AFP Journal Club

The Story Behind the Study

Does Screening Mammography Lead to Overdiagnosis of Invasive Breast Cancer?

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Purpose

In *AFP* Journal Club, three presenters review an interesting journal article in a conversational manner. These articles involve "hot topics" that affect family physicians or "bust" commonly held medical myths. The presenters give their opinions about the clinical value of the individual study discussed. The opinions reflect the views of the presenters, not those of *AFP* or the AAFP.

Article

Kalager M, Adami HO, Bretthauer M, Tamimi RM. Overdiagnosis of invasive breast cancer due to mammography screening: results from the Norwegian screening program. *Ann Intern Med.* 2012;156(7):491-499.

What does this article say?

Jill: This is a prospective historical cohort study looking at the rate of overdiagnosis of invasive breast cancer between 1986 and 2005 in 39,888 Norwegian women 50 to 69 years of age. Norway piloted mammographic screening in four counties that represented 40 percent of the eligible population in 1996 before implementing the program nationwide. Overdiagnosis was said to occur if the breast cancer detected was not likely to become clinically apparent or be the cause of death. This was calculated as the number of incident cases of invasive breast cancer in screened versus unscreened women based on a national registry.

Researchers also compared historical and current incidence rate ratios in counties with and without screening programs to account for temporal changes in incidence. They evaluated overdiagnosis using two statistical approaches: (1) by accounting for the expected decrease in incident cases after screening cessation at 69 years of age, and (2) by comparing incidence in the screening group with that among women two and five years older in the historical screening group (to account for lead-time bias). This assumes that breast cancer, if present, will manifest within five years.

The risk of overdiagnosis of invasive breast cancer from mammographic screening was 18 to 25 percent using the first approach and 15 to 20 percent using the second approach. Put another way, by screening 2,500 women 50 to 69 years of age biennially with mammography, 20 women were diagnosed with invasive breast cancer, one death was prevented, and six to 10 additional women were overdiagnosed. In addition, the incidence of advanced breast cancer was similar in both the screened and unscreened groups.

Should we believe this study?

Bob: Although it isn't the ideal study design (randomized trial with lifelong follow-up), such a study will never be performed. This design and setting are still pretty good because:

- Having a contemporary control group allows the researchers to account for potential changes in incidence caused by temporal trends, and having a historical control group allows us to evaluate the impact of screening on incidence of disease.
- The Cancer Registry of Norway is almost 100 percent complete, providing a relatively large and representative sample size. The screening is the same nationwide for all women 50 to 69 years of age: every two years.

Mark: Another strength is that the authors used two different statistical methods to estimate the rate of overdiagnosis while accounting for lead time. Lead time is the amount of time that would have elapsed between the mammographic diagnosis of breast cancer and when it would have presented clinically had mammography not been performed. The examination of stage-specific trends in cancer incidence further supported results by showing that although the incidence of advanced disease was lower in the current groups than in the historical groups, that difference was similar in the screened and unscreened groups. This suggests that other factors are involved in decreasing the incidence of advanced-stage cancer, aside from earlier detection through mammography.

Bob: There are some limitations, of course. Because the women were put in groups based on residence in specific counties, there is a large potential for bias from

geographic, socioeconomic, and other demographic factors. For example, access to care may be an issue in the more rural counties.

Jill: The fact that the authors excluded women with ductal carcinoma in situ (DCIS) is both a strength and a weakness. It certainly makes the statistical analysis and results cleaner, and it makes sense because DCIS behaves differently than invasive breast cancer.

Mark: Including DCIS would likely further increase the rate of overdiagnosis, because the number of DCIS diagnoses has increased with mammographic screening and because it doesn't always progress to invasive cancer.

Jill: These results may not be entirely generalizable to the American population, because lifestyles and genetics undoubtedly play a role in cancer incidence. The period and frequency of screening are much higher in the United States, with many women having mammography performed annually beginning at 40 years of age (despite the U.S. Preventive Services Task Force recommendation to begin screening at 50 years of age for most women). This is probably offset by the fact that our screening rate is quite a bit lower too, especially in certain ethnic and education level subgroups.[1]

Bob: Studies also show that American radiologists are more likely to interpret results of mammography as positive compared with radiologists in other countries, suggesting that the problem of overdiagnosis in the United States may, in fact, be more severe than in Norway.[2]

What should the family physician do?

Jill: This study adds to the existing literature on cancer overdiagnosis.[3] It highlights the importance of adhering to U.S. Preventive Services Task Force evidence-based recommendations for breast cancer screening to reduce overuse of mammography, and it reminds us to do a better job educating our patients about the possible risks of overdiagnosis. It does not (and cannot) alter our day-to-day practice on responding to mammography results because we cannot yet identify which lesions in women with positive findings (i.e., indolent cancer) will progress to invasive disease.

These results also serve as a reminder that earlier cancer diagnosis may not always lead to improved survival or quality of life for patients. Diagnosing a cancer that is not likely to become clinically significant places a burden on the patient and family in terms of emotional and psychological stress and physical consequences of biopsies, surgeries, radiation, chemotherapy, etc.

Bob: That last point is a salient one—family physicians are often faced with myriad screening options for our patients and we must remember that just because we can do a screening test, it may not always benefit our patients. A quick example: prostate-specific antigen testing in men older than 75 years. Screening this population for prostate cancer provides no proven benefit, but many of the potential harms previously mentioned. Sometimes, less is more.

Mark: Overdiagnosis particularly plagues breast cancer screening when you include DCIS (which the study did not include), because it is estimated that less than 50 percent of low-grade DCIS lesions progress to invasive disease.[4] But as Jill said, when we get positive results on mammography, we ultimately have to move forward with further investigation. I am hopeful that one day we will have a way to tell if a cancer diagnosed by mammography is likely to progress rapidly enough to impact a patient's life.

Main Points

- Implementation of a universal mammographic screening program leads to an increase in the diagnosis of invasive breast cancer, because of improved detection of clinically significant cancer and overdiagnosis.
- Overdiagnosis occurs when a disease or condition is detected or diagnosed by screening, but it would not otherwise lead to symptoms or earlier mortality.
- Universal access to care can help level the playing field and allow more valid longitudinal studies to be done.

EBM Points

Several different types of research bias were addressed in the study design:

- History bias: controlling for temporal trends in disease incidence is important when doing a comparison between contemporary and historical groups.
- Lead-time bias: an important consideration when evaluating a screening intervention. Diagnosing disease earlier with a screening test can appear to prolong survival without actually changing outcomes. The only thing that changes is the period of time that the patient is diagnosed with the disease, not the survival time.
- Sampling bias: representative inclusion of all possible study participants helps to eliminate differences between groups so that more appropriate comparisons can be made.

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