

“Screening for Breast Cancer with Mammography” (2013), by Peter Gøtzsche and Karsten Jørgensen

“Screening for Breast Cancer with Mammography” is a Cochrane systematic review originally published by Peter Gøtzsche and Karsten Jørgensen in 2001 and updated multiple times by 2013. In the 2013 article, the authors discuss the reliability of the results from different clinical trials involving mammography and provide their conclusions about whether mammography screening is useful in preventing deaths from breast cancer. Mammography is an X-ray technique used to detect abnormalities in breast tissue, such as breast cancer, which affects about twelve percent of women in the world and has a significant risk of mortality. The authors concluded that mammography screenings reduced breast cancer mortality, but resulted in problems such as overdiagnosis and overtreatment of screened women. The article “Screening for Breast Cancer with Mammography” contributed to the then ongoing controversy about the usefulness of mammography and provided accessible information about mammograms in seven languages.

Cochrane is a non-profit international collaboration of medical professionals and researchers, headquartered in London, England, who evaluate the validity of information from clinical trials and publish systematic reviews about that information in accessible language, so that the general public can read it. The systematic reviews conducted for Cochrane usually incorporate multiple clinical trials. The authors analyze the data from each trial and determine whether the information is reliable. To determine whether each randomized trial is reliable, Cochrane checks whether randomization was completed properly. That includes determining whether each person in the experimental group had a demographically similar partner in the control group, and whether any people were removed from the results to favor one of the possible outcomes that the study is testing. The Cochrane team also assesses whether the trial was properly conducted and whether the researchers of that trial were biased toward a certain outcome of the study. According to Cochrane, high quality evidence comes from adequately randomized clinical trials only, as those trials include a true sample of a population in both the control and the experimental groups. The experimental group is the group that receives treatment and the control group is the group that does not receive any treatment, but gets monitored for the same outcomes as the experimental group.

In “Screening for Breast Cancer with Mammography,” the authors, Gøtzsche and Jørgensen, perform a systematic review of information gathered from seven clinical trials that studied the long-term effect of mammography on breast cancer mortality. The systematic review was published on the Cochrane website. Gøtzsche was a co-founder of Cochrane, as well as the head of the Nordic Cochrane Center in Copenhagen, Denmark. He was a physician and a researcher at Rigshospitalet, a hospital in Copenhagen. In 2012, Gøtzsche published *Mammography Screening: Truth, Lies and Controversy*. Jørgensen was a Danish researcher who also worked at Rigshospitalet. He published multiple articles on mammography in collaboration with Gøtzsche.

Gøtzsche and Jørgensen start their article with an abstract and a plain language summary. Each of the systematic reviews includes a plain language summary that contains the most important information from the review in a simple form that is accessible for the general population. The authors divide the rest of the article into five sections: background, methods, results, discussion, and the authors’ conclusion. In the background section, the authors discuss the controversy about the usefulness of mammography screening. They state that their main goal is to evaluate the effects of mammography screening on mortality from breast cancer and other conditions. In the methods section, the researchers describe how they measured mortality as well as overdiagnosis, overtreatment, and false positive results. In the following results section, Gøtzsche and Jørgensen describe

the nine clinical trials that they evaluated for the systematic review. In the discussion and conclusion sections, the authors compare the results from different clinical trials and evaluate the main results. They conclude that there is no high-quality evidence that mammography screening is useful for mortality reduction, as too many people are overdiagnosed and overtreated, which leads to psychological stress and trauma.

Gøtzsche and Jørgensen's introductory material consists of the background and objective sections. In the background section, the authors introduce the risks and benefits of mammography. They state that the main benefit is the possibility of reduction of breast cancer mortality and overall mortality, as mammography is a tool that makes it possible to diagnose breast cancers at early stages and thus treat them more effectively than if the diagnosis occurred at a later stage. However, the authors also state that overdiagnosis and overtreatment is possible when women regularly obtain mammograms over time. Overdiagnosis occurs when women who do not have breast cancers detectable without mammogram screenings are diagnosed with breast cancer. Overtreatment refers to the treatment of overdiagnosed women, through surgeries or other interventions. According to Gøtzsche and Jørgensen, there is a controversy about whether or not regular mammography screening is beneficial for women of different ages, as most cases of breast cancer are diagnosed after women reach fifty years of age. The authors note that the objective of their systematic review was to determine whether mammography screening improved survival rates for breast cancer.

Following their introduction, Gøtzsche and Jørgensen describe the methods they used in collecting and analyzing their data. They searched the websites PubMed and World Health Organization's International Clinical Trials Registry Platform for randomized clinical trials that dealt with mammography screening. The authors looked for randomized trials that incorporated women who had not been previously diagnosed with breast cancer. Gøtzsche and Jørgensen describe multiple possible outcomes they used to measure the risks and benefits of mammography. Those included mortality from breast cancer, mortality from any cancer, all-cause mortality, or mortality from any cause including breast cancer and any other causes, use of surgical interventions, use of adjuvant therapy, and harms of mammography. In the methods section, the authors also describe the statistical methods they used for comparison of the randomized trials.

In the results section of the article, Gøtzsche and Jørgensen describe each randomized trial in detail and discuss the risk of bias in each trial. The authors identify eleven trials that tested mammography's effects on mortality, but they incorporate only eight trials into their results, and some did not fit their eligibility criteria. Most of the eligible trials included women forty-five to sixty-four years old. Gøtzsche and Jørgensen identify whether the researchers in each of the trials had any bias as well as how randomized the trial was. They describe the trials as adequately randomized, suboptimally randomized, or not randomized at all. Based on that description, the authors determine whether the information from that trial is reliable based on the quality of evidence of that particular clinical trial.

The first set of trials that Gøtzsche and Jørgensen discuss in detail is the adequately randomized trials. Those trials included the Malmö trial (1976), the Canadian trial (1980), and the UK age trial (1991). The researchers of the Malmö trial collected data on breast cancer mortality through autopsy reports on the women, which is the most reliable way of knowing how someone died. The researchers note that the autopsy rates during the Canadian trial were low. Even with that drawback, Gøtzsche and Jørgensen still rank the Canadian trial as adequately randomized due to good demographical comparability of women in the experimental and control groups. Last in the adequately randomized group is the UK age trial. In that trial, there were twice as many women in the control group to account for possible exclusions from the results. The researchers in that trial obtained cause of death information from the National Health Service. Gøtzsche and Jørgensen conclude that the results from those trials are reliable due to proper randomization and clear assignment of cause of death. The authors note that all three adequately randomized trials do not show a major difference between breast cancer mortality in the experimental group that received regular mammography screening and the control group that did not.

Gøtzsche and Jørgensen identify the next group of trials as suboptimally randomized, meaning that the evidence from those trials was lower quality evidence than that from adequately randomized trials. The suboptimally randomized trials included the New York trial (1963), the Malmö II trial

(1978), the Two County trial (1977), the Stockholm trial (1981), and the Goteborg trial (1982). Each of the suboptimally randomized trials reported a beneficial effect of screening on breast cancer deaths. But the authors claim that that information was not as reliable as the information from the adequately randomized trials.

The authors detail the problems with each suboptimally randomized trial. The New York trial, also known as the Health Insurance Plan trial, took place in New York City, New York. In that trial, 500 more women were excluded from the experimental group than the control group due to possible prior breast cancer. Also, twenty years after the start of the trial even more cases of prior breast cancer were identified in the control group, but those women were not excluded from the trial and the results. That created a bias in favor of mammography screening, as more women with breast cancer were in the control group. Next, the authors discuss the Malmö II trial, or the continuation of the Malmö trial, but they note that little information is available about the Malmö II trial, so Gøtzsche and Jørgensen could not identify any exclusion of women throughout the trial.

The next three suboptimally randomized trials all took place in Sweden, and they included the Two County trial, the Stockholm trial, and the Goteborg trial. The Two County trial was performed in Kopparberg and Östergötland, two counties of Sweden, and enrolled women between 1977 and 1981. Gøtzsche and Jørgensen note that the data between the two counties was not comparable, breast cancer mortality rate fluctuated greatly between the experimental groups of the two counties. More women were excluded from the control group, which also contributed to likely bias in favor of mammography screening. The Stockholm trial incorporated multiple subgroups within the experimental and the control groups. Those subgroups were not consistent and thus Gøtzsche and Jørgensen note that the Stockholm trial was suboptimally randomized. The Goteborg trial randomization was not consistent, as there were older women in the control group than the experimental group. Overall, according to Gøtzsche and Jørgensen, the suboptimally randomized trials could not provide high quality evidence in favor of regular mammography screening, as the groups of women were not properly randomized and thus the results were biased in favor of mammography screening.

The only trial that Gøtzsche and Jørgensen report on separately is the Edinburgh trial (1978), as it was too biased in favor of mammography and thus the data from that trial was completely unreliable. The authors included the results of that trial in a separate table, but they did not take it into consideration for their conclusion. Gøtzsche and Jørgensen note that the process for entry date determination differed throughout the study, as most of the women in the control were not under observation for the first ten years of the study and thus could not be diagnosed with breast cancer early. Also, the authors state that randomization was not appropriate, as almost twice as many women from the highest socioeconomic status were in the experimental group compared to the control group. Because of all those reasons, the authors of the systematic review consider the Edinburgh trial not randomized at all and heavily biased in favor of mammography screening.

The next section of the systematic review is the discussion section, in which the authors describe the benefits and harms of mammography screening. The authors discuss the results of the New York and the Two County trials, which were suboptimally randomized trials that reported that mammography helped prevent more breast cancer deaths than it caused and that led many policy makers to create guidelines for mammography screening. The researchers state that the adequately randomized trials and suboptimally randomized trials all together included 600,000 women aged thirty-nine to seventy-four. The authors state that breast cancer mortality was not a reliable outcome of mammography screening usefulness, as it was not reduced in any of the adequately randomized trials. In addition, many trials, both adequately randomized and suboptimally randomized, misclassified the cause of death due to a low percent of autopsies performed on the bodies of the dead study participants.

The authors also discuss how surgical interventions were far more common in the experimental groups for all trials. Gøtzsche and Jørgensen claim that the increased surgical interventions in the experimental groups were the source of overtreatment and overdiagnosis, as the women who did not need any interventions had to undergo them due to false positive results of mammography screening. The increase in surgeries to remove breast cancer was about 30 percent in each trial, and many of those surgeries were unnecessary. Gøtzsche and Jørgensen note that false pos-

itive mammography results are common, especially when women obtain mammograms regularly. Gøtzsche and Jørgensen note that false positive results cause women psychological distress and pain, as they worry about the possibility of having cancer, which may affect their long-term psychological health. The researchers also state that breast cancer awareness increased over time. They state that breast cancer awareness plays a more significant role in breast cancer prevention than regular mammography screening, as more women know about the possibility of getting breast cancer and different screening options available.

The authors conclude that the harms of regular mammography screening outweigh the benefits. The researchers state that if mammography screening reduces breast cancer mortality by fifteen percent and overdiagnosis and overtreatment is at thirty percent, then for every two thousand women invited for screening throughout ten years, one will avoid dying of breast cancer and ten healthy women will be treated unnecessarily due to the screening. That means that ten times more women will be overdiagnosed and overtreated than will be appropriately diagnosed and treated. Also, from those two thousand women, at least two hundred will experience psychological trauma based on false positive results. The researchers provide a link to a brochure that includes a Cochrane guide that helps women choose whether or not to start regular mammography screening.

The systematic review "Screening for Breast Cancer with Mammography" was cited in the US Preventive Task Force's 2016 recommendation concerning whether or not women should be screened for breast cancer using mammography. The US Preventive Task Force, headquartered in Rockville, Maryland, makes evidence-based recommendations about clinical preventive services for the general public in the US. In their 2016 recommendation, the US Preventive Task Force recommended biennial mammography screening for women ages fifty to seventy-four. For women ages forty-nine and under, they recommended that physicians' decisions to offer biennial mammography screening should take into consideration each patient's values regarding the harms and benefits associated with screening.

Sources

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