Age at menopause in smokers and ex-smokers

Smokers, but not ex-smokers, had an earlier menopause


Summary. This analysis of data from the Japanese Nurses’ Health Study confirms previous studies and a meta-analysis published in Menopause in 2012 concluding that smoking is associated with earlier menopause. In this study, not only was current smoking before menopause associated with earlier menopause, it was also associated in a dose-dependent manner. In ex-smokers, however, a history of premenopausal smoking was not significantly associated with menopause onset.

Comment. The Japanese Nurses’ Health Study is a cohort study of 49,914 female nurses from throughout Japan aged 25 years and older.1 It began in 2001 with a baseline survey, followed by biennial questionnaires. Miyazaki and colleagues add to the growing body of literature suggesting that current smoking is a risk factor for earlier menopause.2,3 A 2012 meta-analysis by Sun and colleagues suggested that smokers experience a final menstrual period approximately 13 months earlier than that of nonsmokers.4 The large population size in Miyazaki’s study permitted dose-response analysis, noting that heavier smokers are more likely to experience an early menopause than those who smoke fewer cigarettes per day. Those who had stopped smoking completely did not have an earlier menopause.

It is not clear why smoking would have this effect on menopause. There are numerous theories, beyond the scope of this analysis, but most suggest mechanisms that culminate in a loss of ovarian follicles, a process previously thought to be irreversible. Miyazaki’s study, which suggests that ex-smokers do not have an earlier menopause, casts doubt on the idea that this is an irreversible process.

These data suggest an important public health opportunity: By promoting smoking cessation, menopause may be postponed, thereby making a difference in the health issues confronting those patients with early menopause, including cardiovascular disease and osteoporosis. Even reducing the number of cigarettes per day seems to be a benefit.

Finally, Miyazaki examined the rate of smoking cessation among pregnant participants. He found that 61.9% of those currently smoking quit while pregnant. He states that this most
likely occurred “because women are aware of and concerned about the effects of smoking on the fetus and childbearing.” I would suggest that perhaps this high rate of cessation might also be because of their contact with a healthcare provider who discussed those risks with the participants and encouraged them to stop smoking. Perhaps we could have similar success with our perimenopausal and postmenopausal women.

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References


**Ductal carcinoma in situ: what we call it matters**

Avoiding the word “cancer” prompted women’s choice of noninvasive management


**Summary.** In her famous utterance, Juliet asked, “What’s in a name?” Many of my patients do not distinguish between preinvasive and invasive cancer and misjudge the clinical implications of the term “ductal carcinoma in situ” (DCIS). Investigators speculated that describing DCIS without using the term “cancer” makes women more comfortable opting for noninvasive approaches over surgery. A total of 394 healthy women without histories of breast cancer were presented with three vignettes in which DCIS was described using the terms “noninvasive breast cancer,” “breast lesion,” or “abnormal cells” (treatment options and likelihood of developing invasive breast cancer or death were identical). Women then chose among surgery, medication, or active surveillance as treatment options.

Overall, medication or active surveillance was selected more often than surgery. When the term “noninvasive cancer” was used, 53% of participants chose nonsurgical management. In contrast, when the terms “breast lesion” or “abnormal cells” were used, 66% and 69% of participants, respectively, chose nonsurgical management.

**Comment.** Ductal carcinoma in situ is a preinvasive malignancy of the breast that is diagnosed in >50,000 U.S. women annually and is often treated with lumpectomy and radiation therapy or mastectomy. However, because DCIS will not necessarily lead to clinical disease in a patient’s lifetime, watchful waiting may be a reasonable option. Consistent with the National Cancer Institute’s recent recommendation, these results suggest that when descriptions of DCIS do not involve the term “cancer,” a large majority of women choose nonsurgical treatments. The authors note that the study population was highly educated with higher-than-average incomes, limiting generalizability. Nonetheless, the findings illustrate that the way in which we describe medical conditions can have a powerful effect on our patients’ perceptions and subsequent choices, leading some women to unnecessary surgery. What’s in a name? For DCIS, think twice before saying “cancer.”

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**Relationship of dairy intake and age at menopause**

*Low-fat dairy associated with delay in natural menopause*


**Summary.** In this analysis of data from the Nurses’ Health Study on age at natural menopause and dairy consumption, the investigators found a significant association between low-fat dairy food consumption and a modest delay in age at natural menopause. Later natural menopause has been associated with certain health risks, including breast and endometrial cancer. The researchers note that hormones and growth factors in dairy foods may be responsible for the delay.

**Comment.** Whether dietary patterns and individual dietary ingredients affect reproductive aging is a relevant question. In Western societies, consumption of refined sugars and saturated fats has risen sharply at the expense of fruit and vegetable intake. This dietary pattern is associated with postprandial oxidative stress, inflammation, and increased insulin resistance, all of which are key to numerous disease processes and could accelerate aging. However, investigations of the effect of diet on the age at which menopause or on markers of hypothalamic-pituitary-ovarian aging are sparse, and the data are inconsistent.¹⁻³

The main finding is a significant delay (about 3.6 months) in the age of onset of menopause in women younger than 51 years who consumed more than three servings per day of low-fat dairy compared with zero to one servings per day. There was no effect of high-fat dairy intake on menopause timing.

This contrasts with previous studies, however. One concluded that greater consumption of low-fat dairy increased risk for anovulatory infertility in premenopausal women, whereas high-fat dairy was beneficial.⁴ In another, nonhuman primates consuming a dairy protein-based diet had reduced ovarian reserve compared with those consuming a plant protein-based diet, all other macronutrients being equivalent.⁵

Regarding potential mechanisms for delayed menopause, the authors of the current study suggest that greater amounts of estrone sulfate in skim milk may have resulted in increased plasma estradiol concentrations and prolonged menstrual bleeding. This hypothesis is intriguing but remains speculative without milk and plasma estrogen measures. Researchers also considered the possibility that frequent consumption of low-fat dairy represents a dietary pattern that is associated with better overall reproductive health. An explanation not considered is the possibility that consumption of high-fat dairy may be indicative of a dietary pattern resulting in increased cardiovascular risk.

Many of the variables previously reported to influence the age at menopause were considered in this study (ie, age at menarche, age at first birth, parity, activity, body mass index, oral contraceptive use, smoking, and marital status). However, cardiovascular risk factors (eg, plasma lipids, blood pressure, insulin resistance) were not reported. These may have been informative because cardiovascular risk markers have been reported to be associated with earlier age at menopause.⁶ Disparate results among studies of dietary effects on age at menopause
are likely because of, at least in part, the inability of cross-sectional data to capture the effects of lifelong dietary patterns. In addition, age at last menstrual cycle represents the cumulative effect of lifestyle and genetic factors on the age at which menstruation ceases and does not provide a picture of the trajectory of reproductive aging. Furthermore, the clinical significance of a few months of prolonged bleeding is also not clear because it does not necessarily represent maintenance of “normal” ovarian function. For example, the endometrium is exquisitely sensitive to circulating estrogen, and menstrual bleeding can occur in women with only a few ovarian follicles remaining. In addition, ovarian follicle numbers decline rapidly after around age 37 years, and ovarian reserve, as measured by antimüllerian hormone (AMH), can fall below the level of detection as early as 5 years before the final menstrual period. Thus, longitudinal investigations using repeated measures of reproductive aging (eg, AMH, antral follicle counts) and dietary patterns, as well as controlled animal experiments, are needed to improve understanding in this area.

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References


**Different progestins: combined oral contraceptives and venous thrombosis**

*Pills containing levonorgestrel were less likely than those with gestodene, desogestrel, or drospirenone to be associated with VT*


**Summary.** Combined oral contraceptives (OCs) have evolved during the past several decades, in terms of both estrogen dose and progestin compound. Now, investigators have conducted a meta-analysis of 26 studies to provide an overview of OC formulation and risk for venous thrombosis (VT).

Women using combined OCs faced an estimated 1 in 1,000 risk for VT each year, 3 to 4 times the very low risk for VT faced by women using no hormonal contraception. Combined pills containing levonorgestrel carried the lowest risk for VT, while pills containing gestodene, desogestrel, cyproterone acetate, and drospirenone all carried a 50% to 80% higher risk for VT than levonorgestrel pills. In addition, modern doses of ethinylestradiol (<50 µg) were associated with lower risk for VT.

**Comment.** Although the relative risks presented in this study were not adjusted for duration of pill use, obesity, or tobacco use, they reinforce the low absolute risk for venous thrombosis.
with use of any oral contraceptive, and the idea that the best pill for a given patient is the one she wants to take. OCs lower women’s risk for ovarian and endometrial cancer and have been associated with lower all-cause mortality compared with no contraceptive use, and pregnancy is associated with higher risk for VT than is OC use (the first 6 weeks postpartum are associated with VT risk 22- to 84-fold higher than in nonpregnant women). That said, those who want to minimize their risk for VT as well as unintended pregnancy are probably best served by intrauterine or subdermal contraception.

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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.

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