Breast cancer risk before & after menopause

An analysis of the relationship of length of reproductive years and risk of different breast cancer types


Summary. Both menarche and menopause affect breast cancer risk. The aim of this meta-analysis of epidemiological studies was to examine how that relates to the tumor type and the length of reproductive life in the women. Data from 117 studies, which included 118,964 women with invasive breast cancer and 306,091 without the disease, were included. The authors calculated adjusted relative risks (RRs) associated with menarche and menopause for breast cancer overall, and by tumor histology and by estrogen receptor (ER) expression. None of the women had used menopausal hormone therapy.

Breast cancer risk increased by a factor of 1.050 (95% CI, 1.044-1.057; \( P < 0.0001 \)) for every year younger at menarche, and by a smaller amount (1.029, 1.025-1.032; \( P < 0.0001 \)), for every year postmenopause. Premenopausal women had a greater risk of breast cancer than postmenopausal women of the same age (RR at ages 45-54 1.43, 1.33–1.52, \( P < 0.001 \)). All three of these associations were weakened by increasing adiposity among postmenopausal women, but did not vary greatly by women’s year of birth, ethnic origin, childbearing history, smoking, alcohol consumption, or hormonal contraceptive use. All three associations were stronger for lobular than for ductal tumors (\( P < 0.006 \) for each comparison). The effect of menopause in women of an identical age and trends by age at menopause were stronger for ER-–positive disease than for ER-negative disease (\( P < 0.01 \) for both comparisons).

The conclusions of this review were that the length of a woman’s reproductive years was not the sole cause of breast cancer risk. The authors feel that endogenous ovarian hormones are more relevant for ER-positive disease than for ER-negative disease and for lobular than for ductal tumors.

Commentary. This well-powered study of hormonal status/exposure and subsequent risks of breast cancer used the power of meta-analysis to confirm what we have known for over 30 years based on another powerful statistical tool: multivariate analysis. In 1989, Mitchell Gail and colleagues at the National Cancer Institute
published a retrospective review of factors associated with the development of breast cancer in a prospective longitudinal study of over 280,000 women.\textsuperscript{1,2} The Gail model demonstrated to us that factors such as age, family history, and prior breast biopsies can be used to predict breast cancer risk. More relevant to this paper, early menarche and late menopause were identified as risk factors for subsequent breast cancer development in the Gail model, but perhaps not as well quantified as in the current study. This current study showed that for every year younger a woman is when she begins menarche, there is an increase in RR by a factor of 1.05 for breast cancer; for each additional year before menopause, there is an increase by a factor of 1.029. The implications of this finding are important, namely that serum estrogen level (SEL) exposure is a quantifiable risk factor for subsequent development of breast cancer. Some other important associated findings are the increased risk for ER-positive cancers over ER-negative, and increased risk for lobular carcinoma over ductal.

We have previously reported the timeline for decrease in SEL in postmenopause.\textsuperscript{3} We believe that this study confirms the role of peripheral estrogen in breast cancer risk. While the risk of breast cancer decreases in the years postmenopause, the magnitude of the decrease was less in women with a body mass index over 25. These women presumably have a higher serum SEL than their thinner counterparts, but we have shown that SEL does not drop immediately postmenopause, perhaps explaining why the incidence of breast cancer does not decrease immediately in the postmenopause years. The SEL stays elevated, but slowly decreases, until a woman is over age 65; and we have described these years as the geripause. A minimum SEL is always present from sources other than the ovary. According to the data presented here, it appears that as time passes from menopause onset, breast cancer risk decreases. However, data from the American Cancer Society shows that breast cancer incidence in the United States remains just as high in the 6th and 7th decades.\textsuperscript{4} It is probable that the peripheral source SEL is responsible for levels of malignancy. This study represents a great leap in quantitative risk assessment, but clearly there are other risk factors we need to measure.

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References:

\textbf{HT for prevention of chronic conditions}

\textit{The USPSTF recommends against the use of EPT for the prevention of chronic conditions in postmenopausal women}


\textbf{Summary.} The USPSTF commissioned a review of the literature to update evidence about the benefits and harms of using menopausal hormone therapy (HT) to prevent chronic
conditions, as well as whether the benefits and harms of HT differ by population subgroups defined by age; the presence of comorbid medical conditions; and the type, dose, and method of hormonal delivery. This recommendation applies to postmenopausal women who are considering HT for the primary prevention of chronic medical conditions. It does not apply to women who are considering HT for the management of menopausal symptoms, such as hot flashes or vaginal dryness. It also does not apply to women younger than age 50 who have had surgical menopause.

- The USPSTF recommends against the use of combined estrogen and progestogen (EPT) for the prevention of chronic conditions in postmenopausal women. (Grade D recommendation).
- The USPSTF recommends against the use of estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy. (Grade D recommendation).

Comment. All menopause practitioners will benefit from this synthesis and summary of information on HT. Please note that recommendations are Grade D: this means the USPSTF recommends against HT for primary prevention of chronic diseases. There is moderate to high certainty that the HT has no net benefit on chronic diseases or that the harms outweigh the benefits and thus the USPSTF discourages HT for this purpose.

This recommendation statement only applies to the use of HT in postmenopausal women for the primary prevention of chronic diseases, such as coronary heart disease or fractures. Questions about treatment of symptomatic conditions are beyond the scope of this work. The USPSTF has clarified the specific form, dosage, and route of administration of the estrogen-progesterone therapy and estrogen-only therapy used in the Women’s Health Initiative (oral conjugated equine estrogen, 0.625 mg/d, with or without oral medroxyprogesterone acetate, 2.5 mg/d) and notes that the estimates of the absolute risks and benefits it describes are derived primarily from this study. There is no convincing evidence to assert that the ultimate balance of benefits and harms might be substantially altered by using different approaches; however, available data are limited, and additional research would be useful to reveal whether any differences do exist.

Some commentators asked the USPSTF to provide information about the use of compounded menopausal bioidentical hormones. According to the FDA, “bioidentical hormone replacement therapy” is a marketing term rather than a formally defined drug classification. To date, the FDA has not approved any type or class of bioidentical HT for the prevention of chronic diseases in postmenopausal women, and the safety and effectiveness of these products have not been evaluated through the FDA’s drug approval process. In its review of the evidence, the USPSTF did not identify any randomized trials that have studied the potential benefits or harms of bioidentical hormones for the prevention of chronic conditions in postmenopausal women.

The USPSTF is in agreement with NAMS 2012 HT position statement. The indication for use is to relieve menopause symptoms and to improve quality of life where this is pertinent, and every clinical decision to use HT must weigh its risks and benefits against both alternative therapies and no use at all.

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CVD & the effect of diet

A higher-quality diet is associated with a lower risk of recurrent CVD events among those age 55 and above with CVD or DM


Summary. Although it is well known that there is a strong relationship between diet and cardiovascular disease (CVD), not much is known about its impact in older people at high risk of CVD who are taking medication for secondary prevention. Dehghan et al assessed the relationship between diet quality and CVD events in a large population from 40 countries with CVD or diabetes mellitus (DM) with end-organ damage taking proven drugs.

From two randomized trials (ONTARGET and TRANSCEND), a total of 31,546 women and men age 66.5 ± 6.2 years were studied. The modified Alternative Healthy Eating Index and the Diet Risk Score were used. Cox proportional hazard regression with adjustment for age, sex, trial enrollment allocation, region, and other known confounders was used to find an association between diet quality and the primary composite outcome of CV death, myocardial infarction [MI], stroke, or congestive heart failure. There were 5,190 events during 56 months of follow-up. Patients in the healthier quintiles of modified Eating Index scores had a much lower risk of CVD (HR, 0.78; 95% CI, 0.71-0.87, top versus lowest quintile). The reductions in risk for CV death, MI, and stroke were 35%, 14%, and 19%, respectively. The protective association was consistent regardless of whether patients were receiving medication.

A higher-quality diet was associated with a lower risk of recurrent CVD events among people age 55 or older with CVD or DM. The authors urge that healthcare professionals strongly recommend eating a healthy diet to ensure reducing CVD and saving lives.

Comment. Dietary and lifestyle modifications have been found to substantially reduce morbidity and mortality in the primary prevention of CVD. The current study reports that healthy lifestyle modifications are also important in the secondary prevention of CVD events, including myocardial infarction and stroke. The role of nutritionists and patient education is often underestimated in CVD management, and patient adherence to recommendations may be lower than expected secondary to poor recall of information, need for additional support, and lack of will power. Effective nutritional education and support can improve blood lipids, body weight, and insulin resistance through the intake of heart-healthy foods, caloric restriction, and improved physical activity levels, even in patients with obesity or the metabolic syndrome. The post CABG trial noted that aggressive lowering of lipids with medications decreased atherosclerotic progression with a subsequent decrease in myocardial infarctions and death. However, few studies have looked at the impact of dietary modifications as a strategy for secondary prevention in individuals with known CVD by measuring outcomes such as myocardial infarction, stroke, and mortality.

Although the current study did not address portion sizes, it did address the types of foods consumed, which may be more helpful to the clinician making assessments in the office setting. An additional strength is the involvement of several countries, leading to greater applicability albeit not necessarily in low-income countries. Most notable was the consistent benefit of a healthy diet regardless of drug therapy or other lifestyle changes, even in patients with diabetes.
As clinicians, once our patient has been diagnosed with CVD we may focus on drug treatment regimens and side effects, with less emphasis on dietary and lifestyle modification counseling. This study lends support to prior ones advocating continued long-term involvement of nutritional counseling until goals are reached, perhaps with involvement of a nutritionist, in the care of patients with CVD.\(^5\)

Patients could be motivated to continue making dietary changes when they learn of the potential 35% risk reduction for death from CVD among the top quintiles of healthy eaters. Healthcare providers caring for those with CVD should be encouraged to keep a sustained focus on this aspect of preventative health.

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References:


**Nonmedical treatments for breast cancer survivors’ menopausal symptoms**

Both cognitive-behavioral therapy and physical exercise improved endocrine and urinary symptoms and physical function but did not decrease frequency of hot flashes.


Younger breast cancer survivors’ quality of life can be adversely affected by treatment-induced menopausal symptoms. Hormone therapy is often contraindicated, and nonhormonal pharmacologic treatment is available but less effective. Nonpharmacologic interventions offer an alternative approach. Dutch investigators randomized 422 disease-free breast cancer survivors (age <50; premenopausal at cancer diagnosis) who were experiencing menopausal symptoms to one of four groups: cognitive-behavioral therapy (CBT; 6 weekly 90-minute group sessions followed by one refresher 6 weeks later), physical exercise (PE; 12 weeks of individually tailored 2.5-3.0-hour weekly home sessions), CBT plus PE, or no structured intervention. General menopause-related endocrine and urinary symptoms (ie, incontinence and its consequences) and specific hot-flash symptoms (including perception that they interfered with daily life) were measured with standardized scales.
Fewer than half the women in each intervention group adhered to minimal protocol requirements; many cited scheduling conflicts as a factor. Nevertheless, results of per-protocol and intent-to-treat analyses were similar: At 12 weeks and 6 months, women in all three intervention groups showed small but significant mean improvements in endocrine and urinary symptoms and in physical function. The CBT and CBT plus PE groups also reported decreased impact of hot flashes and night sweats on quality of life, although the symptoms themselves did not abate.

Comment: Low adherence and lack of a placebo intervention in the comparison group limit the reliability of these results. However, they agree with the growing literature demonstrating that cognitive-behavioral therapy, physical exercise, and other nonpharmacologic interventions can improve quality of life for women with chronic health conditions, alone or in conjunction with other treatment. We need to broaden our awareness of the evidence for (or against) all modalities that might benefit our patients, not just the ones we were trained to provide.

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Originally published in Journal Watch Women's Health at

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**Menopause Editor's picks from December 2012**


This study demonstrated the potential of short-term statin treatment to improve arterial stiffness in postmenopausal women with dyslipidemia. The value of this study lies primarily in its study population of otherwise healthy postmenopausal women with dyslipidemia.

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This observational study investigated menopausal symptoms, attitudes, and understanding of menopause and menopausal therapies in Australian and Laotian women.

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In this study, immigrants from the former Soviet Union and Arab Israeli women were at a significantly higher risk of depressive symptoms as compared to native born/long-term Jewish residents after taking into account socio-demographic and health status differences between the cultural groups.

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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.

- **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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