% Confidence limits -0.07% to 2.02%) and a number needed to treat where the confidence limits can not be defined because range includes zero with its meaningless infinite number needed to treat.
- In the Harvard medical school guide to healthy eating by the famous Harvard nutritional epidemiologist Walter C. Willett titled *Eat, Drink and be Healthy*, there is a whole chapter with the heading “Take a multivitamin for insurance.” This is an excellent evidence-based antidote for the message contained in the study being discussed.

This statistical *tour de force* covers a very long period of 22 years during which medicine changed dramatically, various diseases experienced changes in

mortality, the mineral and vitamin content of food changed, as did the burden of toxins from food and environment, and life expectancy increased for a number of known and unknown reasons. One can thus question if it was possible to fully correct for confounding, an issue that becomes especially important when the HRs are small such as 1.06 for fully adjusted multivitamin risk. It appears totally unjustified for the media to shout from the rooftops that multivitamins kill.

NEWS BRIEFS

LIFESTYLE FACTORS AND RISK OF NEW-ONSET DIABETES

A large 11-year prospective follow-up study has just reported which examined lifestyle factors including diet and the associated risk of being diagnosed with type 2 diabetes.[12] The study involved almost 115,000 men and 96,000 women who were enrolled in 1995 and 1996, were aged 50-71 and had no evidence of heart disease, cancer or diabetes. Low-risk factors involved diet, alcohol, BMI, physical activity and smoking. The characteristic of low-risk were:

1. Diet was classified as low-risk based on a score calculated from the glycemic index, ratio of polyunsaturated to saturated fat, and the intake of fiber and *trans* fat.
2. Low risk in terms of physical activity involved 20 minutes 3 or more times per week
3. For smoking low-risk was either not smoking or having quit for more than 10 years
4. Low-risk alcohol consumption was defined as 5g/day to 30 g/day for men and 15 g/day for women, i.e. higher risk was associated with higher or lower intake.
5. Optimal BMI was 18.5 to 25, a range considered to be normal.

When diet and physical activity were low-risk, there was about a 28% decrease in relative risk for both men and women. Adding low-risk for smoking further lowered the risk to about 32% for both genders. Adding moderate alcohol consumption further lowered risk to 39% and 57% for men and women, respectively. Finally adding BMI yielded relative risk reduction, now for all 5 low risk factors present, to 72% for men and 84% for women. All of these results were statistically significant with rather tight confidence limits. A calculation of the absolute risk reduction based on the data in the tables when all 5 factors were present was about 6.5%, highly significant and to prevent one case, 15-16 individuals would have to have had this low-risk pattern over an 11 year period.

This study adds to a number of earlier studies that found similar strong risk reductions for new-onset diabetes through lifestyle and diet modifications. Prediabetics taking glucose control medication should think seriously about these results.

RADIATION RISKS TO INTERVENTIONAL CARDIOLOGISTS AND HORMESIS

Readers of this Newsletter are aware of the term hormesis that implies a U or J shaped relationship with exposure and in the case of radiation, low-level exposure is protective for radiation-induced disease such as cancer. A recent paper in the *European Heart Journal* examines cellular adaptation response to chronic radiation in interventional cardiologists, i.e. physicians who are chronically exposed to abnormal radiation doses because they specialize in procedures such as cardiac catheterization. The paper points out that they are a unique group available for study and show no adverse effects associated with their occupational exposure. The annual dose ranged from 1.5 to 8.4 mSv corresponding to 75 to 440 chest X-rays per year. The researchers comment that a key issue is that the population of exposed subjects is healthy, despite this level of radiation exposure. It was found that chronic exposure to low-dose radiation was associated with altered oxidation-reduction balance mirrored by increase in a marker and with two possibly adaptive cellular responses. These responses counteracted increasing stress from oxidizing chemicals generated by radiation and an increase in processes that might efficiently remove genetically damaged cells.[13]

The authors do not discuss the subject of radiation hormesis per se or the vast amount of evidence favouring what they are now apparently seeing in this cohort (see the Research Review in the November 2008 issue). These results will come as no surprise to researchers in this now well developed field nor would they express the above mentioned surprise that the subjects were healthy. However, radiation hormesis goes so strongly against the conventional wisdom that most of the literature is condemned to obscure journals and the researchers viewed as crackpots. Science may be about the search for truth, but its history is clear--when results conflict with conventional wisdom, the standard reaction is to ignore them, dismiss them as flawed or resort to ridicule.

GRAPE SEED EXTRACT. AN IMPORTANT ANTI-CANCER SUPPLEMENT

In the September Prostate Monitor section of the Newsletter the remarkable anti-cancer action of grape seed extract for prostate cancer was discussed. This result was from the VITAL study which has just reported on supplements and cancers of the blood, bone marrow and lymph nodes (haematological malignancies).[14] The possibility of an association was examined for a wide range of vitamins, minerals and what the researchers called specialty supplements such as ginseng, garlic, ginkgo biloba and fish oil, 24 in all. Out of this set, only two significant results suggesting cancer inhibition were found. The use of garlic supplements for 4 or more days per week for 3 years reduced the risk of hematologic cancers by 45% and ever use of grape seed extracts was associated with a 43% risk reduction. However, the absolute risk reductions were very small. For example, taking grape seed resulted in only a 0.36% absolute risk reduction that is equivalent to almost 300 individuals taking this extract to prevent one case over a period of 3 or more years. This is a nice example of the subject discussed at the beginning of the Newsletter. The journal article reporting the results provided only relative results.

While statistically significant results were found for these two supplements, perhaps even of more importance is that nothing else worked.

AN APPLE A DAY ETC.

The color of fruits and vegetables indicates the presence of pigmented bioactive chemical compounds (e.g. carotenoids, flavonoids, and anthocyanidins). Intake of some of these chemicals is thought to be beneficial. A recent study attempted to sort out the general picture with respect to stroke incidence in a 10-year prospective follow-up study of green, orange/yellow, red/purple and white fruits and vegetables.[15] When the lowest to the highest quartiles of intake were compared, only white fruits and vegetables provided a statistically significant indication of stroke prevention (52% relative risk reduction (RRR) for a mean of 216 g/day compared to 57 g/day). The white family comprised mostly apples and their sauce and juice and pears (55% RRR) and banana, cauliflower, chicory, cucumber and mushroom at 35% RRR.

The researchers found that apples and pears when considered separately, showed the same effect but it was not statistically significant. Apples are a rich source of fiber and the flavonol quercetin. They also cite a meta-analysis of 6 prospective studies that found that a high intake of flavonols were associated with 20% lower stroke incidence. While the results in the above study were adjusted for a number of confounders, no data was presented which allowed one to calculate the absolute risk reduction associated with the high intake of white vegetables and fruits. Incidentally, a medium size apple weighs about 200 g.

TV, VIDEO GAMES AND CHILDHOOD DEVELOPMENT

This is of course a controversial subject involving a major aspect of the daily lives of a significant number of children where “screen time” occupies a significant fraction of the time awake. At issue is the interaction of the type of TV watched, the type of games played, and the development of the brain during the critical period from birth through teenage. Rather than discussing this subject in the detail it deserves, it is suggested that the reader download and read a free article in the online magazine *Psychiatric Times*, a standard source of information and continuing education for the psychiatric community. The article by Mary G. Burke MD provides a well-documented discussion of this subject that will certainly cause parents to reflect on the levels of exposure

which their children experience. Google the magazine title, then enter the author name in the search box.

The American Academy of Pediatrics has just updated its position in this area. They discourage media use by children under 2 years, discourage placing a TV in a child's room, and caution parents that their own media use can have a negative effect on children. The recommendations are based on lack of evidence supporting educational or developmental benefits from media use by children younger than 2 and the potential adverse health and development effects of parental effects of media use by children under 2 and the adverse effects of background media exposure.[16]

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The Prostate Monitor
Editor: William R. Ware, PhD

Reviews of recent studies from the peer-reviewed literature

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In this issue we start with a brief discussion of a recent episode in the "vitamins are dangerous" saga. The case in point is vitamin E and prostate cancer, a subject that should interest many readers. This is followed by a more lengthy discussion of the prostate biopsy.

A PSA level that exceeds some arbitrary threshold or evidence of a suspicious irregularity or growth felt on the digital rectal exam encourages the recommendation of a biopsy. The conventional wisdom holds that this procedure is relatively benign and millions undergo the procedure each year. In this issue we examine evidence concerning just how benign the procedure is. After all, one would intuitively expect trouble considering what is involved from where the invasive procedure starts to the potential damage that 6 to 18 needle punctures can cause, especially when the procedure is guided by an ultrasound image.

Prostate cancer screening with the simple blood test for Prostate Specific Antigen (PSA) has been in the news again with a panel of experts coming out against the practice on risk vs. benefit considerations. This subject is again discussed in this issue.

Finally, a new study has just reported concerning the incidence of erectile dysfunction after prostate surgery.

Wishing you good health,

William R. Ware, PhD, Editor

VITAMIN E AND PROSTATE CANCER RISK

Readers of the Prostate Monitor will recall the disappointing results reported in 2009 from the SELECT trial that examined selenium and vitamin E for prostate cancer prevention. The SELECT researchers have now extended the follow-up with an unblinded phase which ended in July 2011 and has just reported.[1] They now find that vitamin E is positively associated with prostate cancer risk. This result has received extensive media coverage and no doubt there is now a general impression that vitamin E is dangerous. An examination of the data and the study design suggests a different view.

The hazard ratio (HR, approximately an odds ratio) for the latest round was 1.17 and the 95% confidence interval (CI) was 1.004 to 1.36. Incidentally, using 4 significant figures is unusual in giving CIs. It seems the bio-statistics experts working on the study kept going further into "decimal place space" until they found a non-zero number. The threshold for statistical significance is a CI which does not contain 1.00, which is the null result. The authors apparently regard 1.004 as "significantly" different than 1.000 so the 17% enhanced risk now becomes established as a statistically significant risk qualifying for great excitement in the media and the conclusion in the abstract that "Dietary supplementation with vitamin e significantly increased the risk of prostate cancer among healthy men." If the lower CI had been, for example, just 0.006 lower to give a limit of 0.998 then probably a rather different view would have been espoused. When the 5.5 year results we republished in 2009, the HR was 1.13 with limits of 0.95 to 1.35 and vitamin E was pronounced ineffective. Do these minute differences that come out of statistical equations which themselves contain assumptions have any meaning in real life? This is something the reader will have to decide for himself.

The absolute risk increase depends on how it is calculated but is between 1.1 and 1.6%. The difference in the cumulative probability of getting prostate cancer between the vitamin E group and the placebo group at the end of about 9 years can be taken from a graph and is about 1.1-1.2%. Thus if these results have any meaning at all, we are looking at approximately one out of about 90 men getting prostate cancer because they took vitamin E over about 9 years.

There is another problem. When SELECT was designed, critics pointed out that natural vitamin E should be used since the synthetic version contained an equal mixture to two forms, only one of which was active, and that the other form may interfere with the beneficial effects of the natural form. In addition, even the natural form is not the principal form of vitamin E in food. This is of course why many health conscious individuals take pains to purchase natural vitamin E in general and also perhaps a mix of forms.

IS THE ULTRASOUND-GUIDED PROSTATE BIOPSY BENIGN?

Ultrasound-guided multi-needle prostate biopsies are generally considered relatively benign. In the US just among the Medicare beneficiaries, more than a million such procedures are performed annually. The procedure is generally carried out in the outpatient or office setting. In this population, the risk of subsequent biopsy when the first is negative is about 12% at year 1 and 38% at year 5. However, the list of potential complication suggests that the procedure is somewhat less than benign. Complications associated with repeated (6 or more and sometimes up to 18) needle punctures through the rectal wall into the prostate can be roughly divided into infectious and non-infectious and include:

INFECTIOUS

- Septicemia, a severe infection of the blood which may rapidly worsen and result in septic shock. It can cause kidney failure, circulatory problems, and abnormal lung, neurological and bone complications
- Infections related to the puncture process originating in the rectum which can involve abbesses and urinary tract infections
- Abscesses in the perineum

NON-INFECTIOUS

- Haemorrhages and hematomas with blood in the urine, bleeding from the anus and blood in the semen.
- An arteriovenous fistula
- Tumor cell dissemination of cancer cells into the circulation
- Bladder perforation
- Urinary obstruction resulting from inflammation associated with the multiple insults of the multi-needle process.
- Severe pain
- Strokes
- Erectile dysfunction
- Loss of libido

These are the potential costs of acquiring tissue samples which can provide evidence of cancer and the stage of progression of the disease in various sectors of the prostrate. At present, there is no other way to acquire this detailed information except after surgical removal of the prostate during a radical prostatectomy or at autopsy. The information acquired is critical to treatment decisions. Some so-called watchful waiting (active surveillance) protocols also require an annual biopsy to assess possible progression and the need for definitive treatment, a condition imposed because of the weakness of the PSA test.

A recent study from Johns Hopkins and the National Institutes of Health of complications after prostate biopsy has just been published in the J*ournal of Urology*[2]. The investigation involved obtaining a random sample of 5% of Medicare participants in a large number of regions of the US over the period from 1991 to 2007. This study examined the frequency of hospitalization after prostate biopsy stratified by infectious and non-infectious complications. A random sample of non-biopsied controls was drawn from the same population. Results were presented for the entire period and graphically on a yearly basis

After adjusting for age, race, region of residence, year and comorbidities, prostate biopsy was associated with a 2.7 fold increase in hospitalization. Compared to controls, there was a 2.3 fold increase in hospitalizations for infectious and 8.5-fold increase for non-infectious complication during the 30-day post biopsy period. These results were independent of the positive or negative outcome of the biopsy. In addition, those hospitalized with an infectious complication had a 12-fold increase in the risk of death compared to those admitted for non-infectious complications. However, when the comparison was with the controls, the biopsy population has a lower 30-day mortality, which the researches suggest may reflect selection of healthier men for biopsy. When the time variation was studied, there was a dramatic increase in hospitalizations for infection as the primary diagnosis that occurred between 2000 and 2007 and a less dramatic increase for non-infectious complications over this same period. Between 2000 and 2007, hospitalizations for infection shot up from 0.1% to 1.1% whereas the control group remained essentially constant.

The authors suggest that the increase after 2000 was associated with the concomitant increase in antibiotic resistant bacteria. If guidelines are followed, all patients undergoing prostate biopsy are given prophylactic fluoroquinolones. It is know that fluoroquinolone resistance to E. coli in blood-stream isolates has increased from 0% to 12 % during the period 1998 to 2007; a problem they suggest may be associated with the introduction of the use of this class of antibiotic into animals destined for human consumption.

Those interested in public health like to apply event rates to large populations. When this is done, the study indicates that 69,000 hospitalizations occurred within 30 days of biopsy for infection per million biopsies, i.e. about 7%. While no data is provided for morbidity not requiring hospitalization, it can be assumed that the total burden of morbidity is quite substantial.

These results also have to be viewed in the perspective that the prostate biopsy misses up to 25% of cancers and is also associated with a small number of false positives as well. In addition, when an individual has a high and increasing PSA but a negative biopsy, pressure is frequently present to have one or more additional biopsies soon after healing has occurred. Adverse experience association with an infectious complication would be a danger signal for a similar problem on repeat biopsy.

The researchers suggest that one approach that might mitigate this problem would be pre-biopsy testing for antibiotic resistance in rectal wall swabs.

PSA SCREENING. WHAT ARE THE NUMBERS NEEDED TO SCREEN AND TREAT TO SAVE A LIFE?

In this issue of IHN we discussed at some length the subject of the numbers needed to screen (NNS) or to treat (NNT) to provide benefit or harm. Closely related to this is a study by Loeb *et al* [3] which examined this question over periods of 9 and 12 years in relation to PSA screening. The researchers reanalyzed the data from the European Randomized Study of Screening for Prostate Cancer (ERSPC) which reported results at 9 years and then extended this to 12 years. The ERSPC had a screening arm and a control arm with prostate cancer specific mortality as the endpoint. They found a 20% reduction in mortality for a median follow-up of 9 years which led to an estimate of 1410 needed to screen and 48 needed to treat to prevent one prostate cancer related death.

Loeb *et al* used a somewhat different model to examine this question. They found the NNS and NNT at 9 years to be 1254 and 43 and at year 12 years 503 and 18 for the above endpoint. In their discussion, they emphasize the importance of time in survival-type studies of diseases with a natural history of a sharp increase in events after a long period of development.

MORE ON THE PROSTATE CANCER SCREENING DEBATE

Loeb and Catalona, two of the six authors of the above paper on numbers needed to screen have just taken another look at the issues in a perspective on the screening debate.[4] They make the following points:

- PSA screening itself is not the problem, but there may be problems without careful patient selection. They point to the elderly with a heavy burden of comorbidities, undergoing screening is unlikely to uncover prostate cancer which will cause a morbidity or mortality during the short life expectancy. Studies that restrict the age cut-off get very good results in risk reduction for prostate cancer related mortality.
- Positive screening results must be followed up and the control groups must not receive screening. Both problems strongly impact the mortality study results in the direction of the null. For example, many with a positive screening result do not get a prompt biopsy.
- Mortality studies need to extend well beyond 10 years. The natural history of prostate cancer is such that one frequently sees mortality curves that start to diverge only after 7-8 years. Longer trials are needed to reveal the true merits of screening.
- Screening influences the probability of metastatic disease and this must be added to mortality when judging the effectiveness.
- Screening has the advantage of providing vital information related to the decision to treat or to wait.
- Screening protocols continue to evolve. More is being learned about distinguishing clinical significant from non-significant prostate cancer.

They take the position that the focus should be on maximizing the benefits and minimizing the harms by judicious patient selection, informed management decisions after diagnosis and continued refinement of treatment.

U.S. PREVENTIVE SERVICES TASK FORCE IS IN THE NEWS AGAIN

As extensively reported in the TV and print media, this organization, already well known in non-medical circles because of its recent position on mammography, has recommended against PSA screening on the basis of risk vs. benefit. The arguments are well known to the readers of this Newsletter and some are included in this issue. It is all a matter of what weight they are given and which studies are omitted form reviews. Needless to say, many but not all urologists disagreed, as reported in comments published in Medpage Today (October 12, 2011).

DATA CONCERNING ERECTILE FUNCTION AFTER PROSTATE CANCER THERAPY

A prospective study related to this question has just appeared in the *JAMA*.[5] A cohort of 1027 men receiving one of the standard treatments (surgery, radiation therapy (EBRT), or brachytherapy) were followed for two years. Sexual function prior to surgery and at the end of the study was used to assess the impact of treatment. The results were as follows:

- Erectile dysfunction was reported by 28%, 33% and 47% of men in the surgery, EBRT or brachytherapy groups, respectively.
- Two years after treatment, erectile dysfunction was reported by 63%, 63% and 57% of men in these same groups, respectively.
- Two years after treatment, among men with adequate sexual function prior to treatment, dysfunction was reported in 52%, 42% and 37% of these three treatment groups, respectively.
- Two years after treatment, adequate erectile function was reported for 37% of all patients and 48% of those with adequate function prior to treatment.
- Factors associated with functional erections 2 years after treatment included health related quality of life, age, PSA level, race/ethnicity, BMI and as indicated above, treatment.
- Multivariable regression models estimated 2-year erectile function probabilities from ≤ 10% to ≥ 70%, depending on pre-treatment characteristics and treatment details and the models performed well in validation tests.

The authors point out, stratification by pre-treatment characteristics and treatment details allows prediction of this adverse effect 2 years after treatment. However, while the differences dependent on the treatment used were present, they were not that different.

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