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QUALITY OF LIFE: EXERCISE: As the mantra goes - "Exercise is good for your health" ...

... and that alone should be reason enough to be compliant, but there is a little bit of "Show me" in all of us. Therefore, it is reassuring that basic studies confirm exercises' practical benefits in improving our control over cancer - and possibly even reducing disease incidence. But for us to be consistent in exercising, supportive evidence documenting that our efforts will pay off is always helpful. There is a caveat, however, "*For best results, consistent, and fairly vigorous, effort is required*." The evidence cited here will focus on the benefits of exercise in improving treatment outcome, delaying disease progression, counteracting therapy side effects; and will present molecular data showing how exercise changes gene expression.

Improved Outcome:

The most persuasive and well documented data of exercise improving outcome comes from "Impact of Physical Activity on Cancer Recurrence and Survival in Patients with Stage III Colon Cancer," JCO Aug 2006, reporting on a large CALGB study. Since the "final common pathway" of results of exercise is manifest at the level of gene expression, there is no reason why this study is not applicable to patients with prostate or other cancers.

After setting the stage with the first sentence in the report: "Physically active people have a reduced risk [22% for males] of developing colon cancer," the authors then presented their analysis of the outcome of 832 patients with Stage III, non-metastatic cancer. All received post operative adjuvant chemotherapy. Six months after chemotherapy participants answered a questionnaire about their customary pattern of activity, i.e. average time per week of walking, jogging, swimming laps, racket sports, and many other aerobic exercises.

The unit of evaluation was a "metabolic equivalent task (MET)."

"One MET is the energy expenditure for sitting quietly for one hour." Examples: normal pace walking (2-3 mph), 3 METS; walking at a brisk pace (4+ mph), 4.5 METS; bicycling, 7; ski or stair machine, 6; lap swimming, 7 METS.

Results: Compared to those who engaged in less than 3 MET-hours per week, those performing 18 - 26.9 showed ~ a 50% improvement in disease-free survival, and for >27 MET units the benefit was a 55% increase! That translated to disease-free survival at 4 years for the higher MET cohorts of about ~88% vs. ~75% for the lowest. [That's pretty effective adjuvant therapy!]

Effect of Exercise on Prostate Cancer Risk and Grade of Prostate Cancer:

Antonelli et al., J Urol, Nov 2009, studied 190 men who underwent prostate biopsy and completed a questionnaire on current exercise behavior. They calculated the intensity of exercise in terms of MET-hours per week. The men engaging in more than 9 units "were significantly less likely to have cancer on biopsy, p=0.007." Among men with malignant biopsy results, those reporting moderate exercise (3 - 8.9 MRT-hours/week) were diagnosed less frequently high grade disease (Gleason 7 or greater, p=0.04).

An analysis of prostate cancer characteristics in 2892 men based on the Health Professionals Follow-up Study showed that in men older than 65, those performing at the highest category of vigorous activity (MET-hours/week of 29 vs 0) the diagnosis of advanced prostate cancer was reduced by nearly 75% (Arch Intern Med, 2005 May).

A European consortium reported (Int J Cancer, Aug 2009) that "higher levels of occupational physical activity was associated with lower risk of advanced stage prostate cancer, p=0.024.

Exercise Combats Decline in Body Physical Function Associated with Androgen Suppression.

Body fat increases, lean body mass and muscle strength decline with chronic ADT (Levy, Urology, Apr 2008). Galvao et al. (JCO, Jan 2010) addressed this issue in their study, "Combined Resistance and Aerobic Exercise Program Reverses Muscle Loss in Men Undergoing Androgen Deprivation Suppression for Prostate Cancer Without Bone Metastases: A Randomized Controlled Trial." Twenty nine men on ADT participated in a regimen of "progressive resistance and aerobic training twice a week for 12 weeks" and were compared to 29 men following their usual activities. Whole body and regional lean mass was assessed as well as muscle strength and function and quality of life.

Results: "total body and regional lean mass significantly increased ...,[and] all muscle strength tests, [tests of] functional performance and balance assessment significantly improved. "General health and reduced fatigue were significantly enhanced in the exercise group compared to the control group, and the program was well tolerated...."

Exercise Resets Gene Expression (which controls everything).

Although the molecular mechanisms mediating the beneficial effects of exercise are not fully understood, a prime candidate for an explanation is exercises' reduction of the unhealthy combination of higher circulating levels of serum insulin and a matching decrease in one of its binding proteins (IGFBP1), both associated with obesity and a sedentary life style.

In a seminal paper in J.Urol, Sept 2005, "Intensive Lifestyle Changes May Affect Progression of Prostate Cancer", Dean Ornish, Peter Carroll et al. studied gene expression before and after a 3 month intervention in 93 *untreated* men diagnosed on biopsy with low-risk prostate cancer. Randomization divided the group into intervention vs. control. The regimen was a combination of low-fat diet, >3.6 hours per week of exercise, and stress management. Forty eight genes were up-regulated and were 453 down-regulated. "Pathway analysis identified significant modulation of biologic processes that have critical roles in tumorigenesis ... ."

Results: Serum collected from men after the 3 month intervention showed a 70% decrease in the in-vitro growth of LNCaP cells versus a 9% reduction from the control serum (P=0.001).

Another study on the effect of a high-fiber, low-fat diet/exercise intervention (Cancer Causes Control, 2002 Dec) found that compared to serum collected at baseline, serum obtained after an 11 day or a long-term program decreased serum insulin levels by 25% and 68%,respectively. The post-intervention serum of these two cohorts suppressed growth and enhanced apoptosis/necrosis of the androgen-sensitive cell line, LNCaP, by 30% and 44%!

BOTTOM LINE: As you might expect, some studies are less positive than the ones cited. But the overall message from the accumulating data is quite clear: the old mantra is on target! We'd better get off our duffs!

***The important benefit of exercise in all phases of prostate cancer has not received sufficient recognition. The May/June issue of the PCa Commentary will carry a guest article on this subject by Dr. David Zucker, MD, PhD, Onco-Physiatist, Medical Director and Program Leader, Cancer Rehabilitation Services, Swedish Cancer Institute, Seattle, WA. http://www.swedish.org/body.cfm?id=2304

BASIC SCIENCE & BIOLOGY: About Testosterone: ... It's not all that intuitive.

Testosterone, that infamous molecule, whose name rolls off our tongues with such familiarity, has a biology that offers many surprises. Here are some of them:

(Data source: "Shifting the Paradigm of Testosterone and Prostate Cancer: The Saturation Model and the Limits of Androgen-Dependent Growth," European Urology, 55(2009).

1) In *non-castrate* men increasing serum testosterone (sT) does *not* promote cancer growth; there is *no* direct association between serum T levels and prostate cancer risk. T therapy *does not* cause an increase in intraprostatic T or dihydrotestosterone (DHT), or an increased androgen receptor concentration, or alter gene expression.
2) The increasing incidence of cancer in the aging male occurs in the setting of *declining* sT levels.
3) There is *no* correlation between sT and PSA level or prostate volume.
4) In *hypogonadal* men (i.e. men with sT less than the normal range of 300 - 1000 ng/dl) T replacement *does not* increase PSA or promote the development of prostate cancer.
5) The T flare associated with the initiation of an LHRH agonist *does not* elevate PSA.
6) Many studies have shown that prostate cancers diagnosed in men with *low* sT are more likely to be of high Gleason grade and more aggressive with greater risk of capsular penetration.

How are these seemingly contradictory observations explained? The "Saturation Theory" advanced by Morgentaler, Harvard Medical School, and Traish, Boston University School of Medicine posits that the androgen receptor has a finite capacity to bind and respond to the androgenic ligands T and DHT. Serum T above this level is "excess." "Maximal androgen AR binding is achieved at serum T concentrations well *below* the physiologic range." This threshold is estimated to be at a T level of about

120 ng/dl, and as the amount of androgen binding to the receptor decreases below this saturation level, gene expression transitions to the pattern characteristic of the "castrate" state. While T and its intracellular metabolite, 5alpha-DHT serve as critical factors for prostate tissue growth, Morgentaler cites many studies to explain why "raising T concentration several times higher than the physiologic range produces no measurable change in PSA level or prostate volume among men without cancer." However prostate cancer growth, as it is well known, "is exquisitely sensitive to variations in serum T concentrations at or below the near castrate range," conventionally achieved when an LHRH agonist lowers sT to <50 ng/dl or to the even lower T value of <20 ng/dl by surgical castration.

BOTTOM LINE: The "Saturation Theory" holds that the androgen receptor is "fully saturated" at an estimated serum testosterone level of 120 ng/dl and values higher than this in the *non-castrate* man produce no change in PSA, prostate volume, or the incidence of prostate cancer.

HORMONE INTERVENTION: Male Estrogen Deficiency - Is Testosterone Taking a Bum Wrap ...

... for all the unwelcome side effects of androgen deprivation therapy (ADT), since so many of them actually result from a deficiency of estrogen, testosterone's sister molecule?

The case for a sharing of the blame is presented in "Androgen deprivation therapy and estrogen deficiency induced adverse effects in the treatment of prostate cancer," by Freedland et al. Prostate Cancer and Prostatic Diseases, Dec. 2009.

The key biologic point, as noted by the authors, is since "estrogens are derived in men through the aromatization of testosterone, the reduction of testosterone due to ADT also decreases the levels of estrogen." It is *low serum estrogen* that accounts for increased fracture risk and osteoporosis, hot flashes, gynecomastia, serum lipid abnormalities, and memory loss. Testosterone deficiency takes responsibility for erectile dysfunction, diabetes, muscle weakness, anemia, the loss of lean body mass, and the increase in total body fat.

In the adult male the serum estrogen (17 beta-estradiol) levels range from 10 - 60 pg/ml (and gradually decrease with aging), but ADT can reduce levels to those seen in pre-puberty, 2 - 8 pg/ml, which are similar to the levels seen in postmenopausal women (5 - 18 pg/ml).

Briefly, what biology underlies these estrogen deficiency effects?

1) Osteoporosis results from increased bone remodeling and increased bone resorption due to increased activity and longer lifespan of osteoclasts due to estrogen deficiency.

2) Hot flashes are thought to result from an imbalance of peptide activity in the hypothalamus and a lowering of the body's thermoregulatory set point causing the heat loss mechanism to kick in.

3) Gynecomastia and breast and nipple tenderness result from an increased estrogen/testosterone ration, particularly seen with antiandrogen therapy where increased testosterone levels lead to greater conversion to estrogen.

4) The increased incidence of cardiovascular disease seen with ADT related estrogen deficiency is associated with higher levels of total cholesterol, low-density lipoprotein cholesterol, and serum lipids.

5) Memory loss and cognitive decline may be associated with the deficiency of both testosterone and estrogen since both receptors are found in the brain, but decline in estrogen is thought to be the mediating factor.

In two studies a measurable decrement in various tests of cognition and memory were associated with the decline of estradiol. Beer, J.Urol, Jan 2006, studied the effect of 0.6 mg transdermal estradiol on 18 men on ADT compared to 18 men continuing only on ADT and a matched set of untreated 18 healthy controls. At baseline, men on ADT functioned worse than controls, but after 4 weeks the men treated with estrogen replacement showed improvement in immediate and delayed verbal memory.

QUALITY OF LIFE: Hot Flashes: A frequent and disturbing side effect associated with androgen suppression. What can be done to help?

Awareness of the troublesome side effects of androgen deprivation dates to as early as 1941 with Huggins' classic report on orchiectomy in the treatment of metastatic prostate cancer. Two to 6 weeks after castration there occurred "profuse perspiration, often occurring at night, forcing the patient to throw off the bed covers." Severity may range from mild facial flushing, perception of warmth, and skin reddening, to severe sweating; and frequency varies from minutes to up to an hour. Whereas in women the flushing usually abates in 2 - 5 years; for 50% of men flushes last longer than five years.

The Freedland article (see above) reports a 77% incidence of hot flashes in men treated with an LHRH agonist. "Up to one-third of men consider these symptoms to be the most distressing, and warranting of treatment."

In Lancet Oncology, Dec 2009, Irani et al. report findings from the largest multicenter, double-blind treatment trial comparing an antidepressant (venlafaxine, "Effexor"), medroxyprogesterone acetate (a progesterone, "Megace") and cyproterone acetate, an *non-steroidal* antiandrogen. After 6 months of Lupron therapy, men who asked for treatment or who had 14 or more flushes per week were randomized with about 100 in each cohort. "The primary outcome was the change in the median daily hot-flushes score between randomization and 1 month."

Results: Men taking Megace, 20 mg/day [in the Freedland article the dose was 20 mg twice daily], reported a decrease in flushes at one month of -94.5%; for cyproterone, 100 mg/day, -83.7%; and for "Effexor" the decrease was -47.2%. The authors concluded that medroxyprogesterone "could be the standard of treatment for hot flushes in men" undergoing androgen deprivation therapy.

In a study by Loprinzi (NEJM, Jan 1995) a dose of 20 mg twice daily led to an 85% reduction in flushes. Sartor, South Med J, Apr 1999, reported a single case in which Megace was associated with a rising PSA level in a castrated man, and a subsequent fall of the PSA when the drug was discontinued.

Freedland added information about treatment with estrogen. In a small study the twice weekly use of a 0.1 mg estrogen patch was associated with a 67% moderate or major reduction of flushes in men treated with ADT. In another study, 1 mg DES daily led to a complete resolution of flushing in 12/14 men on ADT with 2 reporting a reduction in severity and frequency. This regimen carried the consequence of gynecomastia and breast tenderness. The reported cardiovascular morbidity and thromboembolic events seen with the prior 5 mg DES dose is rarely seen at this lower dose.

BOTTOM LINE: Hot flashes in men on ADT occur frequently and are often distressing. Treatment options are available.

CASTRATE RESISTANT PCa: A Heads Up: Phase II promising results for Prostvac-VF - A Vaccination for Prostate Cancer.

Philip Kantoff, writing for a consortium of institutions, (Online JCO, Jan 25, 2010), reports "Overall Survival Analysis of a Phase II Randomized Controlled Trial of a Poxviral-Based PSA-Targeted Immunotherapy in Metastatic Castration-Resistant Prostate Cancer."

In the study 125 men with minimally symptomatic metastatic HRPC patients were allocated (2:1) to PROSTVAC-VF plus granulocyte-macrophage colony-stimulating factor vs. control. Objective evidence of metastasis was confirmed by bone scan or CT. Eligibility required a good performance status and Gleason score of $\leq$ 7 on the original biopsy. The study incorporated a crossover design wherein control patients upon PSA failure could receive PROSTVAC-VF. *The vaccinations were administered subcutaneously.*

The PSA antigen was carried by a vaccinia virus vector (rV-PSA) which was administered once (more applications were found to elicit neutralizing antibodies), and followed by 6 monthly s.q. "booster" doses of a fowlpox-based PSA vector. Each vaccine was combined with a cocktail of three "co-stimulatory"

agents, which served to strengthen the response to the initial PSA exposure, resulting in "augmented immune activation and induction of T cells with high avidity for the [PSA] antigen."

Results: The primary study endpoint was progression-free survival and for this parameter there was no difference between treatment vs control, ~3.7 months for each. "However at 3 years post study, PROSTVAC-VF patients had a better overall survival with 25 (30%) of 82 alive versus 7 (17%) of 40 controls, [and a] longer median survival by 8.5 months," a 44% reduction in death rate. Declines in PSA values were rare.

The early PSA progression seen in the PROSTVAC-VF trial led the authors to postulate that more time is required to mount an effective immune response. The Dendreon trial of "Provenge" testing a similar patient population of men with metastatic disease had also shown "early" PSA progression; however, ultimately showed a 4 month prolongation of survival. The outcomes of these two trials cannot be fairly compared due to the likelihood of unmatched study populations.

BOTTOM LINE: The 8.5 month prolongation in overall survival for PROSTVAC-VF patients over placebo was regarded by the authors as "statistically and potentially clinically meaningful," but appropriately needs confirmation in the planned "larger pivotal Phase II trial"