American Researchers Question Effect of Scandinavian Mammography Debate

By Renee Twombly

A public row is taking place among some European investigators over a 22-year-old study that helped lay the foundation for mammography screening worldwide. Some experts question if it could—or even should—affect current practice in the United States.

The dispute centers on the Swedish two-county trial, which reported the largest reduction in breast cancer deaths found in all of the seven randomized mammography screening trials conducted around the world—a 31% decline. Enrolling more than 134,000 women, the 1985 report in The Lancet remains the largest clinical study of the power of mammography to reduce breast cancer deaths, and many say the findings paved the way toward mass screenings in many countries. An updated analysis in 1992 by the same group reduced the estimated drop in mortality to 24%, but that benefit is still higher than most other trials have found. “These were powerful findings that helped lead to widespread support of mammography screening,” said H. Gilbert Welch, M.D., a professor of medicine at Dartmouth Medical School.

But over the years since, questions have arisen about the validity of the study, including allegations of hiding and manipulating data. Now the dispute simmering between two groups of researchers has led to a retracted publication and airing of acerbic complaints in the pages of The Cancer Letter in May.

Among the studies that have questioned conclusions reached in the two-county trial is a 2002 meta-analysis of all Swedish mammography studies, which looked at most of the Swedish population and found a 15% reduction in breast cancer death among screened women and only a 10% decline in mortality for Östergötland. Data from the other county, Kopparberg, have not been made available to outside researchers.

Then in November, researchers from Norway and Denmark published their own data, using what they describe as “simple and crude” comparisons between official Swedish statistics and data reported in the two-county trial studies. They found that 192 breast cancer cases and 43 breast cancer deaths “seem to be missing” from both the original publication as well as two updates of the trial.

“We conclude that the data reported for the two-county trial seem both incomplete and flawed,” the researchers wrote. They added that because the differences in the number of breast cancer deaths between the randomized groups were small, “the mortality reduction would therefore no longer be statistically significant if only a few more breast cancer deaths were added to the study group.”

This study had originally been published in March 2006 on the European Journal of Cancer Web site, but it was taken off, without comment, 3 weeks later. That led the authors to complain about the withdrawal in a letter to The Lancet, and now both groups of researchers are calling foul. The paper has since been published in the Danish Medical Bulletin.

László Tabár, M.D., a professor of radiology at the Falun Central Hospital in Sweden and lead investigator of the two-county trial, said in The Cancer Letter that the Danish Medical Bulletin analysis “is beset by elementary errors and fallacious assumptions.” Tabár, who is from Kopparberg, refused to share his data for the 2002 Swedish meta-analysis, according to researchers who are familiar with the dispute.

The authors of the Danish Medical Bulletin study, including Per-Henrik Zahl, M.D., Ph.D., of the Norwegian Institute of Public Health; Peter Gotzsche, M.D., of the Nordic Cochrane Centre; and Jan Møhløen, M.D., Ph.D., of the Ullevål University Hospital in Oslo, responded by saying the handling of data from the two-county trial “was sloppy at best, that the assessment of cause of death was rather subjective in favor of screening, and that the two-county trial is unreliable.”

Gotzsche is also an author on a 2006 study, a Cochrane Collaboration review, which analyzed six of the seven major mammography randomized trials, including the 1963 New York study, the only randomized trial of screening mammography conducted in the U.S. The review concluded that only two of the trials—a Canadian study and another in Malmö, Sweden—were adequately randomized, and those trials both showed that screening mammography did not reduce breast cancer mortality.

When all six trials were considered together, the researchers concluded that mammography offered only a modest decrease in breast cancer mortality but at a substantial risk of overdiagnosis and overtreatment. They calculated that in a 10-year period, 2,000 women would need to be screened to prolong the life of one woman, but 10 women would undergo unnecessary diagnostic procedures and treatment. Still, some investigators found it hard to take the study seriously because the publication did not disclose the methods used to reach these conclusions.
Complaints were much louder when Gotzsche and Zahl published their short-lived *European Journal of Cancer* article. “They didn’t use any methodology. All they did is indicate that they couldn’t come close to duplicating the Tabár data,” said Donald Berry, Ph.D., professor and head of the division of quantitative sciences at the University of Texas M. D. Anderson Cancer Center.

Researchers watching the debate say it has devolved into over-the-top attacks between the two groups and that charges of falsification have led to a refusal to open up the data to outside scrutiny. The result is that the conclusion reached by the two-county study—that mammography screening is more beneficial than it is harmful—is now clouded by controversy.

**Does It Matter?**

However, experts also differ on whether the ongoing argument between the Scandinavian researchers about the foundations of mammography should affect use of mammography in the United States.

Many people are not paying attention to the debate, contends Robert A. Smith, Ph.D., director of cancer screening at the American Cancer Society. The benefit of the screening has been well established through other randomized and observational trials, Smith said, and so the “world is rather fatigued with the mammography controversy.”

Not so, said M. Carolina Hinestrosa, executive vice president for programs and planning at the National Breast Cancer Coalition Fund (NBCCF). “This debate matters because we have placed so much emphasis on screening mammography as a key tool in the fight against breast cancer,” she said. On the partial basis of the two-county trial, NBCCF has long held that the data showing mammography to be effective “are conflicted and the benefits, if any, are quite modest,” Hinestrosa said.

The debate will not be cleared up until Tabár, the primary author of the original two-county trial, makes all of his data available for independent review, which he has not done in the 22 years since the original paper was published, Hinestrosa said. “NBCCF has been asking for the release of the individual patient data since at least 2002, and doing so will help resolve many of the unanswered questions in this controversy,” she said. “Auditing of data is standard procedure. There is no justification for a different standard in screening mammography, unless we are afraid of the answer.”

Whatever the outcome of the two-county study, suggested guidelines for screening mammography have been morphing in the United States, based on continuing examination of the evidence to date.

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For example, the American College of Physicians (ACP) recently concluded that the balance between benefits and harm from screening mammography is borderline for women in their 40s and “probably positive” for women aged 50–70 years. This analysis has led the ACP to recommend that the younger women talk with their doctors about whether they need a mammogram but not get one automatically. That advice goes against guidelines issued by the American Cancer Society, which calls for annual screenings starting at age 40, as well as the National Cancer Institute and the U.S. Preventive Services Task Force, which recommend that women aged 40 years and older should have mammograms every 1–2 years.

The medical literature on breast cancer screening “has been a place of continual ferment,” said Russell Harris, M.D., an associate professor of medicine at the University of North Carolina, Chapel Hill, in a June editorial on the new ACP guidelines in *American Family Physician*. “It is a comment on the complexity of screening that, even with all this evidence, controversy remains.”

But Harris acknowledges that the burden of knowing what to do about mammography screening now lies with each woman. Talking about the subject with your physician is not that simple, said Harris, who is also a member of the U.S. Preventive Services Task Force and the NCI’s Physician Data Query boards. “Different doctors favor different sets of guidelines,” he said in an interview.

Women appear to be aware of the controversy and are making up their own minds about the issue, said Leslie Laufman, M.D., president of Hematology Oncology Consultants in Columbus, Ohio, and a member of the Physician Data Query editorial board for cancer screening and prevention. “Although mammography is pretty entrenched in both the medical community and in the psyche of the general population, women may be getting more skeptical, as evidenced by the recent dropoff in compliance with annual mammography,” she said. “I think that women would gladly give them up if the medical community could, or would, reassure them that it’s a reasonable choice.”

Welch takes the current debate as part of a long-term discussion about the value of screening. As contentious as the debate is among the Scandinavian researchers, “I think the discussion about screening mammography has gotten more civil and balanced over the last 10–15 years,” he said. “Everyone has learned from prostate cancer that there are pluses and minuses to screening and that there is a closer call between benefit and harm than what many had once thought.”

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