HPV detection at menopause


Summary. A cohort of 843 women aged 35 to 60 years were followed for 2 years in this study of age-specific human papillomavirus (HPV) prevalence, which has a bimodal incidence in many populations, perhaps as a result of cohort effects, new sex partnerships, or HPV reactivation. Researchers were evaluating the reasons for the lack of a second peak in the United States.

Gravitt and colleagues stratified women according to low risk of prior infection (<5 self-reported lifetime sex partners) and higher risk (≥5 self-reported lifetime sex partners). The age-specific prevalence of 14 high-risk HPV genotypes declined with age among low-risk women but not among high-risk women. The population attributable risk for HPV due to greater than five lifetime sex partners was higher among older women (87.2%) than younger women (28.0%). The population attributable risk for a new sex partner was 28% among women 35 to 49 years and 7.7% in women aged 50 to 60 years.

Researchers concluded that a lower probability of HPV infection in US women with a sexual debut before the sexual revolution may be hiding an age-related increase in HPV reactivation.

Comment. A bimodal HPV prevalence has been noted in several countries, with the highest peak among young women around the age of sexual debut and a second peak around the age of menopause. To evaluate this bimodal pattern in the United States, the authors studied a cohort of women in Baltimore who presented for routine care and provided informed consent. Their mean age was 46.6 years and the women were primarily white (73%), with a high school or college education in the majority.

Data revealed that HPV prevalence declined with increasing age, was higher among women reporting a higher number of sexual partners, and was higher if women reported a new sexual partner in the last 6 months.

Interestingly, when data were stratified by the number of lifetime sexual partners, HPV prevalence declined with age only among women with fewer than five lifetime sexual partners. The risk estimates for HPV prevalence for subjects with five or more lifetime sexual partners were higher among those aged 50 to 60 years than among women aged 35 to 49 years.
While still considered controversial, these data suggest the possibility that reactivation of HPV may occur around age 50, coincident with hormonal decline. Prevalence could not be explained by new partner acquisition in this age group. The authors propose “the cohort effect of the sexual revolution in the United States is masking an increase in HPV prevalence at older ages, which may be secondary to reactivation of latent virus.” Further study to evaluate this hypothesis and its implications are needed.

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HT & mammography outcomes


**Summary.** Researchers compared the benefits and harms of screening mammography frequencies by age, breast density, and postmenopausal hormone therapy (HT) use in a prospective cohort of 11,474 women with breast cancer and 922,624 women without breast cancer who had mammography as part of the Breast Cancer Surveillance Consortium mammography registries. Logistic regression was used to calculate odds of advanced stage, large tumors, and false-positive results. They found that biennial mammography for women aged 50 to 74 years did not increase risk of tumors with advanced stage or large size regardless of breast density or HT use. In women aged 40 to 49 years with extremely dense breasts, biennial mammography was associated with a higher risk of advanced-stage cancer (odds ratio [OR], 1.89; 95% CI, 1.06-3.39) and large tumors (OR, 2.39; 95% CI, 1.37-4.18). Women aged 40 to 49 years should be aware that annual mammography may minimize their risk of advanced-stage cancer. However, the risk of a false-positive result will be high.

**Comment.** In 2009, the United States Preventive Services Task Force released guidelines recommending biennial rather than annual mammography. It is difficult to definitively determine the ideal mammography screening interval without randomized trial data. However, given the expense and time required for such a large-scale study, it is unlikely that such a study will ever be done, so our decisions will need to be guided by currently available data. The main strength of the Breast Cancer Surveillance Consortium is its large size and statistical power, but the current study does not present any novel findings. When evaluating the applicability of observational data to the randomized trial setting, it is crucial to first determine whether the populations who underwent the different screening intervals were comparable, as would happen in a randomized trial.

Although *P* values are not provided, the distributions for age, ethnicity, family history, and HT use appear to vary in a linear fashion with screening interval, raising the possibility of confounding. The authors controlled for these factors, but it is still possible that any associations or lack of associations with screening interval may be due to confounding. Another concern about the study is its generalizability, because the current analysis was limited to only a portion of the entire cohort. Only 11,474 breast cancer cases with measured breast density and follow-up examinations were included out of 37,800 cases with screening mammograms prior to diagnosis. Similarly, among 1.9 million women in the original database, only 922,624 were included in the false-positive mammogram analyses because data on breast density, menopause, and HT were required. It is not stated whether the subsets included for analysis were representative of the full cohort.
As for the main results, the current manuscript presents two separate analyses using two discrete populations — one evaluating the association between tumor characteristics and screening intervals among breast cancer patients and the other looking at the chances of a false-positive mammogram and screening interval among patients without cancer. The finding that annual versus biennial mammography was not associated with advanced stage cancer is consistent with prior studies showing no appreciable difference in the effect of mammography using 1 or 2 year screening intervals. The finding that, among women aged 40 to 49 years with extremely dense breasts, biennial screening was associated with an increased risk of advanced stage and large tumor size compared with annual mammography again is to be expected because standard mammography has already been shown to underperform in younger women with dense breasts.

The second part of the analysis, which looked at screening interval and false-positive mammogram, also did not present any novel findings. It has long been known that the more mammograms a woman has over her lifetime, the more likely she is to have a false-positive finding. In fact, these investigators published this finding just last year using a subset of the current study population. As for the HT findings, the Women’s Health Initiative randomized trial already demonstrated that combination menopausal HT is associated with a higher risk of false-positive mammograms and biopsies. Overall, although the analysis was carefully done and limitations were acknowledged, there were not any novel findings that would change current clinical practice.

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References:

Sleep & hypertension in the Nurses’ Health Study


Level of evidence: II-3.

Summary. This study examined the relationship between sleep duration and hypertension in women who self-reported sleep durations in 1986 (n = 82,130) and 2000 (n = 71,658) as part of the Nurses’ Health Study. Hypertension was significantly higher among women who slept 5 hours or less (odds ratio [OR], 1.19; 95% CI, 1.14-1.25) than among those who slept 7 hours. Using Cox regression, the shorter sleep duration (≤5 h/night) was significantly associated with hypertension only in women under age 50 (hazard ratio [HR], 1.20; 95% CI, 1.09-1.31) and not in women aged 50 to 59 years (HR, 1.11; 95% CI, 1.00-1.23). Sleep may be a lifestyle factor that is useful in reducing hypertension.

Comment. The Nurses’ Health Study continues to provide us with valuable observational
information. Questionnaire data and patient-derived log data correlated for the most part, but not perfectly. There was greater discrepancy at the extremes of reported sleep duration. Hypertension was defined as being diagnosed by a physician. To validate this outcome, a random sample of patients was taken and their medical records were retrieved. In one of the validation steps, the sensitivity of self-reported hypertension was 94%. The specificity of a nurse reporting no diagnosis of hypertension was 85%. They assessed prevalence at cross-sectional visits and incident hypertension longitudinally.

Researchers evaluated for over 20 potential confounders including race, age, Dietary Approaches to Stop Hypertension (DASH) diet score, smoking, drinking history, and work shift to find associations with prevalent short sleep of 5 hours or less versus 7 hours and with incident hypertension in younger women only. They found that obesity could be an important mediator of incident hypertension.

The authors acknowledge some important limitations. They could not control for sleep apnea, a known risk factor for diabetes mellitus and cardiovascular disease. The study lacked repeated and objective measures of sleep duration. Hypertension can go unnoticed. Other potential confounders such as anxiety or binge drinking may not have been assessed. How many participants lived in the stroke belt (the southeastern part of the United States)? How did records differ by location for validation?

This is a difficult study to perform because of a significant problem with potential and likely misclassification due to measurement error and potential residual confounding. On the other hand, the authors fairly present this association as an important hypothesis to test. It is common sense to tell your patient to avoid stress, make positive lifestyle changes, eat well, sleep well, laugh, be happy and enjoy life. It might also improve your blood pressure!

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Androgens & body fat distribution after menopause


Summary. To study the relationship between androgens and body fat distribution, researchers examined postmenopausal women divided into an early group (≤5 y since menopause, n = 105) and a late group (≥10 y since menopause, n = 107). These groups were subdivided into normal weight (BMI < 24 kg/m²) and overweight/obese (BMI ≥ 24 kg/m²). Researchers measured fasting total testosterone (T), dehydroepiandrosterone-sulfate (DHEAS), and sex hormone-binding globulin (SHBG); body fat distribution was determined by dual-energy x-ray absorptiometry (DEXA). Late postmenopausal women had more body fat than early postmenopausal women. In overweight and obese women in both the early and late postmenopausal groups, there was a higher likelihood of abdominal fat accumulation than in normal weight women. The overweight women also had higher free testosterone in early postmenopause and higher DHEAS in late postmenopause. There was no direct relationship observed between T levels and body fat distribution in early or late postmenopause (P > .05). Free testosterone in early postmenopause and DHEAS in late postmenopause correlated positively with abdominal fat accumulation.

Comment. Cao and colleagues explored the relationships between testosterone, dehydroepiandrosterone sulfate (DHEAS), sex hormone-binding globulin (SHBG), and body...
fat in early and late postmenopausal women. There are some fundamental methodological concerns regarding the study and issues pertaining to the interpretation of the findings.

The methodological limitations are in the testosterone assay precision and the analytical approach. The Beckman Coulter assay for the measurement of testosterone is relatively imprecise at low concentrations of testosterone (precision ≤ 20% at 1.74 nmol/L),1 such that the ability of the assay to measure small differences in total testosterone levels at the concentrations in these women is highly questionable.

Furthermore, T was calculated according to Vermeulen’s formula2 from measured total testosterone and SHBG. Therefore, the imprecision in the total testosterone assay will affect the calculated T. The determination of T by the equation used depends primarily on total testosterone and SHBG. Calculated T cannot be considered independent of either total testosterone or SHBG. As a result, putting T into a mathematical model with the two factors upon which it depends is essentially flawed. An additional limitation is not taking into account the contribution of estradiol and estrone levels.

In early postmenopausal women, there is a powerful relationship between SHBG and abdominal fat accumulation. This is consistent with findings from other large cross-sectional studies.3,4 Low SHBG is not only associated with greater central fat in postmenopausal women, but is also a strong predictor of insulin resistance and diabetes independent of endogenous sex steroids and body mass index.4,5 Increasingly, attention is being paid to the metabolic role of SHBG independent of its sex steroid-binding function.6 There is emerging interest in the dietary modulation of SHBG and whether changes in SHBG with variations in diet composition merely reflect altered insulin resistance or play an active role in observed changes in insulin resistance. Selva and others have shown in animal models that physiological concentrations of fructose and glucose suppress SHBG production, with dietary fructose having a marked effect.7

As highlighted above, T cannot be considered independent of SHBG or total testosterone because it is a product of these variables. Researchers’ claim that SHBG was not an independent factor associated with abdominal fat accumulation and that T was independent from SHBG and T to predict abdominal fat accumulation does not hold. Mathematical modeling cannot change the fact that if total testosterone is not significantly associated with abdominal fat while low SHBG is significantly associated, then SHBG must be driving the relationship between T and abdominal fat.

It is well established that DHEAS levels decline continuously with age.8,9 Nonetheless, even in the elderly, DHEAS continues to circulate in micromolar concentrations, compared with nanomolar concentrations of testosterone and picomolar concentrations of estradiol. DHEA is a precursor for both estrogen and androgen production, and DHEAS is a circulating reservoir of DHEA. Thus, insufficiency of DHEA as a substrate for extragonadal estrogen and androgen production in older women is unlikely to occur. It has been shown that aromatase activity, which converts androstenedione made from DHEA to estrone, increases in adipose tissue with increasing age in women.10 Without having measured estrogens in this study, it is not possible to hypothesize whether the observed relationship between DHEAS and adiposity is related to peripheral conversion of DHEA to estrogens or testosterone. Considering that the capacity of fat to produce estrogens increases with age,10 it cannot be assumed that the observed relationship between DHEAS and adiposity resides in increased testosterone production.

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**At hysterectomy for benign indications, best to leave the ovaries in**


**Summary.** Routine bilateral oophorectomy (BO) at hysterectomy may be more harmful than beneficial.1 Now, Nurses’ Health Study (NHS) investigators have conducted an updated analysis of posthysterectomy follow-up extended to 28 years in >30,000 participants.

Among women who underwent hysterectomy for benign indications, 17% of those with BO and 13% of those with ovarian conservation had died. BO was associated with lower risk for death from ovarian cancer and (if performed before age 47.5) breast cancer. However — regardless of age at surgery — BO did not lower risk for death from other causes (i.e., coronary heart disease, stroke, and lung and colorectal cancer) or all-cause mortality. For women younger than 50 at surgery, BO was associated with significantly higher all-cause mortality in those who had never used estrogen therapy (ET; hazard ratio, 1.4), but not in past or current ET users.

In another study, researchers analyzed data from 15% of US hospital discharges to assess recent trends in ovarian conservation at hysterectomy for benign indications. Among > 750,000 women who underwent hysterectomies from 2000 to 2010, ovarian conservation was performed in 54%. This practice was more common in younger women (74% of women younger than 40) than in older women (31% of those aged 60–64). Overall rates of ovarian conservation rose throughout the study period.

**Comment.** These updated Nurses’ Health Study findings substantiate the view that, except in women with mutations that raise risk for ovarian cancer (ie, BRCA and Lynch), bilateral oophorectomy should not be performed at hysterectomy for benign indications. In addition, unless they have specific
contraindications, women who undergo BO before age 50 should be encouraged to use estrogen therapy. The NHS authors point out that, in the post-Women’s Health Initiative climate, performing BO before age 50 and then prescribing ET is not prudent, given that women are currently reluctant to use ET and clinicians are reluctant to prescribe it. In this light, it’s encouraging that more US gynecologists are practicing ovarian conservation.

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Menopause Editor’s picks from April 2013

NAMS spotlights selections from the most recent issue of the Society’s official journal, Menopause, chosen by its Editor-in-Chief, Isaac Schiff, MD.

Factors associated with resilience or vulnerability to hot flushes and night sweats during the menopausal transition.
Oonagh K. Duffy, PhD, Lisa Iversen, PhD, Lorna Aucott, PhD, and Philip C. Hannaford, MD.

♦ Reductions in glucose among postmenopausal women who use and do not use estrogen therapy.
Catherine Kim, MD, MPH, Shengchun Kong, MS, Gail A. Laughlin, PhD, Sherita H. Golden, MD, MHS, Kieren J. Mathers, MD, Bin Nan, PhD, John F. Randolph Jr, MD, Sharon L. Edelstein, ScM, Fernand Labrie, MD, PhD, Elizabeth Buschur, MD, and Elizabeth Barrett-Connor, MD, for The Diabetes Prevention Program Research Group.

♦ Effects of applied relaxation on vasomotor symptoms in postmenopausal women: a randomized controlled trial.
Lotta Lindh-Astrand, RN, PhD, and Elizabeth Nedstrand, MD, PhD.

♦ Age-related differences in abdominal fat distribution in premenopausal and postmenopausal women with cardiovascular disease.
Joep van der Leeuw, MD, Annemarie M. J. Wassink, MD, PhD, Yolanda van der Graaf, MD, PhD, Hendrika E. Westerveld, MD, PhD, and Frank L. J. Visseren, MD, PhD, on behalf of the Second Manifestations of ARTERial Disease (SMART) Study Group.
The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented below.

- **Level I** Properly randomized, controlled trial.
- **Level II-1** Well-designed controlled trial but without randomization.
- **Level II-2** Well-designed cohort or case-control analytic study.
- **Level II-3** Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies).
- **Level III** Meta-analyses; reports from expert committees; descriptive studies and case reports.

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