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In this issue we deal with a diverse set of issues starting with a new study which reinforces the growing view of the merits of MRI in screening for breast cancer. Unfortunately left unresolved is the critical question of how to view ductal carcinoma in situ, when it should be treated aggressively and when watchful waiting is appropriate. A recent study is discussed which indirectly addresses this issue in the context of cancer overdiagnosis. Also related to breast cancer is the discussion of the role of alcohol consumption during adolescence and benign breast disease.

This issue introduces to readers a new syndrome, the so-called aerotoxic syndrome, which appears to be caused by neurotoxins in the cabins of commercial aircraft. With the industry in denial, all one can do is take defensive measures, and the only one apparently available is described.

Three recent studies are described which relate to diet and heart disease. In one, data is discussed that relates to the dangers of processed meats. The other study reports on the investigation of the risks of a heart attack associated with making the wrong choices in carbohydrates to replace fats when one chooses this option, which incidentally is rapidly being discredited as a preventive approach to heart disease. The third study involves a demonstration of the importance of oral hygiene and health in heart disease prevention and reinforces the theory that preventing infections plays an important role.

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 a safe and happy summer,

William R. Ware, PhD, Editor

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MRI VS. MAMMOGRAPHY, ULTRASOUND, AND CLINICAL BREAST EXAMINATION

In the February 2010 issue we discussed the mammography debate which is really a screening debate. But mammography is not

the only breast cancer screening procedure and contrast enhanced magnetic resonance imaging (MRI) has been incorporated into national guidelines in some Western countries. A new study comparing MRI, mammography, ultrasound and clinical breast examination for screening of premenopausal women at elevated risk due to family or personal history has just reported.¹

Screening is generally judged in terms of sensitivity and positive predictive value. Sensitivity (SEN) reflects the percentage actually having the disease who were found positive for the disease out of the total number with the disease in the screening cohort, whereas the positive predictive value (PPV)

gives the percentage out of those with a positive screening result that indeed have the disease. To calculate these one needs true positives (TP) as determined by biopsy or an equivalent measure, and also the total false negative (FN) screening results and the total false positive (FP) screening results, where false positive refers to being positive on screening but having the disease on biopsy or other measure and false negative indicates the disease was present but not found by screening. But with breast cancer it is of course not possible to verify negative screening results with biopsy since there is no biopsy target and no biopsy is done. The approach used in this study was to use several rounds of screening 6 months or a year apart, and in addition to look for clinical manifestations of disease during the time between rounds for those with negative screening results. An uneventful follow-up at 12 months was accepted as a disease negative. The mean follow-up time was about 30 months. This is different, for example, from prostate screening with PSA as the test, since everyone enrolled in a study can receive a biopsy. If one ignores the fact that the biopsy is far from perfect, the information acquired in prostate studies provides the required set of four results. The prostate biopsy does not require imaging identified tissue abnormalities. Clearly, establishing the validity of the false negatives represents a weakness in studies of breast cancer screening which is unavoidable. The PPV and SEN are calculated as follows:

$$\text{PPV} = \text{TP}/(\text{TP} + \text{FP}) \text{ and } \text{SEN} = \text{TP}/(\text{TP} + \text{FN})$$

Decisions on positive vs. negative screening results were based on an American College of Radiologist rating system with scores running from 0 to 5. Only scores 4 and 5 indicating possibly malignant or malignant qualified the result as a screening positive. Scores of 4 and 5 are generally considered justification for a biopsy. The other issue is deciding true and false positives from the histopathologic examination of biopsy samples. In this study, the diagnosis by biopsy of invasive cancer or ductal carcinoma in situ (DCIS) was taken as disease positive and all other histologic results were viewed as disease negative. Thus an individual with a screening positive followed by a disease positive result on biopsy becomes a true positive.

The results for the positive predictive value for MRI, mammography, ultrasound and clinical breast examination were 48, 39, 36, and 0.9% respectively. The corresponding sensitivity values were 93, 33, 37, and 3% respectively. This multicenter German study confirmed an earlier study from the same group based on only one center, except the more recent study obtained a higher positive predictive value for mammography (39 vs. 24%).² An important result was that no significant improvement in diagnostic benefit was found from combining any two of the screening protocols.

The PPV is really a measure of true and false positives. It is worth noting that this study found about 50% of the screening positives were really cancer which leaves 50% that were not. In the perfect world, the PPV of screening would be 100% and there would be no "unnecessary" biopsies. But screening is not perfect, and to agree to screening is to agree to the risk of being strongly advised and probably agreeing to undergoing an invasive procedure which has a significant probability of yielding a negative result. If one waits until there is a lump or other clinical manifestations, the approach in the pre-imaging era, there is still a very large probability that the now more urgent biopsy will be negative. There is also no guarantee that this delayed identification of a potential malignancy increases mortality.

This study found a high percentage of cases of ductal carcinoma in situ (DCIS). In the accompanying editorial it was pointed out that while the cohort was selected for genetic predisposition, there was a very low percentage of participants who had the high-risk genetic profile, i.e. *BRCA 1/2* positive, and thus there were mostly women of moderate risk in the cohort.³ The editorialist also agrees with the researchers that given the cohort involving young women who were genetically predisposed to breast cancer, sooner or later the DCIS would probably progress into invasive cancer and thus deserve to be treated. In other words, he is justifying the inclusion of DCIS in the disease positive group. The fact that he discusses this indicates that there is controversy regarding DCIS. Finally he points out that there are still no randomized trials that address the issue of screening and mortality and if MRI screening is done starting at age 25-30 there are issues

with kidney disease associated with frequent exposure to the MRI contrast chemicals.

Consistent with most other studies, MRI came out the winner. Clinical breast examination was a dismal fourth. It is important to realize that centers offering MRI for breast cancer screening may differ in the extent to which they match the results obtained in this study

which used so-called quality assured MRI imaging in centers where performance was continually monitored, and each center was also required to offer verifiable experience with MR-guided biopsy. Also, the screening results depend on a judgement call based on how the radiologist evaluates what he or she sees. This surely is at best a “soft science.”

BREAST CANCER OVERDIAGNOSIS

The above discussion presents the conventional attitude regarding overdiagnosis in breast cancer. The editorialist did not seem concerned that ductal carcinoma in situ (DCIS) was really an issue. When it is identified, treat aggressively. Early detection saves lives according to this dogma. Intervention is necessary because the indolent nature of some lesions can not be ascertained so treatment is recommended simply because medical science in this field has not reached the level of sophistication where it can tell the difference.⁴ But overdiagnosis, especially in breast cancer and prostate cancer, is in fact a very much an issue and has recently been featured in the *Journal of the National Cancer Institute*, a journal that is certainly mainstream.⁴⁻⁶

One of these papers was a review in which Welch and Black⁵ point out that for breast cancer, of nine randomized trials of mammography only one reported long-term follow-up! This trial ended at 10 years but follow-up was extended another 15 years. On the basis of data accumulated in this trial, they estimate that 24% of the cancers detected by mammography represent overdiagnosis, i.e. cancer that would not go on to cause symptoms or death. In other words, these were lesions that the patients would not have needed to know about during their lifetimes. For lung cancer overdiagnosis was estimated at 50% and for PSA detected prostate cancer it was 60%.

In an accompanying editorial, Esserman and Thompson⁴ comment that intervention is motivated by the belief that it prevents disease progression, metastasis and death and is based on a philosophy that early detection is always better. Patient fear and clinician's

concern about malpractice are also driving forces. Thresholds for biopsy have been lowered to the point where when one looks at the overall picture, 75% of biopsies are negative. But this approach overlooks the profound consequences of diagnostic interventions and treatment. They emphasize the acute need to reclassify “indolent” lesions with a term other than “cancer.” They also agree with Welch and Black that for many small radiographic findings, evidence of growth over time may help sort out which lesions merit biopsy. The editorialists also question the notion that it is too risky not to biopsy and thus miss a cancer. Rather, they contend that it is too risky to continue with the present ideology where clinicians feel compelled to know what every lesion is as well as the “reflexive need to treat anything that resembles cancer.” Thus it is clear that the essential problems are gaining recognition. But real solutions appear elusive and point to the critical need for better ways to differentiate indolent cancer from the real thing, ideally without a biopsy, but certainly with a biopsy. Patients may well be unaware of the uncertainties in this important area of medicine. They simply assume that in 2010 the experts must surely by now have this all figured out.

Finally, a large study was reported in the same issue of the JNCI where the use of biomarkers to help distinguish high from low risk DCIS was investigated. This is clearly one of the major challenges today in breast cancer detection and treatment. As discussed above, as more sophisticated screening tools are introduced, the percentage of lesions that are described as DCIS increases, and it appears that they are all viewed as requiring the “full treatment.” The study by Kerlikowske *et al*⁶

was in response to the fact that up until now studies had failed to identify low from high risk DCIS, with those at low risk probably not requiring the full treatment or even any treatment. They found three biomarkers which can identify women with diagnosed DCIS who are at high or low risk of subsequent invasive cancer, whereas histological examination of biopsy tissue was not able to accomplish this differentiation. However, this study actually addressed the question of the need for additional (adjuvant) treatment following lumpectomy for DCIS. While this is of course

also an important issue given the side effects of the adjuvant treatments used today, it still does not directly address the question of avoiding unnecessary biopsies of indolent lesions. In an accompanying editorial,⁷ questions were also raised about the statistical power and design of the biomarker study. However, this appears to be where we stand today, and it is clear that there is a long way to go and millions of women are destined to be unnecessarily treated before modern medical science solves what appears to be a fundamental problem.

THE AEROTOXIC SYNDROME

It is likely that many readers have never heard of the aerotoxic syndrome. Medline (PubMed) brings up only three references, but it is clear that the term was in use by 2002. The best sources of information appear to be outside the peer-reviewed literature. While this normally discourages your editor from bringing up a topic, in this case the subject is so interesting and relevant to all of us who fly on commercial airliners that it seems to merit a brief discussion. He apologizes if this story spoils your next air trip. Some of the information below was derived from an investigative report in the British paper *The Independent* (March 17, 2009).

At issue here are toxic fumes that occasionally are fed into an airliner's cabin air due to a malfunction of the system whereby "fresh" air is brought into the cabin to mix with the "stale air" being circulated, the so-called bleed air. Contrary to what one might assume, the fresh outside air is not simply scooped up by an intake, heated and pumped into the cabin. Quite the contrary, the air is obtained from the engine compressor system and needs to be cooled. The problem arises when hydraulic oil or fuel leaks into this hot air, burns, and contaminates the air stream used to "freshen" the cabin air. Filters used in the air circulating system do not remove the toxic components of the contamination. Significant exposure is episodic and these events are characterized by the odour suggestive of smoke or fumes in the cabin. In a large number of reported incidents, what follows next are neurological symptoms. Passengers and crew become nauseated, suffer extreme tiredness,

dizziness, have trouble breathing, and in severe cases some have been reported close to unconscious. Impairment of judgement, cognition and the ability to function has been reported on a number of occasions by pilots who resort to the breathing pure oxygen. In one reported incident, this was done too late and one of the two pilots actually became incapacitated and the other pilot had to manage the flight while also under the influence of what appears to be neurotoxic substances. One can easily imagine the potential for disaster.

There are reports of permanent health damage both among passengers and crew according to the article which appeared in *The Independent*. Pilots and cabin crew have been forced into early retirement due to neurological health problems. Passengers are left with a mystery disease. This has been discussed in the literature in the *American Journal of Electroneurodiagnostic Toxicology*⁸ where it is pointed out that the connection with the flight is rarely made when the individual seeks medical advice and the result is neurological tests for a mystery disorder (respiratory irritation, memory loss, insomnia, and involuntary movements, etc). The *Independent* article also points out that this system for generating bleed air is common to most airliners one encounters today. The new Boeing 787 Dreamliner is apparently the first aircraft in over 40 years to switch to a different system.

One hypothesis is that the active toxin is tricresyl phosphate which is used as an anti-

wear additive to jet-engine fuel. All of the above symptoms are well known to be associated with organic phosphate toxicology although a variety of toxic chemicals may be generated during the exposure of the contaminating vapour to high temperatures found in the compressed gas. *The Independent* quotes Dr. S.M. Ross, a clinical neuropsychologist at the University of London, who commented that the aerotoxic syndrome could be affecting up to 200,000 passengers a year. The journalist points out that some regard this as conservative. The article also describes studies on 27 pilots with cognitive dysfunction. Blood and fat tests done at University College London found highly abnormal amounts of chemicals related to or present in jet-engine oil and fuel.

Passengers can detect a so-called “fume event” from a bluish haze or smoke in the cabin, or by a smell that has been variously described a sweaty socks, wet dog, vomit, or sweet oily smell. However, at low levels passengers may notice nothing other than mild neurologic symptoms such as a headache which are easily associated with simply being tired. It is interesting in this connection that the article in *The Independent* describes a test carried out by German and Swiss investigative journalists where swabs from aircraft cabins were taken secretly and analysed for tricresyl phosphate at the University of British Columbia. Out of 31 swabs, 28 tested high. Individuals who are very sensitive to organic phosphate neurotoxins may experience reactions in the absence of a fume event just from the contamination of the aircraft. Your editor knows someone who gets a severe headache

within a half-hour of entering some, but not all aircraft.

The reader is referred to the website www.aerotoxic.org for a very detailed discussion of this problem and a large number of incident reports (20) are made available in both English and German. It seems doubtful that this is all made up. In fact, it appears that the industry-related unions are very much interested in this problem and there are obvious legal ramifications. It also appears that the industry is in denial. It is interesting that on this website there is a page where special masks designed to filter out the suspected toxins are offered for sale. It is naturally recommended that one pull out their mask at the first hint of a fume event. The masks fold flat and are £5.00 each or £46.00 for 10. Another relevant site is www.gcaqe.org. GCAQE is a global coalition of health and safety advocates committed to raising awareness and finding solutions to air quality problems in aircraft. In the opinion of some, filters could be installed in the air stream into the cabins to remove these toxins at a small cost per plane, but the cost to the industry as a whole would be high and probably unacceptable given that the financial health of the airlines continues to be fragile.

Finally, a website worth visiting is AFA-CWA air safety, health and security department. This site makes it quite clear that this is a high profile topic among airline flight attendants. http://ashsd.afacwa.org/?zone=/unionactive/viaw_article.cfm&HomeID=1396&page=Healthissues.

FRACTURES, FALLS, AND VITAMIN D IN OLDER WOMEN

A study just published in *JAMA* claimed to have found that among older community-dwelling women, an annual oral administration of a high-dose of vitamin D3 resulted in an increased risk of falls and fractures.⁹ This should be a welcome result for the anti-supplement fraternity. It also brings up a broader subject, the role of vitamin D status and chronic pain, muscle weakness and incapacitation in older women. But first, the falls and fracture study.

A group of older women (median age 76) was randomized to 500,000 IU of D3 or a placebo every fall to winter for 3-5 years. This was delivered orally over 10 days in equal doses. At the start of the study the vitamin D status for treated and controls, as measured by 25-hydroxyvitamin D (25(OH)D), was about 50 nmol/L or about 20 mg/mL, which is generally considered only borderline deficient. Severely deficient would be ≤ 20 nmol/L and profoundly deficient is ≤ 10 nmol/L. Thus one can argue

that the study group would be expected to exhibit a small or no benefit. When the results were adjusted for calcium intake, it was found that only the frequency of falls was significantly increased (16%, statistically significant). Fractures and non-vertebral fractures were not significantly increased. An editorial¹⁰ pointed out that improving the vitamin D status could have encouraged more mobility and activity, a well known effect, and thus more falls, and thus the interpretation of the study was open to question. The editorialists also questioned the very high short-term dose protocol used has the potential for a deleterious effect due to feedback mechanisms. However, large single doses, generally vitamin D2, have been used for some time to treat severely deficient individuals and toxicity has never been observed except in unusual cases of accidental doses such as 1,700,000 UI/day for several months or accidental doses that achieved levels of 25(OH)D of over 1200 nmol/L. See *Vitamin D: Is the Need and Evidence for Supplementation Being Ignored* http://www.yourhealthbase.com/D_vitamin.htm But D2 is different in many respects from D3.

Falls and fractures are not the only problems confronting the elderly and the frail, or for that matter anyone deficient or severely deficient in vitamin D. Other problems include severe muscle weakness or near total muscle failure and severe chronic pain, frequently not localized.¹¹ When vitamin D deficiency is severe in adults it can cause osteomalacia which is characterized by decrease serum calcium and phosphate levels and elevated parathyroid hormone. X-rays will not necessarily exhibit abnormalities. Individuals with osteomalacia present with muscle pain, frequently in the lower back region and thighs, and the pain spreads to the arms and ribs. Muscle weakness is also present. In severe cases, it becomes difficult or impossible to climb stairs or even walk. Needing a wheelchair is common. When the root cause is vitamin D deficiency, large weekly doses (e.g. 10,000 IU) for up to six weeks will generally result in dramatic improvement. Either oral dosing or injections can be used, the latter taking into account the possibility that the oral dose may be poorly absorbed.^{12,13}

Muscle pain and weakness can also be present when the deficiency is not sufficiently

severe as to produce a diagnosis of osteomalacia, and studies of the prevalence of muscle pain and weakness find thresholds below about 50 nmol/L (20 ng/mL) of 25(OH)D. Severe deficiency is generally set at ≤ 20 nmol/L (8 ng/mL) and is associated in some cases with severe muscle pain and weakness, including incapacitation and the need for a wheelchair.¹³⁻¹⁵

It would appear from an examination of the literature, that it is not uncommon for cases such as severe muscle weakness or severe chronic pain to present a puzzling if not insoluble diagnostic problem, especially in the emergency department setting.¹⁶ These cases appear to be mainly elderly women. The impression one obtains from the literature is that it is common that severe or profound vitamin D deficiency is not considered during the differential diagnosis exercise when an attempt is being made to figure out what is really going on. If indeed the cause is severe or profound vitamin D deficiency and this is not recognized and treated, then the treatment and potential cure of the individual is doomed to failure and the result will probably be inappropriate and ineffective long-term medication. In the case of the elderly, this may be an issue where knowledgeable family members can play a critical role if they can force the issue of a vitamin D status determination and its proper evaluation on the basis of the literature pertaining to vitamin D related chronic pain and muscle weakness.

It is interesting in this context that in at least one university based hospital serving a large medical school in the province of Ontario, the 25(OH)D test is not done in-house with the resultant delay of a number of days to obtain a result. Excluding hypovitaminosis D when attempting to diagnose patients presenting with mysterious muscle weakness and generalized pain is apparently not considered important enough to have the in-house capability to rapidly produce an assay. In fact this possibility may not even be considered, even though it appears well established that some individuals can have a vitamin D deficiency which causes this spectrum of symptoms and not exhibit pronounced blood abnormalities nor radiological manifestations which might suggest osteomalacia. This is particularly bizarre when one considers that it should be universally appreciated that vitamin

D deficiency is very common in the elderly, especially those who are housebound, and the extent of the deficiency can easily explain muscle weakness and generalized pain. Establishing or excluding the link with vitamin D status requires the 25(OH)D test. Readers with elderly family or friends struggling with

muscle weakness and generalized pain, either at home or in a nursing home, need be aware of this potential diagnosis and insist on an exploration of vitamin D status, especially given the high probability of severe deficiency in this age group.

PROCESSED MEAT AND RISK OF CHD AND DIABETES

The conventional wisdom of mainstream medicine and nutrition is that red meat consumption should be moderated. This recommendation traditionally based on the belief in the adverse effects of saturated fat and dietary cholesterol in red meat. Readers of this newsletter should be aware of the shaky and rapidly disintegrating evidence-based foundation for this justification. This was discussed in a recent Research Review (June 2009 IHN issue). If one looks at clinical endpoints such as coronary heart disease (CHD), stroke and type 2 diabetes, the evidence from studies is conflicting and inconsistent. In the past, studies have lumped processed and unprocessed meats together in spite of the fact that the former consist of a grand mixture of meat and chemicals. The first study with clinical endpoints to separate these two types of meat has just appeared in the journal *Circulation*.¹⁷ This was a systematic review and meta-analysis of studies where it was possible to separate out the results according to the type of meat. Twenty studies met the inclusion criteria and involved over 1.2 million individuals. In some instances where published data was inadequate, study authors were contacted and provided data separated into processed and unprocessed consumption.

Red meat was not associated with CHD or type 2 diabetes. In sharp contrast, consumption of processed meats was associated with statistically significant 42% increase in the relative risk of CHD and a 19% increase in the relative risk of diabetes which was also statistically significant. Consumption of either red or processed meat was not associated with stroke risk, but the number of studies and events was limited and the

statistical power low. Relative risk estimates were on the basis of consumption of 100 g/day of red meats or 50 g/day of processed meats.

The authors suggest that the enhanced risk associated with processed meats is due to the very high levels of salt and preservatives such as nitrates. Nitrates and their by-products are known from experimental studies to promote atherosclerosis and vascular dysfunction, reduce insulin secretion, and impair glucose tolerance, and a nitrosamine-related compound found in cooked processed meat is a known diabetogenic chemical. Thus while this analysis of observational studies does not prove causality, there is biologic plausibility for the findings. Incidentally, in the studies used, the saturated fat and cholesterol content of both types of meat was similar.

Thus it appears that while we evolved over eons on a diet that included lean red meat, there has not been time for us to adapt to eating the chemical feast offered by processed meats. It seems that every month there is new evidence that the famous and catchy phrase "better things for better living through chemistry" is misleading. Obviously, if official recommendations are to be consistent with what evidence is available, the public health statement should be to avoid processed meats. Strong, effective industry opposition would be expected. In the above study, processed meat was defined as any meat preserved by smoking, curing or salting or addition of chemical preservatives and included bacon, salami, sausages, hot dogs and processed deli or luncheon meats. Unprocessed meat included beef, pork and lamb.

HEAVY ON CARBS AND HOLD THE FAT. THE WRONG CALL

As has been discussed repeatedly in this newsletter, in the era when fat was considered the ultimate dietary evil, there was widespread flight to low-fat or even near zero-fat diets and the calorie deficit was made up with carbohydrates, mostly selected without care or knowledge as to their varying impact on metabolism. The view that this was neither evidence-based nor desirable, and in fact might be dangerous fell on deaf ears as does anything contrary to established dogma. Finally, we now have a study that directly addressed this subject and utilized myocardial infarction (MI--heart attack) as an endpoint and also addressed the question of the glycemic index of the substituted carbohydrates.

This was a prospective cohort study involving almost 54,000 men and women free of MI at baseline. The substitution of fat with carbohydrates was examined with stratification according to the glycemic index. The glycemic index is based on the area under the two-hour glucose response curve after ingestion of a fixed portion of a carbohydrate. Both pure glucose and white bread are used as a reference. In this study, it was white bread. Thus the glycemic index reflects the extent to which a fixed amount of a given carbohydrate source elevates blood sugar and how it influences the rate of glucose metabolism.

Over a 12-year follow-up there were 1943 incident MI cases. There was no significant association between the risk of MI and the substitution of saturated fat with low-glycemic index carbohydrates. However, when the substitution involved high-glycemic index

carbohydrates, there was a 33% increase in the risk of MI per 5% increase in the increment of energy intake from this source. For a 2000 calorie diet, this corresponds to 25 g of carbohydrate, which incidentally is not very much (two slices of white bread or one bagel). There was no observable increase in risk for medium-glycemic index carbohydrates, nor was any gender difference observed. The inconsistent results from other studies where carbohydrates were substituted for saturated fat may in part be explained by the failure to properly differentiate the effect of glycemic index.

If one wished to load up their shopping cart with high-glycemic index foods, they should select bread, rolls, other baked goods, pizza, white rice, most ready-to-eat cold cereals, sugar and sugar-sweetened beverages. This is not a complete list! In the supermarket, lengths of the cold cereal and soft drink aisles and the huge selection is always impressive.

In an editorial, Harvard's Frank Hu, a leading nutritional epidemiologist, commented that this study is notable for its size, long duration of follow-up, and detailed assessment of dietary and lifestyle factors (for dealing with confounding). He concludes that "In this era of widespread obesity and insulin resistance, the time has come to shift the focus of the heart-diet paradigm away from restricted fat intake toward reduced consumption of refined carbohydrate."¹⁸ It is interesting that this has been the message of many low-carb weight-loss diets promoted in best-selling books over the past several decades. They were called fad diets to emphasize mainstream contempt.

NEWS BRIEFS

ANTIPSYCHOTIC DRUGS FOR TODDLERS

There appears to be growing use of antipsychotic drugs prescribed to very young children. A study recently published in *Journal of the American Academy of Child and Adolescent Psychiatry*¹⁹ examined the growth in the use of this class of medication between 1999-2001 vs. 2007 in children age 2 to 5 in the privately insured setting. This is not a misprint. Children as young as 2 are now being given these drugs which are approved for only a very few indications in older children. The change over the period studied was from one per 1300 children to one per 560 children. The approved disorders for older children (age > 6 years) are schizophrenia, behavioural symptoms of autism, Tourette's disorders and mixed or manic bipolar episodes. Off-label disorders being treated in

toddlers include disruptive behaviour and attention deficit hyperactivity disorder. This same so-called off-label use in older children as well as an increasing trend in use has also recently been reported.²⁰ In the case of the very young children, the study found that treatment was initiated in about half those treated without mental health assessment, a psychotherapy visit or a visit to a psychiatrist.

It is safe to say that no one knows the long-term potential for harm associated with giving a 2-year old an antipsychotic drug for an off-label indication when there presumably are no long-term studies on either safety or efficacy. These children are really being used for uncontrolled and perhaps ill-advised experiments, presumably in response to parental requests for a solution to a perceived behavioural problem that has the simplicity of simply giving a pill. These drugs are certainly not free of side effects. What is known is that the second-generation antipsychotic drugs, the most commonly used, have cardiometabolic risks during first-time use which involve significant drug induced weight gain and adverse changes in metabolic and cardiovascular risk markers.²¹

A cynical view of the long-term result of what appears to be serious and significant over-medication may be that by early adulthood, almost everyone will be on several anti-psychotic prescriptions in an attempt to meet controversial and in some cases totally unjustified targets associated with various behavioural parameters, interventions frequently justified by weak or statistically insignificant studies. In psychiatry it is rumoured that the new handbook of mental diseases will be expanded to include almost every slightly abnormal behaviour, label it as a disorder or disease, and open the door for pharmaceutical intervention.

ALCOHOL, BENIGN BREAST DISEASE AND RISK OF BREAST CANCER

The period between menarche (the beginning of menstruation) and first pregnancy is considered critical with respect to exposures related to the risk of breast cancer since the mammary gland cells are undergoing rapid proliferation and may be more vulnerable to malignant transformation. A recent study has examined the relationship between adolescent alcohol consumption and the incidence of benign breast disease (BBD) which predicts an increase risk of later breast cancer for certain cellular subtypes.²² This study involved a cohort made up of daughters of the Nurses' Health Study participants. The follow-up included a 2003 survey which contained a series of alcohol related questions and surveys between 2005 and 2008 which inquired about diagnoses of BBD. The age at the time of the alcohol survey was 19-20.

It was found that after adjusting for age and body mass index, the risk of biopsy-confirmed BBD increased by 50% per drink per day. Girls who drank typically 6 or 7 days/week were at almost 5 times higher risk compared to those who never drank or who drank less than once per week. These results remained essentially unchanged when the data was further adjusted for age at menarche, age when regular drinking began, and maternal history of BBD or breast cancer. The authors point out that these results are consistent with observational studies where data regarding adolescent drinking was collected later in adulthood.

While BBD is, as the term indicates, a benign disease, its clinical presentation generally prompts both anxiety and an invasive biopsy. Furthermore, the association with the risk of later developing breast cancer should give teenage girls pause to reflect on their alcohol consumption habits, especially in college where alcohol has an important if not central place in the culture, at least at some institutions. Furthermore, if greater than very moderate drinking becomes a habit during the late teens or at college, it may carry over to adulthood, and the increase in the risk of developing breast cancer is real and significant independent of BBD. Exceeding between one or two drinks a day for an adult woman crosses the threshold of increased risk.

ORAL HYGIENE AND CARDIOVASCULAR DISEASE

In the June issue of the Newsletter there was included a Research Review concerning the hypothesis that atherosclerosis and cardiovascular disease (CVD) were triggered by chronic and acute infections. Closely related to this review is a paper which just appeared in the *British Medical Journal*.²³ The study of oral hygiene and CVD was based on the Scottish Health Survey which draws on a nationally representative sample of the general population in Scotland. The study had a follow-

up of about 8 years and 12,000 men and women (mean age 50) participated. The endpoints of interest were cardiovascular events or death and data was collected to allow correction for confounding. As well, C-reactive protein and fibrinogen measurements at baseline were available for a subset. Participants were stratified into three groups, those who brushed twice a day, once a day or rarely or never.

For those who rarely or never brushed, a 70% increase in risk for CVD events was found when the comparison was with twice a day brushing. Comparing once to twice a day produced an enhanced risk of 30%. These results were statistically significant and adjusted for a number of confounding factors. If the only adjustment was age/gender, the corresponding relative risks were 130% and 40%. Poor oral hygiene was also associated with higher C-reactive protein and fibrinogen levels.

Poor oral hygiene is the major cause of periodontal disease which involves a chronic infection of the tissue surrounding the teeth. It is one of the most common chronic infections and is associated with moderate systemic inflammatory response. It is also associated with increased risk of coronary plaque. The results of this study were not explicitly adjusted for oral hygiene provided periodically by dentists, but the adjusted models were corrected for visits to the dentist. But it was found that a much higher percentage of those who rarely brushed also only rarely visited the dentist (63%) whereas among those who were more concerned about oral hygiene by brushing twice a day, only 16.5% rarely visited a dentist.

Whether or not one finds the arguments that associate CVD-CHD with infections convincing or strongly suggestive, this study should provide incentive for frequent brushing, flossing and frequent dental check-ups including cleaning. It is appreciated that it is unlikely that readers of this newsletter are among those who rarely if ever brush their teeth or visit a dentist, but this study is of considerable academic interest and as well should inspire parents to strongly encourage their children to develop good oral hygiene habits.

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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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This issue contains Part III of Hans Larsen's review of androgen deprivation in the context of radiation therapy. Part III starts with a short description of the side effects of radiation therapy. This is followed by a discussion of the adverse effects of androgen deprivation. This is vital information for men considering this option since such decisions must be made by carefully considering the risks vs. benefits and this is far from a simple matter.

The review concludes with a detailed set of conclusions which readers should find very informative.

Wishing you good health,

William R. Ware, PhD, Editor

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RESEARCH REPORT

Radiation Therapy and Androgen Deprivation

Part 3 – Adverse Effects and Summary

by
Hans R. Larsen, MSc ChE

Side Effects of Radiation Therapy

Radiation therapy (RT) to the pelvis is associated with both short- and long-term side effects. The development of more accurate focusing techniques such as 3-dimensional conformal radiation therapy and intensity modulated radiation therapy (IMRT) has significantly reduced the incidence of these side effects and most of them are reversible.

Short-term side effects include skin irritation in the irradiated area, abdominal discomfort, diarrhea, excessive gas and cramping, and fatigue. Radiation may also increase urinary frequency and cause a burning sensation during urination.

Longer term side effects include changes to the lining of the rectum, colon or bladder, and a narrowing of bowel (colon) diameter. The incidence of serious bowel injuries with 3D-CRT is about 17%. These changes might result in diarrhea, bleeding from the rectum, blood in the urine, and increased frequency of urination. The incidence of radiation cystitis is 6 to 7%. [13] Scarring around the nerves close to the prostate may cause impotence (erectile dysfunction) in 40 to 50% of men with a higher rate among older men. About 75% of patients with post-irradiation erectile loss find medications such as sildenafil (Viagra) to be helpful. [17]

RT is associated with a substantial increase in highly reactive free radicals. Thus it is not surprising that the therapy is associated with an increased incidence of secondary cancers. Researchers at the University of Virginia compared the incidence of various secondary cancers among 140,000 prostate cancer patients at least 5 years after prostate cancer diagnosis between a group of men who received EBRT and a group of PC patients who received no radiation treatments. Highlights of their findings are presented below: [18]

<u>Secondary Cancer</u>	<u>Incidence, %</u>	
	<u>EBRT</u>	<u>No RT</u>
Bladder	1.46	0.89
Colon	0.40	0.35
Rectal	0.44	0.28
Lung	2.05	1.64
Pancreas	0.28	0.30

The incidence of rectal and bladder cancer is 64% and 57% higher respectively among patients who received EBRT than among those who did not receive RT. Nevertheless, the absolute percentage of men who develop these cancers is relatively low.

Adverse Effects of Androgen Deprivation Therapy

Medical castration is another term for treatment with LHRH agonists (ADT) alone or in combination with antiandrogens (CAB). It essentially achieves the same effect as surgical castration (orchiectomy) which removes the testicles and thereby essentially eliminates testosterone production. However, medical castration is at least partially reversible. The adverse effects of testosterone elimination (hypogonadism) are many and varied and include:

- | | |
|----------------------|-----------------------------------|
| Anemia | Weight gain |
| Hot flushes | Breast enlargement (gynecomastia) |
| Loss of libido | Depression |
| Erectile dysfunction | Cognitive problems |
| Loss of muscle mass | Osteoporosis |
| Loss of body hair | |

There is now also compelling evidence that androgen deprivation therapy may induce metabolic changes leading to the development of the metabolic syndrome, atherosclerosis, and diabetes, and increasing the risk of heart attack, stroke and sudden cardiac death.[19,20]

Three years ago Christopher Saigal and colleagues at the University of California at Los Angeles warned that just one year of ADT was associated with a 20% increased risk of developing serious cardiovascular disease and that patients began incurring this higher risk within 12 months of treatment. They conclude that, “ADT is associated with significantly increased cardiovascular morbidity in men with prostate cancer and may lower overall survival in men with low-risk disease”.[21]

In October 2009 Anthony D’Amico and colleagues at the Dana Farber Institute reported that men with intermediate- and high-risk PC and moderate to severe comorbidities (heart disease in particular) have very poor overall survival when given 6 months of CAB in conjunction with EBRT. The results are given below:

<u>8-year survival</u>	<u>EBRT</u>	<u>EBRT + CAB</u>
Intermediate-Risk Disease		
PCSS	100%	94%
OS	50%	28%
High-Risk Disease		
PCSS	100%	100%
OS	44%	0%

It is clear that, while ADT may have a small favorable effect in preventing death from PC in men with moderate to severe comorbidity, this effect is vastly overshadowed by the unfortunate tendency of even short-term CAB to increase death from other causes dramatically.[22]

The finding that ADT increases the risk of cardiovascular disease was disputed in two articles by Jason Efstathiou, et al. at Massachusetts General Hospital who concluded:

“GnRH agonists do not seem to increase cardiovascular mortality in men with locally advanced prostate cancer.”[23]

“Longer duration of adjuvant GnRH therapy does not appear to increase cardiovascular mortality in men with locally advanced prostate cancer.”[24]

Nevertheless, by late 2009 and early 2010 the evidence of serious metabolic and cardiovascular problems associated with even short-term use of ADT became clear. European prostate cancer specialists reported that even 3 months of treatment with ADT increased cholesterol levels and

decreased insulin sensitivity. In addition, men who received ADT had a 42% increased risk of developing diabetes, a 20% increased risk of coronary heart disease, and an 11% increased risk of experiencing a heart attack when compared to patients not receiving ADT. Finally, the researchers pointed out that, “*Even short-term use of ADT may lead to numerous side effects, such as osteoporosis, obesity, sarcopenia, lipid alternations, insulin resistance, and increased risk of diabetes and cardiovascular morbidity. Despite these side effects, ADT is commonly used in various clinical settings in which a clear effect on improved OS has not been shown.*”

They conclude that, “*It is obvious that a substantial number of patients are exposed to ADT without evidence-based proof of efficacy. Because ADT may lead to numerous side effects and because medical castration is costly, it may be inappropriate to offer ADT in some clinical setting.*”[25]

The January 6, 2010 issue of the *Journal of the National Cancer Institute* contained an article by Nancy Keating and colleagues from Harvard Medical School. The article described the conclusions reached from a study of 37,443 veterans diagnosed with PC during the period 2001 to 2004. They found that men whose treatment involved ADT were 28% more likely to develop diabetes, had a 19% higher risk of coronary artery disease, a 28% higher risk of suffering a heart attack, sudden cardiac death (35% increased risk) and stroke (22% increased risk) than did men whose treatment did not include the use of ADT. The authors conclude that, “*Androgen deprivation therapy with GnRH agonists was associated with an increased risk of diabetes and cardiovascular disease.*”[26]

Finally, on February 16, 2010 the American Heart Association, the American Cancer Society, and the American Urological Association issued a joint *Science Advisory* confirming that adverse effects such as increases in cholesterol and triglyceride levels, decreased insulin sensitivity, and an increased risk of coronary heart disease became evident within 4 months of starting ADT. The group concludes that ADT may be associated with an increased risk of cardiovascular events and that, while the benefits of ADT likely outweigh the risks in the case of high-risk PC, this may not be the case if using ADT in the treatment of localized cancer, or in the case of biochemical failure.[27]

Adverse Effects on Bone Mass

In addition to it's, by now well-established, risk profile concerning diabetes and heart disease, ADT also has a profound, negative effect on skeletal health. In November 2008 a group of Canadian researchers reported that PC patients receiving ADT had a significantly lower BMD (bone mass density) than did those not receiving ADT. Decreases in BMD after 1 year of ADT ranged from non-significant to a BMD loss of 4.8% at the spine and 3.8% at the hip. There is also evidence that PC patients as such have a substantially increased risk of hip fracture. The researchers conclude that, “*Androgen deprivation can be considered a risk factor for the development of osteopenia, osteoporosis, and bone fracture.*”[28]

Researchers at Duke University School of Medicine point out that because estrogen in men is derived through aromatization of testosterone, the reduction in testosterone through ADT also decreases estrogen levels. This can lead to a number of estrogen deficiency induced side effects such as hot flashes, gynecomastia, memory loss, elevated cholesterol level, and increased bone fracture risk.

A Danish study compared a control group of 47,149 men with 15,716 men who had suffered a fracture. They found that men with PC who had been treated with ADT had a 70% increased risk of any fracture and a 90% increased risk of hip fracture. Finally, a Medicare claims-based cohort study involving 11,661 PC patients concluded that men who received ADT had a 21% increased risk of any fracture and a 30% increased risk of hip fracture.

Several studies have found that even men who receive less than 6 months of ADT experience a significant loss of bone mass (reduced BMD). Average decreases in BMD associated with short-

term ADT were – 2.5% at the hip, - 2.4% at the trochanter, and – 4.0% at the spine. Furthermore, among men who received long-term ADT there was a 3-year reduction in overall median survival after a fracture.

Nearly 70% of men receiving ADT experienced hot flashes which in 50% of cases continued for 5 years or more following discontinuation of ADT.

The Duke researchers conclude that, *“Adverse effects associated with estrogen deficiency that results from ADT, includes increased fracture risk, hot flashes, gynecomastia, adverse lipid changes and memory loss. Not only do these adverse effects create physical and psychological distress, but as is the case with increased fracture and lipid changes, they can also greatly impact patients’ overall health and have a significant impact on survival.”*[29]

Vahagn Shahinian and colleagues from the University of Texas studied the records of over 50,000 PC patients and found that among men who survived at least 5 years after diagnosis, 19.4% of those on ADT experienced a fracture as compared to 12.6% in the group not receiving ADT. They conclude that, *“Androgen-deprivation therapy is associated with an increase in the risk of fracture among older men with prostate cancer. The risk increases with the number of doses of a gonadotropin-releasing hormone agonist administered during the first year after diagnosis.”*

The University of Texas group also makes this thought-provoking statement, *“Androgen-deprivation therapy for prostate cancer can reduce morbidity, palliate metastases, and improve survival in locally advanced disease when combined with radiation. However, androgen-deprivation therapy alone, in the form of gonadotropin-releasing hormone agonists, is increasingly being used in men with localized prostate cancer (cancer confined to the prostate) and in men in whom the level of prostate-specific antigen (PSA) rises after prostatectomy – both situations in which most patients are minimally symptomatic and no survival benefit has been demonstrated.”*[30]

Testosterone Recovery

The Canada Multicenter study reported that total testosterone level returned to a value within the normal range in 92% of men treated with EBRT and CAB at a median of 6 months following completion of EBRT.[1]

Heymann, JJ, et al. (Study H) observed that serum testosterone concentration returned to normal (≥ 270 ng/dL) in 69% of patients within a median of 9 months. Patients who recovered testosterone levels after CAB were significantly more likely to survive for 5 years (95% did so) than were patients whose levels did not recover (70% survival). Sixty-nine percent of study participants were sexually potent when entering the study. Most lost potency during treatment, but 65% (of the 69%) recovered potency after a median of 10 months.[14]

In contrast, a study by Anthony D’Amico, et al. involving 220 men with high-risk PC found that it could take as much as 3 years for some men to regain baseline testosterone levels after having undergone EBRT + ADT and that only 38% of men had achieved baseline testosterone levels 12 months after stopping ADT. Older men tended to return to normal testosterone levels at a slower rate than did younger men.[22]

Summary

Nine major clinical trials aimed at determining the benefits of radiation therapy (RT) accompanied by androgen deprivation therapy (ADT) or complete androgen blockage (CAB) were reviewed. The majority of patients enrolled in the trials had locally advanced PC (tumor stage T3 or higher), but 461 patients with localized cancer were also included. The following conclusions were reached:

- Patients with localized disease and a Gleason score of 7 or less derive little if any benefit from adding ADT or CAB to EBRT. However, patients with unfavorable localized disease, especially those with a Gleason score of 8 to 10, can derive substantial benefits, especially if hormone therapy is tailored to achieve a PSA nadir prior to the start of EBRT. Long-term adjuvant therapy would likely provide little additional benefit over short-term therapy in patients with localized cancer.
- Patients with locally advanced PC and a Gleason score below 7 may benefit from a short course of CAB in combination with EBRT. For patients with a Gleason score of 7 to 10, long-term therapy (28 to 36 months) may provide improved survival.
- Biochemical failure (BF) at 5 years is inversely correlated with disease-free survival (DFS), PC-specific survival (PCSS), and overall survival (OS) at 5, 8 and 10 years (from initiation of treatment) and also predicts the probability of distant metastasis at 5 years. BF, in turn, is directly associated with initial PSA value and inversely correlated with duration of androgen deprivation.
- PCSS is directly correlated with DFS and inversely correlated with tumor stage, initial PSA value, BF, and distant metastasis at 5 years.
- OS is directly correlated with DFS and inversely correlated with BF and distant metastasis at 5 years.
- There is a strong direct correlation between PCSS and OS with a Gleason score greater than 7 and a tumor stage of T3 or greater increasing the proportion of overall mortality associated with PC or its treatment.
- Continuing ADT or CAB beyond 6 months following EBRT results in a PCSS increase of less than 0.1%/month of continued therapy. In contrast, the first 6 months of therapy is associated with a 1.3% to 2.5% gain in PCSS per month of therapy. Corresponding numbers for OS is 0 to 0.14%/month improvement for treatment beyond 6 months versus 1.8 to 2.7%/month for the first 6 months.
- Long-term PCSS (8 to 10 years from initiation of EBRT) is directly correlated with DFS and inversely correlated with tumor stage, initial PSA value, BF, and distant metastasis at 5 years.
- Long-term OS is directly associated with longer DFS and inversely correlated with BF, distant metastasis, initial PSA value, and tumor stage.
- Both EBRT and ADT have the potential for serious adverse effects. Recent research has shown that even a short course of ADT or CAB can have profound negative effects including increased risk of cardiovascular disease, diabetes, heart attack, sudden cardiac death, and osteoporosis.

- It is likely that early recovery of normal testosterone levels is associated with better survival, but the literature is by no means unanimous when it comes to estimating how long it will take to return to normal levels.
- As in any medical intervention, there is a trade-off between benefit and risk when it comes to ADT or CAB as an adjuvant to RT. The review of the 9 clinical trials and recent information regarding serious adverse effect would lead one to the conclusion that ADT and CAB should not be routinely used in low-risk and intermediate-risk localized cancer. In the case of high-risk localized disease (Gleason score 8 to 10), benefits should be carefully weighed against risks and ADT and CAB should not be used in patients with moderate to severe comorbidities (particularly cardiovascular disease). The benefit/risk ratio of long-term ADT or CAB is probably not favorable in localized disease, especially in patients with osteopenia or osteoporosis. Long-term therapy may have a place in the treatment of high-risk (Gleason of 8 to 10) locally advanced PC (tumor stage T3 or higher), although the evidence for this is not entirely consistent.

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