

Unequal breast cancer risk found with use of HRT progestogens

Clinical question Do hormone replacement therapies (HRTs) for postmenopausal women carry different breast cancer risks?

Bottom line In this large French cohort of postmenopausal women, the risk of breast cancer among those who used estrogen plus progesterone was the same as for those who never used HRT. Women who used estrogen alone had increased risk and those who used estrogen plus other progestogens had the highest risk. This is the first large study reported in which combined HRT included progesterone as the progestogen used by women in sufficient numbers for comparison. (Level of evidence = 2b)

Synopsis This is a large, well-designed, cohort study of French women, initiated in 1990 with follow-up until July 2002. It is the French component of the European Prospective Investigation into Cancer and Nutrition (EPIC). The study enrolled women (N = 98,995) aged 40 to 65 years. Follow-up for this analysis started in 1990 if the woman was already postmenopausal or at the date of menopause. Women were excluded if they reported cancer other than basal cell carcinoma prior to 1990 or if the date of HRT use was unavailable, leaving 80,377 who contributed 652,972 person-years for life-table analysis. The majority of women (70%) reported HRT use for a mean duration of 7.0 years. Women were followed up until either a diagnosis of cancer, they completed their final questionnaire, or July 2002, whichever came first. There were 2,365 cases of breast cancer among these women, of which 95% were confirmed by pathology reports. The oral estrogen was estradiol in more than 98% of women who used estrogen. There was no difference in breast cancer risk between oral and transdermal routes of estrogen administration. Compared with never-users,

women who used estrogen alone had a relative risk (RR) of breast cancer of 1.29 (95% CI, 1.02-1.65). There were marked differences in breast cancer risk with combined therapy, depending on the progestogen used: progesterone, RR = 1.0 (0.82-1.22); dydrogesterone, RR = 1.16 (0.94-1.43); and for all progestogens, RR = 1.75 (1.54-1.99). The main limitation to these observational data is that the cohort may not be representative of the population studied. The cohort was composed of the volunteers from a population of approximately 500,000 who were willing to respond to the questionnaires (less than a 20% response rate).

Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat.* 2008;107(1):103-111.

Single intra-articular injection of hyaluronic acid is equal to placebo

Clinical question Is a single intra-articular injection of hyaluronic acid effective in reducing pain or improving function in patients with symptomatic degenerative joint disease (DJD) of the hip?

Bottom line A single intra-articular injection of hyaluronic acid to the hip of patients with symptomatic DJD was no better than placebo in decreasing pain or improving function. (Level of evidence = 2b)

Synopsis To be eligible for this study, patients had to be aged 30 to 80 years; have radiographically confirmed, moderately severe DJD involving the hip; have had daily pain for at least 1 month with a severity of at least 40 mm on a 100-mm visual analog scale (VAS) in spite of treatment with acetaminophen or NSAIDs. These patients were randomly assigned (concealed

allocation) to receive a single fluoroscopically guided intra-articular injection of hyaluronic acid or a placebo. After the injection, patients could use NSAIDs or stronger analgesics only if the pain did not respond to optimal doses of acetaminophen (4 g/d). The main outcomes—change in pain ratings and some measures of function—were analyzed by intention to treat. The researchers estimated they would need 122 patients to find a difference in pain response of 20 mm on the VAS. This is the minimal clinically important difference for pain scores. They only studied 85 patients because recruitment was slow and their supply of medication had expired. At the end of 12 weeks, the patients who received active therapy saw their pain scores decrease by the same amount as those who received placebo (average = 8 mm compared with 9 mm). Additionally, approximately one third of the patients in each group were categorized as responders (not defined by the researchers).

Richette P, Ravaud P, Conrozier T, et al. Effect of hyaluronic acid in symptomatic hip osteoarthritis: a multicenter, randomized, placebo-controlled trial. *Arthritis Rheum.* 2009;60(3):824-830.

Early treatment is beneficial for patients with PTSD

Clinical question Is early treatment after a traumatic stress event beneficial?

Bottom line Identification of a traumatic stress event within 3 months and treatment using trauma-focused cognitive behavioral therapy (CBT) is beneficial for patients who meet *DSM-IV* criteria for the diagnosis of posttraumatic stress disorder (PTSD). It is uncertain whether individuals would benefit if they are symptomatic but do not meet diagnostic criteria for PTSD. (Level of evidence = 1a-)

Synopsis This is a meta-analysis of randomized controlled trials of psychological interventions (of more than one session) to reduce traumatic stress symptoms within 3 months of a traumatic stress event compared with pla-



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cebo or other control (eg, waiting list or usual care). The authors identified 25 studies that met inclusion criteria. Intervention for individuals involved in a traumatic event, irrespective of symptoms, showed no difference between any intervention and control groups. Among individuals with traumatic stress symptoms irrespective of symptoms, trauma-focused CBT was more effective than waiting list or supportive counseling (relative risk [RR] = 0.72; 95% CI, 0.50-1.05), especially those meeting criteria for diagnosis of PTSD (RR = 0.54; 0.31-0.95). Trauma-focused CBT was defined as “any intervention that focused on the trauma using exposure to trauma memories and trauma reminders with or without cognitive therapy and other cognitive-behavioral techniques.”

Roberts NP, Kitchiner NJ, Kenardy J, Bisson JI. Systematic review and meta-analysis of multiple session early interventions following traumatic events. *Am J Psychiatry*. 2009; 166(3):293-301.

PSA screening does not reduce mortality from prostate cancer

Clinical question Does screening with prostate-specific antigen (PSA) reduce mortality?

Bottom line The initial results of the Prostate Lung Cancer Ovary (PLCO) screening trial found no benefit as measured by prostate cancer-specific mortality. Although this study does not report quality-of-life data or consequences of treatment, such as impotence and incontinence, there were almost 500 more cases of cancer found in the screened group, so screening is an important issue. Men should only choose PSA screening if they understand the lack of proven mortality benefit even in this very large study. (Level of evidence = 1b)

Synopsis Men aged 55 to 74 years at 10 centers were randomized to annual PSA screening for 6 years plus digital rectal examination (DRE) for 4 years, or no screening. Patients with a histo-

ry of prostate, lung, colon, or ovarian cancer or a PSA in the previous 3 years were not eligible for the study. Further testing was done in the event of a PSA greater than 4.0 ng/mL or an abnormal DRE. Cancer diagnoses were determined by annual mailed surveys, and cancer-specific and all-cause mortality were determined by review of death certificates. A total of 76,693 patients were enrolled in the study; 86% were non-Hispanic white, 7% had a family history of prostate cancer, and they were well distributed across the age range. There was considerable contamination, which would tend to dampen any benefit of screening. The rate of PSA screening was 85% in the screening group, it was 40% to 52% in the control group (increasing between years 1 and 6). At this time, there has been complete follow-up for 7 years and partial follow-up for 10 years. Data collection will continue until all patients have had at least 13 years of follow-up. Diagnosis of prostate cancer was significantly more common in the screening group (3,452 vs 2,974 persons, or 9.0% vs 7.7%); most were stage II and more than half had a Gleason score of 5 or 6. There was no difference between groups in patients with advanced cancers. Additionally, there was little difference in prostate cancer-specific mortality between groups (92 in the screening group and 82 in the control group). There was also no difference in all-cause mortality.

Andriole GL, Crawford ED, Grubb RL 3rd, et al; PLCO Project Team. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med*. 2009;360(13):1310-1319.

BNP testing does not lower hospitalization rate

Clinical question Does B-type natriuretic peptide (BNP) testing in the emergency department improve outcomes or affect hospitalization rates?

Bottom line In contrast to results from an earlier study, testing the BNP levels of patients with severe dyspnea does

not decrease rates of admission or length of stay. We now have conflicting evidence regarding whether routine BNP testing is warranted in the emergency department. (Level of evidence = 1b)

Synopsis These Australian researchers enrolled 612 patients presenting with severe shortness of breath, defined as requiring assessment by a physician within 30 minutes of arrival, at either of two emergency departments. The patients—with an average age of 74 years; 54% were men—were randomized, allocation concealment uncertain, to have BNP measured, or not, along with routine investigations. Emergency department physicians were instructed that a BNP level of less than 100 ng/mL made the diagnosis of heart failure unlikely, and a level of more than 500 ng/mL made heart failure likely. Heart failure, determined by two physicians masked to BNP results, was diagnosed in 45% of the enrolled patients, and almost all patients (85.1%) were admitted. Admission rates, length of stay, intensive care unit admissions, mortality within 30 days, and use of appropriate heart failure medication did not differ with the knowledge of patients' BNP levels. These results conflict with another study conducted in Switzerland (*N Engl J Med*. 2004; 350[7]:647-654) that found that BNP testing in the emergency department decreased hospitalizations from a similar 85% to 75%. This earlier study, though, used point-of-care BNP testing that produced results within 20 minutes, whereas the test used in this study required approximately 1 hour for processing.

Schneider HG, Lam L, Lokuge A, et al. B-type natriuretic testing, clinical outcomes, and health services use in emergency department patients with dyspnea. *Ann Intern Med*. 2009; 150(6):365-371.

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Is PCI more beneficial than CABG for three-vessel/left main CAD?

Clinical question Is percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) preferred in patients with three-vessel or left main coronary artery disease (CAD)?

Bottom line You would have to treat 14 patients with CABG instead of PCI to prevent one revascularization, and 60 patients with PCI instead of CABG to prevent one stroke (although this is partially offset by fewer MIs in the CABG patients). Put another way, patients and physicians will have to decide whether 4 to 5 revascularizations equals one stroke. Revascularization is especially likely in patients with more complex lesions. (Level of evidence = 1b)

Synopsis Previous randomized controlled trials compared CABG with PCI using bare metal stents. Newer drug-eluting stents reduce the need for revascularization, but have not been compared with CABG in large, randomized controlled trials. In this study,

patients with three-vessel or left main disease were approached for inclusion. Those patients who were thought by an interventional cardiologist and thoracic surgeon to have disease that could be treated equally well by CABG or PCI (n = 1,800) were randomized to receive PCI with drug-eluting stents or CABG. The mean age of the patients was 65 years, 77% were men, 20% were smokers, and 25% had diabetes. Groups were balanced, and the analysis was by intention to treat. This was a noninferiority study, in which the null hypothesis is that there is a difference, and the study tries to prove that there isn't a difference (which is the opposite of a typical study). There were more withdrawals in the CABG group (40 vs 7), which is not explained, but crossovers and losses to follow-up were similar between groups. After the procedure, patients who underwent CABG were less likely to be taking an antiplatelet drug (24% vs 97%; $P < .001$), but were more likely to be taking warfarin or amiodarone. After 1 year, the “all bad

things” outcome was more likely in the PCI group (17.8% vs 12.4%; $P = .002$; number needed to treat to harm = 18), primarily due to an increased risk of repeat vascularization (13.5% vs 5.9%; $P < .001$). The risk of stroke was slightly higher in the CABG group, balanced by a similar reduction in the risk of MI (although the latter was not statistically significant). All-cause mortality was 4.4% in the PCI group and 3.5% in the CABG group, a nonsignificant difference. When results were stratified by the complexity of the lesion, those with less complex lesions did just as well with either procedure, whereas those with very complex lesions had many more revascularizations with PCI.

Serruys PW, Morice MC, Kappetein AP, et al; SYNTAX Investigators. Percutaneous coronary intervention versus coronary artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360(10):961-972.

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