INTERNATIONAL HEALTH NEWS

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Welcome to our summer issue. In it we continue with the second part of Bill Ware's MUST READ article on the choices facing a man diagnosed with prostate cancer. Should he proceed with radical treatment, reject it completely, or wait and see? Thought-provoking indeed.

Also in this issue we show new evidence that the use of cell phones and cordless phones may be bad for your health, vitamin C may have significant anti-inflammatory properties, vitamin D supplementation may help in the prevention and treatment of congestive heart failure and its metabolite, calcitriol may help prevent blood clotting and stroke. All this and more in this combined July/August issue.

I very much appreciate your continuing patronage of our on-line vitamin store – http://www.yourhealthbase.com/vitamins.htm. I believe our association with papanature.com is very much to our mutual benefit in that it provides you with the best prices, freshest products, and fastest delivery available on the Internet, while it provides us with the financial support we need to continue the publication of IHN.

Enjoy a safe and healthy summer!!

Hans

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Further support for link between cellphones and brain tumors

OREBRO, SWEDEN. Recent findings from Sweden are likely to re-open the debate on the safety of cellular and cordless telephones. A team from Orebro University Hospital conducted a study based on 317 patients aged 20 to 80 years (mean 54 years) with malignant brain tumors diagnosed from 2000 to 2003, and 692 healthy control participants matched for age. Portable analog phones became available in Sweden in 1984, and portable digital phones in 1991. Cordless telephones have been used since 1988. Using a case-control design, the researchers investigated the effect of cellular and cordless telephone use. Telephone use was assessed by mailed questionnaire. Details of the tumor were obtained from the national cancer registry and, if necessary, pathology departments.

The researchers calculated that analog cellular phone use was linked to a 2.6 times greater risk of brain tumor, compared with non-use. Digital cellular telephones were linked to a smaller, but still significant, increase of 1.9 times the risk for non-users. Cordless telephones were associated with a 2.1 times higher risk compared with non-use. The authors report that the odds of developing a brain tumor increased in line with hours of telephone use. Links were strongest with high-grade astrocytoma - a form of brain tumor arising in the supportive cells (astrocytes) of the brain.

They conclude that a significantly increased risk for high-grade astrocytoma was found for all three studied phone types, the highest risk being for tumors with a latency period of 10 years or more.

This research group has previously published several studies suggesting that use of cellular phones is linked to brain tumors. However, their findings have been widely disputed, and larger studies have found no evidence of a link. For example, a UK study of 966 brain tumor patients and 1,716 controls published in January 2006 failed to find a link. This finding is consistent with most but not all published studies. Nevertheless, some research supports the link between cellular phone use and impaired brain function, and further investigation is needed to rule out any threat.

Hardell, L., Carlberg, M. and Hansson Mild, K. Case-control study of the association between the use of cellular and cordless telephones and malignant brain tumors diagnosed during 2000-2003. Environmental Research, Vol. 100, February 2006, pp. 232-41
Hepworth, S. J. et al. Mobile phone use and risk of glioma in adults: case-control study. British Medical Journal, Vol. 332, January 20, 2006, pp. 883-87

Editor's comment: The findings of the Swedish study add to the mounting evidence that the use of cordless phones and cell phones can be bad for your health. Apart from the brain cancer link, their use has now been linked to headaches, sleep disturbances, uveal melanoma (eye cancer), and increased blood pressure. It would seem prudent to limit their use to essential calls and to avoid allowing children to use them altogether.

Breast cancer risk from magnetic fields investigated

SEATTLE, WASHINGTON. The possibility that magnetic fields may increase the risk of breast cancer has recently been investigated by scientists at the Fred Hutchinson Cancer Research Center. They suggest that exposure to magnetic fields may interfere with the usual rise in melatonin levels at night. Melatonin is a hormone that is secreted by the pineal gland in the brain in response to darkness, and is important for the regulation of circadian rhythms. As melatonin is thought to be an oncostatic agent (i.e. a deficit can lead to an increased risk of cancer), the researchers speculate that disruption to melatonin production could raise breast cancer risk either by direct oncostatic action, or by increasing circulating levels of reproductive hormones related to the development of breast cancer. Support for their theory comes from animal studies, which show that exposure to magnetic fields can disrupt the nocturnal release of melatonin.

They examined whether exposure to a 60-Hz magnetic field was associated with a decrease in melatonin among 115 women ages 20 to 40 years, as measured by levels of 6-sulfatoxymelatonin in the urine at night. They also measured levels of the reproductive hormones luteinizing hormone, follicle-stimulating hormone, and estrogen.
The women were exposed to 60Hz magnetic fields 5 to 10mG (milligauss) above normal background levels for five consecutive nights, after which a nighttime urine sample was taken. Magnetic field exposure was linked to decreased melatonin levels, but not to a significant degree until certain participants were excluded (on grounds of eligibility). No changes in the reproductive hormones were found.

However, the authors propose there may be subgroups of individuals who are more susceptible to the effects of magnetic field exposure on hormone levels, such as obese women, those on certain medications, and women during a menstrual cycle in which they do not ovulate. The authors conclude that, on the basis of this study, any breast cancer risk posed by magnetic fields through lowered melatonin levels does not occur via corresponding changes in reproductive hormones.
Davis, S. et al. Effects of 60-Hz Magnetic Field Exposure on Nocturnal 6-Sulfatoxymelatonin, Estrogens, Luteinizing Hormone, and Follicle-stimulating Hormone in Healthy Reproductive-age Women: Results of a Crossover Trial. Annals of Epidemiology, published online February 2, 2006

Editor's comment: The official maximum allowable continuous (24/7) electromagnetic (60 Hz) exposure level in North America is 1000 mG. Apparently this is the level above which body temperature tends to rise. The finding that exposure to as little as 5 mG can cause serious disruption to vital melatonin production clearly shows that the official limit is at least 200 times higher than it ought to be. While this state of affairs clearly gives power companies and government authorities wide room to avoid having to deal with the consequences of transmission towers and faulty wiring, it does nothing to protect the individual from harmful radiation and its consequences. The best defense is to make sure that electromagnetic radiation (EMF) does not exceed 1 mG in the bedroom and that this room is completely dark at night in order to encourage melatonin production.

Can vitamin C control inflammation and cut heart disease risk?

LONDON, UNITED KINGDOM. Further study on the possible links between vitamin C and ischemic heart disease suggests that vitamin C has anti-inflammatory effects and is associated with lower levels of markers for inflammation and hemostasis (blood clotting). Researchers from the Royal Free and University College Medical School gathered data on 3,258 British men aged 60 to 79 years, who were free of heart disease and diabetes. The men's fruit and vegetable and vitamin C intakes were measured using a questionnaire.

Results showed that higher vitamin C levels in the blood plasma, higher fruit intake, and higher dietary vitamin C intake were all linked significantly with lower levels of markers of inflammation and hemostasis - specifically C-reactive protein, and tissue plasminogen activator (t-PA) antigen, a marker of endothelial dysfunction (damaging changes to the cells lining the heart and blood vessels). Those in the top quarter for plasma vitamin C had a 44 per cent lower risk of elevated C-reactive protein, and a 21 per cent lower risk of elevated t-PA, compared with the lowest quarter, report the authors. Plasma vitamin C was also inversely linked to fibrinogen concentrations and blood viscosity. The reduction in risk in the highest quarter for fruit intake was 24 per cent for both elevated C-reactive protein and t-PA. Weaker links were found for vegetable intake. Dietary vitamin C was significantly associated with C-reactive protein and t-PA.

These results confirm previous findings that plasma and dietary vitamin C levels have are inversely associated with some markers of greater risk of cardiovascular disease among white men. Large randomized trials of the effect of vitamin C supplementation on markers of inflammation and hemostasis would be useful, they conclude.

In an accompanying editorial, researchers from the University of California, Davis Medical Center discuss whether vitamin C is an anti-inflammatory agent by considering possible mechanisms behind the effect. They explain that attempts to control inflammation may prove central to the fight against cardiovascular disease, and the antioxidant vitamin C may play a role, although its effects on inflammation remain unclear. They point out several limitations of the UK study, adding that supplementation studies have failed to find reductions in inflammatory markers, and conclude that the effect is far from certain.

Wannamethee, S. G. et al. Associations of vitamin C status, fruit and vegetable intakes, and markers of inflammation and hemostasis. American Journal of Clinical Nutrition, Vol. 83, March 2006, pp. 567-74

Jialal, I. and Singh, U. Is vitamin C an antiinflammatory agent? American Journal of Clinical Nutrition, Vol. 83, March 2006, pp. 525-26

Large study supports calcium benefit on colon cancer risk

STOCKHOLM, SWEDEN. It has been proposed that a higher calcium intake may reduce the risk of colorectal cancer. There are several biological mechanisms through which the effect could take place, however, results have so far been mixed and inconclusive. Nevertheless, a modest association has recently been reported between higher calcium intake and lower colorectal cancer risk.

A team from the Karolinska Institutet set out to study the possible link by analyzing data on intakes of calcium and dairy foods among Swedish men - a population with a generally high intake of dairy foods. A total of 45,306 healthy men aged 45 to 79 years were recruited in 1997, when they completed food questionnaires recording dairy food intake, and from which calcium intake from food and supplements could be calculated. The men were followed until the end of 2004 - a mean follow-up of 6.7 years. During this time 449 men were diagnosed with colorectal cancer. Men in the highest quarter for calcium intake (median 1,665mg per day) were 32 per cent less likely to have developed colorectal cancer than those in the lowest quarter (median 809mg), after several other risk factors were taken into account. This reduction was statistically significant, as was the 54 per cent reduced risk among men consuming 7 or more servings of dairy food per day, compared with those eating 2 or fewer. The associations did not vary significantly by cancer site in the colorectum. The authors conclude that men with higher intakes of calcium and dairy foods, in particular milk, had a significantly lower risk of colorectal cancer.

However, in an editorial, an expert from Purdue University suggests that the effect of dairy intake on colon cancer risk may not solely be due to the

calcium content. He explains that several findings from the study point to the influence of dairy-associated factors, which require further investigation. The study did not consider vitamin D status, he adds, which interacts with calcium metabolism and would ideally be measured in future studies.

Larsson, S. C. et al. Calcium and dairy food intakes are inversely with colorectal cancer risk in the Cohort of Swedish Men. American Journal of Clinical Nutrition, Vol. 83, March 2006, pp. 667-73

Fleet, J. C. Dairy consumption and the prevention of colon cancer: is there more to the story than calcium? American Journal of Clinical Nutrition, Vol. 83, March 2006, pp. 527-28

Editor's comment: The finding that a high calcium intake may reduce colon cancer risk is not new; however, other research has found that both a high calcium intake and a high vitamin D level are required for meaningful protection. Men should bear in mind that a high calcium intake, especially from dairy products, has been linked to an increased risk of prostate cancer; thus, exceeding the officially recommended intake of 1200 mg/day is probably not a good idea.

Vitamin D holds promise for treatment and prevention of heart failure

BONN, GERMANY. New research suggests that congestive heart failure (CHF) may be partly caused by raised levels of pro-inflammatory cytokines - proteins released by cells that direct the actions of other cells including tumor necrosis factor alpha and interleukin 6. CHF is a chronic condition involving loss of pumping power by the heart. Patients experience shortness of breath and fatigue because the inefficient blood flow limits oxygen delivery to tissues and organs.

Laboratory-based research indicates that vitamin D has the ability to suppress pro-inflammatory cytokines and increase anti-inflammatory cytokines, so a team from the University of Bonn examined the effect on CHF patients of supplementation with vitamin D. They analyzed data on 93 patients, half of whom received 50 micrograms/day (2000 IU/day) vitamin D3 and 500mg calcium. The remaining half received calcium alone, with a placebo. Survival to 15 months did not vary between the groups, neither did left ventricular function, however, participants on vitamin D3 showed significant increases in levels of 25-hydroxyvitamin D, parathyroid hormone, interleukin 10, and tumor necrosis factor alpha, after nine months. Specifically, 25-Hydroxyvitamin D (the biologically active form of vitamin D) was significantly increased in the vitamin D group compared with the control group. In the vitamin D group, levels of parathyroid hormone were significantly reduced following supplementation. This is beneficial, as parathyroid hormone removes calcium from the bones and other body stores.

Furthermore, levels of the anti-inflammatory cytokine interleukin 10 went up after vitamin D supplementation. The pro-inflammatory cytokine tumor necrosis factor alpha was found to have increased in the control group, whereas it stabilized in the vitamin D group. The team concludes that vitamin D3 may prove a useful anti-inflammatory agent for CHF patients. They add that a problem with the vitamin D/parathyroid hormone/calcium axis may contribute to the worsening of CHF.

In an editorial, experts from the University of Toronto point out that a nutritional intervention for CHF would be extremely valuable. They write that the study suggests a protective effect for vitamin D on the heart and on the atherosclerosis (hardening of the arteries) that may trigger CHF.

Schleithoff, S. S. et al Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. American Journal of Clinical Nutrition, Vol. 83, April 2006, pp. 754-59

Vieth, R. and Kimball, S. Vitamin D in congestive heart failure. American Journal of Clinical Nutrition, Vol. 83, April 2006, pp. 731-32

Editor's comment: A large proportion of people in North America and Western Europe are deficient in vitamin D. This study adds to the evidence that daily, unprotected sun exposure in the summer and supplementation with 1000 IU/day of vitamin D3 in the winter are beneficial not only in the case of CHF, but also in protecting against osteoporosis and breast, prostate and colon cancers.

Glycemic index of the diet may contribute to age-related vision loss

BOSTON, MASSACHUSETTS. One of the leading causes of irreversible vision loss is age-related macular degeneration (AMD), which affects the macula, located in the center of the retina. The macula allows us to see fine detail clearly and is responsible for central vision. AMD can affect adults from the age of 40, and is present in more than 10 per cent of those over the age of 80 years.

Dietary modifications may provide one of the most effective prevention strategies, so researchers from Tufts University examined the possible role of dietary carbohydrate. They chose this food group since the retina is dependent on adequate glucose delivery to maintain healthy function. They measured long-term dietary glycemic index (GI) and total carbohydrate intake among 526 women, free from early stage AMD known as age-related maculopathy (ARM), taking part in the US Nurses' Health Study. The GI for a food describes the glycemic response (effect on blood glucose levels) after consumption of the food. Dietary GI was calculated as the total of the GI scores for the food consumed. Participants were followed for 10 years, during which food questionnaires were given on average four times.

Analysis showed that dietary GI was linked to ARM, specifically to retinal pigmentary abnormalities. Those in the highest third for dietary GI had 2.71 times the odds of developing ARM, compared with those in the lowest third. Total carbohydrate intake was not associated with ARM. The researchers also found that neither dietary GI nor total carbohydrate intake was linked to drusen - yellow or white deposits found under the macula, which are often found in AMD. They conclude that a diet that is high in foods with a high GI is linked to ARM, independent of total carbohydrate intake and several known risk factors.

In an editorial, experts from the University of Wisconsin write that antioxidant nutrients and oily fish have previously been linked to lower rates of AMD. They point out that diets with a lower GI are often healthier in general, so it may be that GI score reflects a broader diet pattern that protects against AMD.

Chiu, C. J. et al Dietary glycemic index and carbohydrate in relation to early age-related macular degeneration. American Journal of Clinical Nutrition, Vol. 83, April 2006, pp. 880-86

Mares, J. A. and Moeller, S. M. Diet and age-related macular degeneration: expanding our view. American Journal of Clinical Nutrition, Vol. 83, April 2006, pp. 733-74

NEWSBRIEFS

Children learn to love or hate fruit, but inherit their taste for meat

A recent study on children's food choices by researchers at University College London, UK set out to examine the origins of food preferences. Through gathering data on 103 pairs of (genetically) identical twins and 111 pairs of non-identical twins, they were able to calculate the relative influence of genes and environment. Results indicated that food preferences for meat and fish are highly heritable (i.e. genetic), but preference for fruit and vegetables is shaped to a greater extent by the environment. The researchers stated that it is not clear exactly what environmental factors are influential when it comes to fruit and vegetables. But they suggest that children who witness their parents show enthusiasm or distaste for certain types of fruit or vegetables are likely to follow suit. Alternatively, it might be that if particular foods are always available, children learn to like them. The findings add to our knowledge about the factors that may lead to bad eating habits.

Breen, F. M., Plomin, R. and Wardle, J. Heritability of food preferences in young children. Physiology and Behaviour, published online 5 June, 2006

Hope for thrombosis benefit of vitamin D for cancer patients

Thrombosis in cancer patients may be prevented by taking a form of vitamin D, suggests a clinical trial of 250 patients with advanced prostate cancer. Alongside treatment with the chemotherapy drug Docetaxel, half of the patients were given high-dose calcitriol - a naturally-occurring hormone and the biologically active form of vitamin D. The remainder took a placebo. The study set out to examine the effects of calcitriol on PSA levels, but the researchers discovered that those on calcitriol had a "significant reduction in both venous and arterial thromboses" compared with the placebo group. This reduction of thrombosis (clots in blood vessels) was not anticipated; say the researchers from Oregon Health and Science University, USA. They explain that thrombosis affects between 15 and 20

per cent of cancer patients, and can be serious. This finding offers an avenue of investigation that could result in a new class of anticoagulants, which could in turn, significantly improve outcomes for cancer patients.

Venner, P.M. et al. Reduced thromboembolic events with DN-101 (high-dose calcitriol) treatment of androgen-independent prostate cancer: Hypothesis for a new class of anticoagulants. Journal of Clinical Oncology, 2006 American Society of Clinical Oncology (ASCO) Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006: Abstract number 4505

Older anti-inflammatory drugs just as risky as COX 2 inhibitors

Some older generation painkillers may increase a patient's risk of heart attack, finds a new analysis of research data. Traditional non-steroidal anti-inflammatory drugs (NSAIDS) include aspirin, ibuprofen, naproxen and diclofenac. They are widely used for pain and inflammation, but these new findings cast doubt on their safety. Researchers from the University of Oxford, UK examined a total of 138 reliable trials comparing COX 2 inhibitors (newer types of NSAIDS including Vioxx) and traditional NSAIDs against placebo. As expected, COX 2 inhibitors were linked to an increased risk of vascular events, mainly heart attack. But high doses of some of the traditional NSAIDS were linked to a similar rise in cardiovascular risk. The risk was higher among patients on high-dose ibuprofen and diclofenac, but not high-dose naproxen (aspirin was not studied). The authors conclude that, for every 1,000 patients on NSAIDS or COX 2 inhibitors, about three extra people per year will have a vascular event.

Kearney, P.M. et al. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. British Medical Journal, Vol. 332, June 3, 2006, pp. 1302-08

Dieters need support groups for long-term success

Support groups help dieters keep off the weight they have lost, finds a new study. The study was part of a BBC television series which tracked the progress of 300 people on four popular weight loss diets. It found that the diets were all useful for losing weight. They were: the Slim-Fast Plan (meal replacements), Weight Watchers (energy controlled diet with weekly meetings), the Atkins diet (self-monitored low carbohydrate plan), and Rosemary Conley's eat yourself slim (low fat diet and weekly exercise class). All four led to significant body fat loss and weight loss after 6 months - a weight loss of 5.9 kg and fat loss of 4.4 kg on average. But those with support groups led to better weight maintenance after a year, even though only 45 per cent were still on their diets. The authors conclude that these data could help practitioners in managing patients' expectations of weight loss targets.

Truby, H. et al. Randomised controlled trial of four commercial weight loss programmes in the UK: initial findings from the BBC "diet trials". British Medical Journal, Vol. 332, June 3, 2006, pp. 1309-14

Wrinkles indicate higher risk of progressive lung disease

Heavy facial wrinkling appears to be linked to risk of chronic obstructive pulmonary disease (COPD) in smokers. There could be a common underlying factor, say researchers at the Royal Devon and Exeter NHS Foundation Trust, UK, who investigated risk factors for COPD - a range of common progressive chronic lung diseases, including emphysema and bronchitis. Smoking is the main cause of COPD, and the team predicted that, as smoking also causes premature wrinkling, the two effects maybe linked. From analyzing data on 149 middle-aged smokers and ex-smokers, they found that the 17 per cent who were heavily wrinkled were five times as likely to have been diagnosed with COPD. They also had significantly poorer lung strength, and three times the risk of severe emphysema. The authors report that facial wrinkling is strongly associated with the risk of airflow obstruction, independent of smoking history. Severe facial wrinkling may be a useful marker of COPD susceptibility, they conclude.

Patel, B. D. et al. Smoking related COPD and facial wrinkling: is there a common susceptibility? Thorax, published online June 14, 2006

RESEARCH REPORT

PROSTATE CANCER

To Accept Or Reject Treatment, Or Compromise? – Part II

By William R. Ware, Ph.D.
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Studies that follow untreated patients reveal the so-called natural history of PC, which can be an important component in the process of selecting among the treatment options. Two factors combine to confuse this natural history. These are the advent of PSA testing in the late 1980s and the fact that PC is in many cases a very slowly developing disease. For example, estimates of the chances of dying of untreated PC are based mostly on the study of individuals diagnosed in the pre-PSA era and would be expected to be considerably higher than the probabilities for individuals diagnosed with PSA screening [10] because in the pre-PSA era most PC was diagnosed at an advanced stage. However, due to the slow progression of this disease in many individuals, there are insufficient data for the required analysis at present, mainly because the clinical characteristics of the present-day population with newly-diagnosed PC have only more or less stabilized recently. However, there have been attempts to model this problem based on existing data. The work of Nicholson and Harland [10] is of particular interest. They calculate the 10-year and 15-year probabilities of death from prostate cancer in a PSA-era population assuming no definitive treatment after diagnosis. Involved is an estimated lead time of 9 years due to the early detection feature of PSA screening. After this lead time, the older mortality data was applied. For men with Gleason Score of 6 tumors (relatively slow-growing tumors), they obtain the results given in Table 2.

Table 2. A model of the natural history of untreated prostate cancer. Probability (%) of being alive, dying of prostate cancer (PC) or dying from other causes 10 and 15 years after diagnosis by biopsy prompted by PSA screening for men with a Gleason score of 6 [10].

	PROBABILITIES (%) (no definitive treatment)		
Age at screen diagnosis	Alive	Death from PC	Death—other causes
	Ten-year results		
50	85.0	6.3	8.7
60	74.0	5.8	19.6
70	55.6	6.3	38.1
80	11.7	3.4	84.9
	Fifteen-year results		
50	72.1	12.2	15.7
60	56.3	11.1	32.6
70	31.4	10.5	58.1
80	2.2	4.0	93.8

Thus a man who is 50 at the time of diagnosis will have by age 60 a 6.3% chance of dying from PC which jumps to 12.2% at 65 years, and an 8.7% chance of dying from other causes which increases to 15.7% at 65 years. However, for a man diagnosed at age 80, the probability of death from PC by age 95 is only 4% but the chances of death from other causes is now almost 94%. These are just gross estimates since no account it taken of the stage or aggressiveness of the disease. Clearly, comorbidities also enter into the picture. Nevertheless, this model illustrates the rather small probabilities of dying of PC subsequent to diagnosis during the following 10 or 15 years.

These numbers can be compared, for example, to pre-PSA results where, for untreated men between 65 and 75 years of age with Gleason Scores of 6, 20% were expected to die of PC over the following 15 years [11]. Comparison with the data of Bill-Axelson *et al* is also interesting. Nicholson and Harland also give data for age 65 (not shown) which is the average age of the Scandinavian cohort, which also had about 50% of participants with Gleason 5-6. Ten-year numbers from Nicholson and Harland were 66.3%, 6.0% and 27.7% for being alive, death from PC or death from other causes, respectively. Comparable numbers from Bill-Axelson *et al* (Table1) were 69.5%, 14.4% and 16.1% respectively. Thus if the Scandinavian survival study had involved a more modern cohort, the death-rate from untreated PC might have been substantially lower. However, survival after RP might have been higher and the overall survival advantage between the treated and untreated groups might have disappeared or at least narrowed. This underscores the problems caused by the changing characteristics of the modern-day recently diagnosed population as compared to a less recent cohort.

Parker [12] points out that even the numbers for PC-specific death of Nicholson and Harland may in fact be too large since the mortality data they used may be too high given recent decline in PC-specific mortality. Thus it is important for men to recognize that older, much less favorable survival figures, which still influence clinical decisions, should be questioned. When confronted with this argument, they should inquire as to whether or not the PSA-era lead time has been factored into the survival data.

Other aspects of the natural history of PC that relate to the question of treatment are as follows [8].

- The lifetime risk of PC is 16% in the US but the risk of PC-specific death is only about 3%.
- The median time from diagnosis to death for men with biopsy detected PC prompted by elevated PSA is about 17 years, whereas at age 65, the life expectancy is 16 years. This raises the question of the extent to which treatment will add years to a man's lifespan, which of course depends on age.
- Up to 1/3 of men in PSA screened populations undergoing radical prostatectomies (RPs) have small (< 0.5 cc), low-grade (≤ 6 Gleason scorer) tumors. Such small tumors may not impact the lifespan in older men. Walsh [13] gives a slightly lower estimate.
- Approximately 30% of men older than 50 have PC at autopsy after dying of non-PC related causes, but the diagnosis rate for this age group is only about 11% [14].
- Average age at diagnosis in the pre-PSA era was approximately 70. Now it is 60 [15].
- If the lead time due to PSA screening is 5-7 years; this is equivalent to 10-12 years to the symptomatic stage of untreated PC. A lead time of 9 years gives 14 years.
- At present in the US, 75% of men diagnosed with PC have non-palpable disease (negative DRE) and have a biopsy because of elevated PSA (stage T1c).

Two recent studies concerning the natural history of localized PC merit mention. Albertsen *et al* [11] presented the results of a 20-year follow-up of patients treated only with either observation or immediate or delayed hormone treatment. Their results, which received considerable media coverage, did not support the aggressive treatment of localized low-grade PC. However, editorial comment [16] pointed out that the authors failed to emphasize that the cohort studied had a preponderance of very low-grade (Gleason 2-4) tumors which are rarely if ever seen today. And as well, the work was criticized for not really describing the natural history of untreated PC since 42% of the patients received hormone therapy within 6 months of diagnosis [17].

In the second study, the opposite conclusion was reached by Johansson *et al* [18]. They found that for early, localized cancer an indolent course for 15 years can be followed by significant local progression and metastatic disease over the next 5 years. Given that a number of patients have a 20-year or greater life expectancy, this result impacts treatment decisions. However, as Neugut and Grann point out in an accompanying editorial [19], these results may have been influenced by better detection of progressing disease near the end of the study, resulting in a false impression of more aggressive disease late in the natural history of untreated PC. However,

the chance that these results are valid raises questions as to the relevance of shorter-term studies including those discussed above and strengthens the commonly held view that young men with PC should be encouraged to have definitive treatment even if the cancer appears organ confined and non-aggressive. The results presented by Johansson *et al* may never be confirmed since it is probably true that 20-year follow-up studies involving a large number of untreated men with prostate cancer, all recently diagnosed, are now for the most part impossible to organize and implement. Thus major questions persist and will probably continue to persist.

What can be concluded? The above discussion should indicate the complexity of the treatment question, its many aspects, and the impact of PSA screening on the clinical characteristics of present-day populations. As well, new, important studies appear regularly. The widely held view that treatment has not been shown to improve overall survival has now been challenged with a randomized trial. Some physicians may be unaware of this study. Some may regard it as inconclusive. Some may not consider overall survival that important compared with local progression and the development of metastatic disease, two aspects of the disease that appear to be significantly influenced by therapy, or at least by surgical treatment, as discussed above.

Some men will favor treatment but do not want an unnecessary therapy. Some of these men may be interested in the possibility of active surveillance and will want to inquire about the clinical characteristics of their cancer in the context of criteria such as that being used at Johns Hopkins. This may involve getting answers to questions not normally posed during the post-diagnosis conference, questions about the details of the actual biopsy cores and the PSA density at the time of diagnosis. The latter requires knowledge of the prostate volume which should be available from the transrectal ultrasound-guided biopsy. It is generally acknowledged that the DRE provides a highly uncertain value for this volume, as does abdominal ultrasound. Active surveillance as defined above is not that common as yet, and in addition, men interested in this option may find different criteria both for eligibility and treatment triggers depending on the physician involved in the treatment decision. The criteria for both eligibility and what constitutes an indication for treatment in the context of active surveillance have recently been reviewed in the journal *Urologic Oncology* by Warlick, Allaf and Carter from Hopkins [20] with the favored parameters still as indicated above. However, they favor an additional condition, age > 65, but comment that as their experience with active surveillance grows, they may favor broadening the inclusion criteria, especially age, because younger men may in fact be the patients benefiting most from this option. Full-text of this review can be obtained from the Science Direct website

http://www.sciencedirect.com/science/journal/10781439.

Just-diagnosed patients can be thought of in terms of several groups. There are those who reject treatment out of hand and as well, those who say, “doctor, just tell me what to do,” i.e. they have no opinion or preferences or simply wish to follow what they perceive as expert advice. Also, there are those who regard the cancer as a definitely unwanted foreign invader and emphatically want it eradicated no matter what, even given the risk of an unnecessary operation or the risk of complications and side effects that may diminish their quality of life. They may even elect or demand definitive treatment knowing that the chances of durable disease-free period are poor. This group is unable to live with the untreated disease, the stress of which would also pose a health problem. Evidence based arguments will have little or no impact on the decision making process for most of these men.

Another group may have extensively researched the question of risk vs. benefit associated with definitive treatment for their clinical presentation. This group would then divide into those who rejected treatment and those who embraced it, although some might elect active surveillance if it was offered. While they would probably maintain that the decision was rational and evidence-based, this in some cases was perhaps imaginary since the weight given to various probability arguments may in part have been emotional and/or irrational. The bottom line is that there appears to be no simple or satisfying answer with regard to the decision to accept or reject treatment. Unfortunately, the decision is not like deciding whether or not to have an appendectomy! However, there is growing evidence to support the merits of a middle ground, active surveillance, for carefully selected patients. In addition, young men diagnosed with prostate cancer should weigh carefully the fact that in general they have a long life expectancy and there is general agreement that when the cancer is organ confined and non-aggressive, early treatment provides a high cure rate. While active surveillance may be a highly attractive option provided suitable criteria are met, if the picture changes and treatment is indicated, the recommendation, it would seem, should be taken very seriously since a cornerstone of active surveillance is that

when treatment is indicated, a cure is still highly probable. The quotation given at the beginning of this review neatly summarizes the situation.

NOTE: This review is based in part on the introduction to Chapter 6 of the book *The Prostate and Its Problems* by Hans R. Larsen and William R. Ware, which is currently in press and will be available shortly from International Health News (http://www.yourhealthbase.com)

PLEASE SEE PART I FOR REFERENCES

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