Cochrane for Clinicians

Putting Evidence into Practice

Effect of Mammography on Breast Cancer Mortality

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The Cochrane Abstract on the next page is a summary of a review from the Cochrane Library. It is accompanied by an interpretation that will help clinicians put evidence into practice. Dr. Wilkinson presents a clinical scenario and question based on the Cochrane Abstract, followed by an evidence-based answer and a critique of the review. The practice recommendations in this activity are available at http://www2.cochrane.org/reviews/en/ab001877.html.

EB CME

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Clinical Scenario

A 54-year-old woman is new to your practice and has never been screened for breast cancer. She is concerned about false-positive results, and wonders if mammography does more harm than good.

Clinical Question

Do the potential benefits of mammography outweigh the potential harms?

Evidence-Based Answer

Although mammography can lead to false-positive results, emotional stress, and unnecessary biopsies, it appears to reduce deaths from breast cancer by about 15 percent.[1] (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

Breast cancer is the second most commonly diagnosed cancer (after skin cancer) in U.S. women.[2] Most primary care physicians recommend screening mammography in women every one to two years starting at 40 to 50 years of age. Widespread use of mammography and improvements in breast cancer treatment are thought to be responsible for the drop in breast cancer mortality since about 1990.[3] In 2009, the U.S. Preventive Services Task Force (USPSTF) reevaluated its recommendation on mammography that was released in 2002.[4] After reviewing new and existing literature,[5] the USPSTF now recommends against routine screening mammography in women 40 to 49 years of age, and encourages physicians to make the decision to screen these women on a patient-by-patient basis.[6] The review accompanying the USPSTF recommendation found a mortality benefit in all women, but an increased number of false-positive results in women 40 to 49 years of age.[7] Women in this age group also have a lower incidence of breast cancer. This Cochrane review examines the risks and benefits of mammography for all age groups.[1]

The authors examined eight clinical trials comparing the effect of mammography with no mammography on breast cancer mortality and morbidity. One trial was excluded because of bias. The excluded trial reported different socioeconomic profiles of the control and intervention groups, and had differing exclusion criteria for each group.[8] The remaining seven trials (n = 600,000) were divided into two groups: three trials with adequate randomization that showed a 10 percent reduction in breast cancer mortality (not statistically significant), and four trials with suboptimal randomization that showed a 25 percent reduction in breast cancer mortality (statistically significant).

The problems with randomization included insufficient data to determine who was excluded from the intervention and control groups and why, and in some cases, insufficient information about how practices or participants were randomized. It was not clear if the Cochrane authors knew whether the trials had employed suboptimal randomization practices in every case, or whether there was insufficient information about every step of the process. If the latter is true, then the most conservative approach would be to exclude those trials from the analyses, although it is possible that some or all of the randomization practices in those trials were acceptable. The overall risk reduction in breast cancer mortality for all seven trials was statistically significant (19 percent), but the reduction in all-cause mortality was not statistically significant.

Cochrane Abstract

Background: A variety of estimates of the benefits and harms of mammographic screening for breast cancer have been published, and national policies vary.

Objectives: To assess the effect of screening for breast cancer with mammography on mortality and morbidity.

Search Strategy: The authors searched PubMed (November 2008).

Selection Criteria: The authors selected randomized trials comparing mammographic screening with no mammographic screening.

Data Collection and Analysis: The authors independently extracted data. Study authors were contacted for additional information.

Main Results: Eight eligible trials were initially identified. The authors excluded a biased trial and included 600,000 women in the analyses. Three trials with adequate randomization did not show a significant reduction in breast cancer mortality at 13 years (relative risk [RR] = 0.90; 95% confidence interval [CI], 0.79 to 1.02); four trials with suboptimal randomization showed a significant reduction in breast cancer mortality (RR = 0.75; 95% CI, 0.67 to 0.83). The RR for all seven trials combined was 0.81 (95% CI, 0.74 to 0.87). The authors found that breast cancer mortality was an unreliable outcome that was biased in favor of screening, mainly because of differential misclassification of cause of death. The trials with adequate randomization did not find an effect of screening on cancer mortality, including breast cancer, after 10 years (RR = 1.02; 95% CI, 0.95 to 1.10) or on all-cause mortality after 13 years (RR = 0.99; 95% CI, 0.95 to 1.03). Numbers of lumpectomies and mastectomies were significantly larger in the screened groups (RR = 1.31; 95% CI, 1.22 to 1.42) for the two adequately randomized trials that measured this outcome; the use of radiation therapy was similarly increased.

Authors' Conclusions: Screening is likely to reduce breast cancer mortality. Because the effect was lowest in the adequately randomized trials, a reasonable estimate is a 15 percent reduction corresponding to an absolute risk reduction of 0.05 percent. Screening led to 30 percent overdiagnosis and overtreatment, or an absolute risk increase of 0.5 percent. This means that for every 2,000 women invited for screening over 10 years, one will have her life prolonged, and 10 healthy women who would not have been diagnosed if there had not been screening will be treated unnecessarily. Furthermore, more than 200 women will experience important psychological distress for many months because of false-positive findings. It is not clear whether screening does more good than harm. To help ensure that women are fully informed of benefits and harms before they decide whether to attend screening, the authors have written an evidence-based leaflet for patients, which is available at http://www.cochrane.dk/screening/mammography-leaflet.pdf.

The authors expressed concerns about how the cause of death was ascertained in some studies (i.e., by researchers and experts who may have known whether the participant was in the intervention or control group, instead of using a cause-of-death registry). Most of the trials were initiated in the 1960s and 1970s. In the past 30 to 40 years, standards of data reporting for clinical trials have changed, as have breast cancer treatments and the quality of available mammography technology. Because of these improvements, it is not known whether the breast cancer mortality benefit would be similar if these trials were repeated today. It also is not known what proportion of participants in the control group underwent mammography outside of the study, raising the question of potential bias toward the null hypothesis (i.e., making the reduction in mortality appear closer to zero than it actually is).

The authors discussed potential harms from mammography: the emotional stress and biopsies associated with a false-positive result, and the potential for cardiovascular effects from radiation therapy for early-stage cancers, particularly ductal carcinoma in situ, which is often diagnosed by mammography and does not always progress or recur. However, despite the shortcomings of the trials, screening appears to lower breast cancer mortality.

The review points out that the benefits of mammography may not be as great as originally thought, and that the risks may be underestimated. However, other sources have found sufficient evidence to continue using mammography for breast cancer screening. The American College of Physicians concluded that mammography is beneficial, but that the magnitude of the benefit should be interpreted with caution.[9]

The American Cancer Society recommends annual mammography starting at 40 years of age,[10] and a National Cancer Institute fact sheet states that mammography reduces deaths from breast cancer in women 40 to 74 years of age and especially in women 50 to 74 years of age.[11] The USPSTF recommends routine biennial screening mammography in women 50 to 74 years of age.[6]

There is not enough agreement about the current evidence for mammography to recommend a change in practice based on this review alone. Primary care physicians should continue to recommend mammography every two years in women 50 to 74 years of age, and to individualize their recommendation in women 40 to 49 years of age and in women older than 74 years. When discussing the risks and benefits of mammography with patients, physicians should mention the risk of false-positive results, especially in younger women, and the stress those results may cause. Physicians should interpret evidence-based recommendations based on each patient's clinical situation.[6]

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Author disclosure: Dr. Wilkinson has received grant funding from the American Cancer Society and the National Cancer Institute to conduct mammography research.

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Cochrane Briefs

Management of Constipation in Patients Receiving Palliative Care

Clinical Question

Are laxatives or methylnaltrexone (Relistor) helpful for the management of constipation in patients receiving palliative care?

Evidence-Based Answer

There is insufficient evidence to recommend one laxative over another for the treatment of constipation in patients receiving palliative care. Methylnaltrexone can increase the frequency of bowel movements at four hours (odds ratio = 7.0; 95% confidence interval, 3.8 to 12.6) and at 24 hours (odds ratio = 5.4; 95% confidence interval, 3.1 to 9.4). Methylnaltrexone also may increase the risk of flatulence and dizziness. (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

Constipation affects up to 48 percent of all patients receiving palliative care,[1] and up to 87 percent of patients receiving palliative care who also are taking opioids.[2] For some patients, opioid-induced constipation may be so severe that they avoid opioid therapy and choose inadequate analgesia over constipation.[3] Although constipation is difficult to define or quantify because normal bowel

movements can range from one to three stools per day, three sets of factors can predispose patients to constipation: lifestyle-related factors, disease-related factors, and medications that predispose to constipation. Laxatives have long been recommended for prevention and treatment of palliative care–associated constipation, and methylnaltrexone is a peripherally acting opioid antagonist that is licensed for treatment of opioid-induced constipation when usual measures are ineffective.[4]

To determine the effectiveness and safety of treating constipation in patients receiving palliative care, the authors searched for randomized controlled trials comparing laxatives or methylnaltrexone with another active treatment or with placebo. The authors found seven studies including 616 patients. Four trials of laxatives that included a variety of agents (i.e., senna, lactulose, misrakasneham, co-danthramer, and magnesium hydroxide with liquid paraffin) found no differences in stool frequency response. In all four trials, some patients experienced vomiting and colicky pain, and some required additional interventions for constipation. Three trials evaluated methylnaltrexone and found improved stool frequency at four and 24 hours. However, methylnaltrexone was associated with increased risk of flatulence and dizziness, and one patient had severe diarrhea, dehydration, and cardiovascular collapse.

Palliative care involves balancing symptom relief with avoidance of iatrogenic adverse effects from palliative treatments. For patients with constipation, especially those with opioid-induced constipation, there is insufficient evidence to recommend one laxative over another. The choice of laxatives should be based on past patient experience, tolerability, and adverse effects. Methylnaltrexone is a newer agent that may be useful especially for patients with opioid-induced constipation that has not responded to standard laxatives, but there is limited evidence of potential adverse effects. Therefore, judicious use preceded by a discussion with patients about known risks and benefits is warranted.

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Author disclosure: No relevant financial affiliations to disclose.

SOURCE: Candy B, Jones L, Goodman ML, Drake R, Tookman A. Laxatives or methylnaltrexone for the management of constipation in palliative care patients. *Cochrane Database Syst Rev.* 2011;(1):CD003448.

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