



## Selección de Resúmenes de Menopausia

Semana del 8 al 14 de Octubre de 2014

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**Maturitas. 2014 Sep 22. pii: S0378-5122(14)00291-6. [Epub ahead of print]**

### **Lifestyle influences on the association between pre-diagnostic hormone replacement therapy and breast cancer prognosis. Results from The Danish 'Diet, Cancer and Health' prospective cohort.**

Holm M, Olsen A, Kroman N, Tjønneland A.

**OBJECTIVES:** The association between pre-diagnostic hormone replacement therapy (HRT) and breast cancer specific mortality as well as potential influences from other lifestyle factors on the association was investigated. **STUDY DESIGN:** Female participants from the prospective cohort "Diet, Cancer, and Health" diagnosed with breast cancer (BC) were identified and their pre-diagnostic HRT use evaluated for association with tumour biology and breast cancer outcome in multivariate analysis. **MAIN OUTCOME MEASURE:** Breast cancer specific mortality. **RESULTS:** Of the 1212 patients originally considered 1064 were included. Of these, 105 women died from breast cancer during a median follow-up of 6.3 years (range 0.2-14.3 years). In multivariate analyses women who used HRT at enrolment into the cohort study had 47% lower risk of dying from breast cancer as compared to women who had previously or never used HRT (adjusted HR: 0.53; 95% CI, 0.37-0.85). Pre-diagnostic HRT use was associated with smaller tumour size at the time of diagnosis and a higher frequency of receptor positive breast cancer. Paradoxically, a high pre-diagnostic intake of vitamin D supplements was associated with HRT use but also with a higher BC specific mortality (HR: 1.47; 95% CI, 1.07-2.00) **CONCLUSIONS:** HRT use at enrolment was associated with breast tumours of smaller size at the time of diagnosis and positive receptor status, and with a lower BC mortality. The found association between vitamin D from supplements and higher BC mortality warrants further exploration.

**Cancer Res. 2014 Oct 10. pii: canres.1784.2014. [Epub ahead of print]**

### **Molecular modulation of estrogen-induced apoptosis by synthetic progestins in hormone replacement therapy: An insight into the Women's Health Initiative study.**

Sweeney E, Fan P, Jordan VC Obe.

Hormone replacement therapy (HRT) is widely used to manage menopausal symptoms in women, and can comprise an estrogen alone or an estrogen combined with a progestin. The Women's Health Initiative demonstrated in their randomized trials that estrogen alone HRT decreases the risk of breast cancer in post-menopausal women, while combined estrogen plus a progestin (medroxyprogesterone acetate, MPA) HRT increases this risk. Long-term estrogen-deprived MCF-7:5C cells were used to model the post-menopausal breast cancer cell environment. MPA is able to modify E2-induced apoptosis in MCF-7:5C cells. MPA, similar to dexamethasone (Dex) increases GR transcriptional activity, increases SGK1, a GR target gene, and can be blocked by RU486 (an antiglucocorticoid), suggesting it functions through the GR. Norethindrone acetate (NETA), another progestin used in HRT, acts like an estrogen at high doses, up-regulating ER-target genes and generating apoptosis in MCF-7:5C cells. The data suggests that women taking HRT comprising an estrogen plus MPA may have an increased the risk of breast cancer due to MPA acting as a glucocorticoid and blunting E2-induced apoptosis in this environment. Therefore, perhaps other approved progestins (e.g. NETA) should be considered as alternatives to MPA.

**J Clin Endocrinol Metab. 2014 Oct 10;jc20142751. [Epub ahead of print]**

### **Alternative Activation of Human Macrophages Is Rescued by Estrogen Treatment in Vitro and Impaired by Menopausal Status.**

Toniolo A, Paolo Fadini G, Tedesco S, Cappellari R, Vegeto E, Maggi A, Avogaro A, Bolego C, Cignarella A.

**Context and Objective:** During their reproductive years, women are generally protected from cardiovascular disease events by their estrogen-replete status. Our starting hypothesis was that lower estrogen levels after menopause are associated with macrophage activation profiles skewed towards pro-inflammatory phenotypes. **Research Design and Setting:** This was an in vitro and ex vivo study in human blood-derived macrophages. **Subjects:** We obtained blood from 12 healthy male donors for the in vitro study, and from 5 pre-menopausal and 8 post-menopausal women for the ex vivo study. **Outcome:** measurements:

We determined macrophage immunophenotypes in resting state and after activation with M1- (LPS/IFN $\gamma$ ) or M2-associated (IL-4/IL-13) stimuli, as well as expression of estrogen receptors (ER) and other transcription factors. Results: Unpolarized macrophages expressed both ER $\alpha$  and ER $\beta$ , and ER $\alpha$  but not ER $\beta$  levels were decreased by M1 stimuli. LPS/IFN $\gamma$  also induced downregulation of CD163 and CD206, markers of alternative activation, and increased cell-bound TNF- $\alpha$  and IL-10. These effects were prevented by E2 treatment through impaired nuclear factor (NF)- $\kappa$ B liberation. In agreement with a role for E2 in attenuating the inflammatory response, M1/M2 subpopulations were similar in monocytes and unstimulated macrophages from pre- and post-menopausal donors. In contrast, M2 activation appeared to be blunted in macrophages from post-menopausal women, leading to increased M1/M2 response ratio. Conclusions: Estrogen treatment prevented LPS/IFN $\gamma$  action on human M2 macrophage markers and cytokine production, whereas menopausal estrogen loss was associated with impaired response to alternative activation, suggesting that these mechanisms affect cardiovascular risk profile in relation to menopausal status.

**J Bone Miner Res. 2014 Oct 7. doi: 10.1002/jbmr.2384. [Epub ahead of print]**

### **Fruit and vegetable intake and risk of hip fracture: A cohort study of Swedish men and women.**

Byberg L, Bellavia A, Orsini N, Wolk A, Michaëlsson K.

Dietary guidelines recommend a daily intake of five servings of fruit and vegetables. Whether such intakes are associated with a lower risk of hip fracture is at present unclear. The aim of the present study was to investigate the dose-response association between habitual fruit and vegetable intake and hip fracture in a cohort study based on 40,644 men from the Cohort of Swedish Men (COSM) and 34,947 women from the Swedish Mammography Cohort (SMC) (total n=75,591), free from cardiovascular disease and cancer, who answered lifestyle questionnaires in 1997 (age 45-83 years). Intake of fruit and vegetables (servings/day) was assessed by food frequency questionnaire and incident hip fractures were retrieved from the Swedish Patient Register (1998-2010). The mean follow-up time was 14.2 years. One third of the participants reported an intake of fruit and vegetables of >5 servings/day, one third >3 to  $\leq$ 5 servings/day, 28% >1 to  $\leq$ 3 servings/day, and 6% reported  $\leq$ 1 serving/day. During 1,037,645 person-years we observed 3,644 hip fractures (2,266, 62%, in women). The dose-response association was found to be strongly non-linear (P<0.001). Men and women with zero consumption had 88% higher rate of hip fracture compared with those consuming 5 servings/day; adjusted hazard ratio (HR), 1.88 (95% CI, 1.53-2.32). The rate was gradually lower with higher intakes; adjusted HR for 1 vs 5 servings/day, 1.35 (95% CI, 1.21-1.58). However, more than 5 servings/day did not confer additionally lower HRs (adjusted HR for 8 vs. 5 servings/day, 0.96 (95% CI, 0.90-1.03). Similar results were observed when men and women were analyzed separately. We conclude that there is a dose-response association between fruit and vegetable intake and hip fracture such that an intake below the recommended 5 servings/day confers higher rates of hip fracture. Intakes above this recommendation do not seem to further lower the risk

**Geburtshilfe Frauenheilkd. 2012 Jun;72(6):527-531.**

### **Impact of Phytoestrogens on Serum Lipids in Postmenopausal Women.**

Terzic M, Micic J, Dotlic J, Maricic S, Mihailovic T, Knezevic N.

Objectives: The aim of the study was to assess the impact of soy- and red clover-derived isoflavones on serum lipid levels in postmenopausal women and to compare the effects to the lipid levels of healthy postmenopausal women without phytoestrogen supplementation. Materials and Methods: Blood levels of triglycerides, total cholesterol and cholesterol fractions were assessed. Measurements were performed before treatment and at 6-month intervals over a period of 18 months. The investigation included 74 healthy postmenopausal women randomized into three groups according to treatment. The first group of 23 patients received soy-derived isoflavones, the second group (26 patients) was given red clover-derived phytoestrogens, while the third control group (25 patients) received no supplements. Results: Mean triglyceride, cholesterol and LDL levels of patients in the control group were significantly higher than in both the soy and the red clover groups (p<0.001) at all three time points, while mean values did not differ significantly between the soy and the red clover groups. The mean HDL levels of patients in the control group was significantly lower than in both the soy and the red clover groups (p<0.001). Conclusions: Phytoestrogen supplementation had a positive metabolic effect on serum lipid levels in postmenopausal women. The impact on serum lipids levels was similar for soy and red clover.

**Endocr Pract. 2014 Oct 8:1-24. [Epub ahead of print]**

## Menopausal hormone therapy and chronic disease risk in the WHI: Is Timing Everything?

Bhupathiraju SN, Manson JE.

**Objective:** This review provides a comprehensive overview of the most recent findings from the Women's Health Initiative (WHI) hormone therapy (HT) trials and highlights the role of age and other clinical risk factors in risk stratification. **Methods:** We review the findings on cardiovascular disease, cancer outcomes, all-cause mortality, and other major endpoints in the two WHI HT trials (conjugated equine estrogens [CEE: 0.625 mg/d] with or without medroxyprogesterone acetate [MPA: 2.5 mg/d]). **Results:** The hazard ratio (HR) for coronary heart disease (CHD) was 1.18 (95% confidence interval (CI): 0.95-1.45) in the CEE+MPA trial and 0.94 (95% CI: 0.78-1.14) in the CEE-alone trial. In both HT trials, there was an increased risk of stroke and deep vein thrombosis, and a lower risk of hip fractures and diabetes. The HT regimens had divergent effects on breast cancer. CEE+MPA increased breast cancer risk (cumulative HR=1.28, 95% CI: 1.11-1.48) while CEE-alone had a protective effect (cumulative HR=0.79, 95% CI: 0.65-0.97). The absolute risks of HT were low in younger women (ages 50-59) and those who were within 10 years of menopause onset. Further, for CHD, the risks were elevated for women with metabolic syndrome or high LDL-C concentrations, but not in women without these risk factors. Factor V Leiden genotype was associated with elevated risk of venous thromboembolism on HT. **Conclusion:** HT has a complex pattern of benefits and risks. Women in early menopause have low absolute risks of chronic disease outcomes on HT. Use of HT for management of menopausal symptoms remains appropriate, and risk stratification will help to identify women in whom benefits would be expected to outweigh risks.

**Clin Cases Miner Bone Metab. 2014 May;11(2):117-9.**

### Correlation between osteoporosis and cardiovascular disease.

Sprini D, Rini GB, Di Stefano L, Cianferotti L, Napoli N.

Several evidences have shown in the last years a possible correlation between cardiovascular diseases and osteoporosis. Patients affected with osteoporosis, for example, have a higher risk of cardiovascular diseases than subjects with normal bone mass. However, the heterogeneous approaches and the different populations that have been studied so far have limited the strength of the findings. Studies conducted in animal models show that vascular calcification is a very complex mechanism that involves similar pathways described in the normal bone calcification. Proteins like BMP, osteopontin, osteoprotegerin play an important role at the bone level but are also highly expressed in the calcified vascular tissue. In particular, it seems that the OPG protect from vascular calcification and elevated levels have been found in patients with CVD. Other factors like oxidative stress, inflammation, free radicals, lipids metabolism are involved in this complex scenario. It is not a case that medications used for treating osteoporosis also inhibit the atherosclerotic process, acting on blood pressure and ventricular hypertrophy. Given the limited amount of available data, further studies are needed to elucidate the underlying mechanisms between osteoporosis and cardiovascular disease which may be important in the future also for preventive and therapeutic approaches of both conditions.

**Fam Cancer. 2014 Oct 5. [Epub ahead of print]**

### Long-term outcomes of risk-reducing surgery in unaffected women at increased familial risk of breast and/or ovarian cancer.

Heiniger L, Butow PN, Coll J, Bullen T, Wilson J, Baylock B, Meiser B, Price MA.

This study prospectively investigated long-term psychosocial outcomes for women who opted for risk-reducing mastectomy (RRM) and/or risk-reducing salpingo-oophorectomy (RRSO). Unaffected women from high-risk breast cancer families who had completed baseline questionnaires for an existing study and subsequently underwent RRM and/or RRSO, completed measures of perceived breast and ovarian cancer risk, anxiety, depression, cancer-related anxiety, body image, sexual functioning, menopausal symptoms, use of hormone replacement therapy and decision regret 3 years post-surgery. Outcomes were compared to age- and risk-matched controls. Participants (N = 233) were 17 women who had RRM (39 controls), 38 women who had RRSO (94 controls) and 15 women who had RRM + RRSO (30 controls). Women who underwent RRM and those who underwent RRM + RRSO reported reductions in perceived breast cancer risk and perceived breast and ovarian cancer risk respectively, compared to their respective controls. RRM women reported greater reductions in cancer-related anxiety compared with both controls and RRSO women. RRSO women reported more sexual discomfort than controls and more urogenital menopausal symptoms than controls and RRM only women. No differences in general anxiety, depression or body image were observed. Regret was associated with greater reductions in body image since surgery and more sexual discomfort, although overall regret levels were low. Women who undergo RRM experience psychological benefits associated

with reduced breast cancer risk. Although women who undergo RRSO experience some deterioration in sexual and menopausal symptoms, they do not regret their surgery decision. It is vital that women considering these procedures receive detailed information about potential psychosocial consequences.