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Hot Breaking News

Prostate cancer is the most common incident cancer and the second leading cause of cancer mortality in US males. High consumption of calcium and/or dairy products has been relatively consistently associated with an increased risk of prostate cancer, especially advanced prostate cancer, although this relationship is controversial. Using data from the Health Professionals Follow-up Study, a group of researchers at Harvard University recently published a study that examined calcium intake in relation to prostate cancer risk. The results of this study were that higher calcium intake (over 1500 mg/d) was not appreciably associated with total or nonadvanced prostate cancer, but was associated with a higher risk of advanced and fatal prostate cancer. REF #1

Finding effective, less harsh ways to eradicate H. pylori are of continuing interest, given the association of H. pylori with gastritis, gastroduodenal ulcers and gastric cancer. The current approach to the treatment of H. pylori is triple therapy (a proton pump inhibitor [PPI] or bismuth salts with two antibiotics). A recent study has been published showing that talking lactoferrin with triple therapy can improve treatment outcome. Lactoferrin was once thought to mainly act as a transport of iron in the blood, but it has now been shown to have other activities, including inhibiting certain microbes. The authors of the study documented that treatment success rose from 77% to 90% eradication when lactoferrin was given with triple therapy. The conclusions of this study were that bovine lactoferrin is an effective adjuvant to 7-day triple therapy for eradication of H. pylori infection, and may decrease the need for longer term triple therapy treatment. REF #2

Bioidentical Hormone Replacement Therapy and Anti-aging: Confusion and Controversy

Over the next 10 years, up to 30 million women or more may be going through menopause. These women and the clinicians they consult have many issues to consider and choices to make before deciding whether or not to embark on a course of hormone replacement therapy. The availability of science-based sources of information—both for clinicians and the public—is essential.

Dr. Bland discusses two books with different levels of support for the information they put forth: *Merchants of Immortality* by Stephen S. Hall (Houghton Mifflin, 2003) and *Ageless: The Naked Truth about Bioidentical Hormones* by Suzanne Somers (Crown, 2006). REF #3-4

Hormones and Carcinogenesis

Determining the association between circulating sex steroid hormone levels and breast cancer may provide insight into the etiology of the disease and may help identify women who are at high risk and would benefit from increased screening or chemoprevention. The relationships between circulating estrogen and androgen levels and breast cancer

risk are well established among postmenopausal women, but most prospective studies among premenopausal women have been small and have produced inconsistent results. The results of a prospective, nested case-control study within the Nurses' Health Study II cohort were recently published in the *Journal of the National Cancer Institute*. Investigators used blood samples timed within the early follicular and midluteal phases of the participants' menstrual cycles to examine separately the associations between levels of sex steroid hormones in each phase and breast cancer risk in premenopausal women. They concluded that levels of circulating estrogens and androgens may be important in the etiology of premenopausal breast cancer. REF #5

There has been conflicting data on risks of ovarian cancer in users of menopausal hormone therapy. Studies to date have not provided clear evidence on ovarian cancer risk associated with common patterns of hormone use in the United States. Methodologic issues such as small sample size, use of oral contraceptives, or hysterectomy may be contributing factors in discrepancies. A group of investigators has now analyzed data from the National Institutes of Health (NIH)—AARP Diet and Health Study, a large prospective study of US women. The findings of this analysis were published in the *Journal of the National Cancer Institute* in 2006. While use of unopposed estrogen for fewer than 10 years was not associated with ovarian cancer, long durations of use of unopposed estrogen and of estrogen plus progestin (especially sequential regimens) are associated with increased risk. REF #6

Women carrying a mutation in the BRCA1 gene face a high risk of breast and ovarian cancer. Researchers have struggled to understand how the protein encoded by a normal BRCA1 gene works. Early research showed that BRCA1 protein orchestrates the repair of damaged DNA, but because this process occurs continuously in every cell of the body, this finding failed to explain how a mutated BRCA1 would predispose a woman specifically to cancers of the breast or ovaries. A study done on mice now suggests the possibility that the BRCA1 protein moderates the effect of progesterone in breast cells; the protein appears to calm those cells when progesterone urges them to divide and grow. This animal study was reported in a 2006 issue of *Science News*. REF #7

Folate Cycle Nutrients and Carcinogenesis

Epidemiologic studies generally suggest an inverse association between dietary intake and blood measurements of folate and breast cancer risk. However, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial has reported for the first time a potential harmful effect of high folate intake on breast cancer risk. In this study, the risk of developing breast cancer was significantly increased by 20% in women reporting supplemental folic acid intake greater than or equal to 400 μg/day compared with those reporting no supplemental intake. The data from the PLCO trial support the suggestion that folate possesses dual modulatory effects on the development and progression of cancer depending on the timing and dose of folate intervention. REF #8

Hormone Replacement Therapy:
Issues to Consider in the Management of Menopause and Related Health Risks

In a 2006 issue of *Alternative Medicine Review*, a comprehensive review by Dr. Deborah Moskowitz on the safety and efficacy of bioidentical hormones was published. Bioidentical hormones are thought to match the structure and function of the body's endogenous hormones, and have been demonstrated effective in addressing menopausal symptoms. Studies reviewed by Dr. Moskowitz suggest bioidentical progesterone does not have a negative effect on blood lipids or vasculature, and may carry less risk of breast cancer incidence as well as blood clots. She concludes that there is currently enough evidence to support the preferred use of bioidentical hormones over synthetic preparations. REF #9

Until 2003 (when the results of the results of the Women's Health Initiative [WHI] and the Million Women Study [MWS] were published), the majority of investigators believed cardiovascular benefit would be obtained by administering estrogens to postmenopausal women, and that these vascular benefits were specifically linked to the pharmacological effects on the HDL and LDL cholesterol levels provoked by the first pass effect of estrogens in the liver (which can only be achieved by oral administration). In the United States, since the 1960s, some 90% of hormone therapy prescribed for menopausal women was oral administration of a pharmacological estrogen therapy.

The pharmacological accumulation of estrogens in the liver induces metabolic modifications that include increased triglycerides (linked to a decrease in the size of LDL particles), higher levels of C-reactive protein, and activation of coagulation. C-reactive protein (CRP) is one of the most important acute-phase proteins suggested as an independent predictor of adverse cardiovascular events in otherwise healthy women. There is a danger that a pharmacological (oral) method of administration reduces—not increases—the anti-atherogenic effects of estradiol, and therefore also increases the risk of venous and arterial thromboembolism. Recent studies have confirmed the superiority of transdermal estradiol to oral formulations on the main intermediate risk markers. This data supports the assertion that route of administration may be an important consideration in minimizing side effects of estrogen replacement therapy on cardiovascular outcomes. REF #10-11

A clinician prescribing hormone replacement therapy is, in some ways, put into the challenging position of mimicking Mother Nature. The goal is to prescribe the right molecule in the right amount for each particular patient. Drug compounding is a process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient. Until the advent of drug manufacturing in the 1950s, compounding was the exclusive method of preparing medications for clinical use. Bioidentical hormones are manufactured by compounding pharmacists. REF #12-13

Estrogen-related Receptors and Cellular Activity

Estrogen receptor-targeted therapeutics have been successful in the treatment of breast cancer. Orphan estrogen-related receptors (ERRs) represent novel targets for future

development. The emerging role of ERRs in modulating estrogen responsiveness, substituting for ER activities, and serving as prognosticators in breast and other cancers is providing an impetus for the identification of compounds that target these proteins. The development of synthetic ligands for the ERRs may soon provide new agents to supplement current antihormonal therapies to combat breast cancer. REF #14

Estrogen signaling pathways are mediated by two estrogen receptors, ERα and ERβ, which have different biological roles. Studies suggest that drugs targeted selectively to only ERα or ERβ will produce more selective clinical effects, rather than the global effects elicited by estrogens used in current hormone replacement regimens that regulate both ER subtypes. Recent evidence suggests selective activation of the ERβ subtype inhibits breast cancer cell proliferation. A group of investigators recently studied whether the estrogenic activities present in an herbal extract, MF101, are ERβ-selective. MF101 promoted ERβ (but not ERα) activation of an estrogen response element, and also selectively regulated transcription of endogenous genes through ERβ. The investigators concluded that ERβ-selective estrogens may be a safer alternative for hormone therapy compared to estrogens that non-selectively activate both ER subtypes. REF #15

Another paper recently published in the journal *Maturitas* describes a prospective, randomized, double-blind, placebo-controlled trial of a standardized hop extract to alleviate menopausal discomforts. The subjects in this study were healthy women between the ages of 45 and 60 years, who had an intact uterus and had not experienced menses for at least 12 months. A decisive criterion for inclusion in the study was mild to severe menopausal discomfort specifically due to hot flushes (2-5 per day). A secondary criterion for inclusion was abstention from hormone replacement therapy for a minimum of 3 months. The results of this study showed that administration of a hop extract to postmenopausal women over 6 weeks and 12 weeks reduced discomforts and complaints. Rapid improvement of the incidence of hot flushes was evident. The authors of the study assert that hop-derived prenylated flavonoids may provide an alternative treatment for relief of hot flushes. REF #16

Clinician/Researcher of the Month

Bethany Hays, MD, FACOG
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Dr. Bethany Hays is a board certified obstetrician and gynecologist who trained at Baylor College of Medicine in Houston, Texas. She has been in practice for more that 20 years. Dr. Hays is the founder of True North in Falmouth, Maine, a unique integrative practice created by a group of practitioners of conventional and complementary modalities. In addition, Dr. Hays has been a presenter at several International Symposia on Functional Medicine and is a faculty member of *Applying Functional Medicine in Clinical Practice*.

Dr. Bland and Dr. Hays discuss the recent media coverage about the appropriate use of bioidentical hormone therapy. Dr. Hays shares her unique perspective on some of the more controversial comments that have been made.

Dr. Hays discusses her views about why women seek hormone therapy and talks about the processes she uses for evaluating patients before recommending a treatment program. She includes detailed information about laboratory tests and analysis, as well as the usefulness of genomic testing. The influence of diet on hormone metabolism is discussed, and also evidence of a gut-hormone connection (supported by a study published in *JAMA* that showed a potential association between the use of antibiotics and increased risk of breast cancer). REF #15

Questions and Answers
Dr. Bland concludes the issue with a brief discussion about red wine and symptoms of sulfite sensitivity. Listeners are welcome to submit questions for future issues to *info@jeffreybland.com*.

References

1. Giovannucci E, et al. A prospective study of calcium intake and incident and fatal prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2006;15(2):203-210.
2. Di Marlo F, et al. Bovine lactoferrin for Helicobacter pylori eradication: an open, randomized, multicentre study. *Aliment Pharmacol Ther*. 2006;23(8):1235-1240.
3. Hall SS. *Merchants of Immortality: Chasing the Dream of Human Life Extension.* 2003. Houghton Mifflin Company, New York, NY.
4. Somers S. *Ageless: The Naked Truth about Bioidentical Hormones*. 2006. Crown Publishers, New York, NY.
5. Eliassen AH, Missmer SA, Tworoger SS, Spiegelman D, Barbieri RL, et al. Endogenous steroid hormone concentrations and risk of breast cancer among premenopausal women. *J Natl Cancer Inst*. 2006;98(19):1406-1415.
6. Lacey Jr. JV, Brinton LA, Leitzmann MF, Mouw T, Hollenbeck A, et al. Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health—AARP diet and health study cohort. *J Natl Cancer Inst*. 2006;98(19):1397-1405.
7. Seppa N. Cancer link: gene regulates progesterone effect on breast cells. *Science News*. 2006;170(23):355.
8. Kim YI. Does a high folate intake increase the risk of breast cancer? *Nutr Rev*. 2006;64(10):468-475.
9. Moskowitz D. A comprehensive review of the safety and efficacy of bioidentical hormones for the management of menopause and related health risks. *Altern Med Rev*. 2006;11(3):208-223.
10. Modena MG, Sismondi P, Mueck AO, Kuttenn F, de Lignieres B, et al. New evidence regarding hormone replacement therapies is urgently required: transdermal postmenopausal hormone therapy differs from oral hormone therapy in risks and benefits. *Maturitas*. 2005;52(1):1-10.
11. Abbas A, Fadel PJ, Wang Z, Arbique D, Jialal I, et al. Contrasting effects of oral versus transdermal estrogen on serum amyloid A (SAA) and high-density

lipoprotein—SAA in postmenopausal women. *Arterioscler Thromb Vasc Biol*. 2004;24:164-167.
12. Benda W. Bioidentical hormones set the current political stage. *Integrative Med*. 2006;5(5):58-61.
13. Hays B. Giving menopause its proper place. *Integrative Med*. 2006;5(5):32-35.
14. Ariazi EA, Jordan VC. Estrogen-related receptors as emerging targets in cancer and metabolic disorders. *Curr Top Med Chem*. 2006;6(3):181-202.
15. Cvoro A, Paruthiyil S, Jones J, Tzagarakis-Foster C, Clegg NJ, et al. Selective activation of estrogen receptor β transcriptional pathways by an herbal extract. *Endocrinology*. 2007;148(2):538-547.
16. Heyerick A, Vervarcke S, Depypere H, Bracke M, De Keukeleire D. A first prospective, randomized, double-blind, placebo-controlled study on the use of a standardized hop extract to alleviate menopausal discomforts. *Maturitas*. 2006;54(2):164-175.
17. Velicer CM, Heckbert SR, Lampe JW, Potter JD, Robertson CA, et al. Antibiotic use in relation to the risk of breast cancer. *JAMA*. 2004;291:827-835.