

# ***When evidence challenges opinion***

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# Evidence & Opinion

## *evidence, n.*

Ground for belief; testimony or facts tending to prove or disprove any conclusion.

## *opinion, n.*

What or how one thinks about something; judgment or belief.

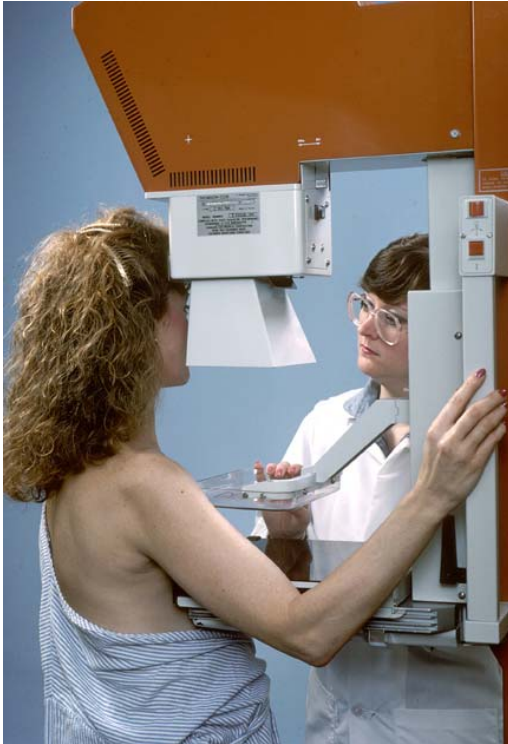
*In my opinion:* according to my thinking; as it seems to me.

*A matter of opinion:* a matter about which each may have his or her own opinion; a disputable point.

What happens when evidence & opinion are perceived to conflict?

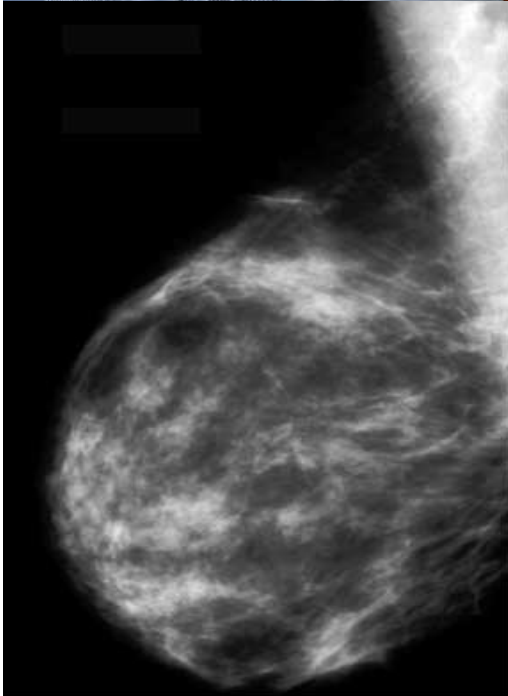
## 2 Case Studies

- Screening mammography for breast cancer
- Albumin for fluid resuscitation



# Screening mammography

- Australian nationwide program since 1992
- Approx 1.25 million women screened each year (70% target)
- Early detection allows early treatment & better chance of cure



**Public health**

## Is screening for breast cancer with mammography justifiable?

*Peter C Gøtzsche, Ole Olsen*

**Findings** Baseline imbalances were shown for six of the eight identified trials, and inconsistencies in the number of women randomised were found in four. The two adequately randomised trials found no effect of screening on breast-cancer mortality (pooled relative risk 1.04 [95% CI 0.84–1.27]) or on total mortality (0.99 [0.94–1.05]). The pooled relative risk for breast-cancer mortality for the other trials was 0.75 (0.67–0.83), which was significantly different ( $p=0.005$ ) from that for the unbiased trials. The Swedish meta-analysis showed a decrease in breast-cancer mortality but also an increase in total mortality (1.06 [1.04–1.08]); this increase disappeared after adjustment for an imbalance in age.

**Interpretation** Screening for breast cancer with mammography is unjustified. If the Swedish trials are judged to be unbiased, the data show that for every 1000 women screened biennially throughout 12 years, one breast-cancer death is avoided whereas the total number of deaths is increased by six. If the Swedish trials (apart from the Malmö trial) are judged to be biased, there is no reliable evidence that screening decreases breast-cancer mortality.

*Lancet* 2000; **355**: 129–34

See Commentary page xxx

# CORRESPONDENCE

## Screening mammography re-evaluated

Sir—In the results section of their meta-analysis Peter Gotzsche and Ole Olsen<sup>1</sup> indicated that they found no data on age distribution of the randomised groups in the Canadian National Breast Screening Study (CNBSS). We have reported that the distributions by single year of age were identical.<sup>2,3</sup> For your information we provide age data across allocations in CNBSS 1 and 2 (table). Distributions by single year of age are available from us on request.

In his commentary Harry de Koning<sup>4</sup> stated "The quality of the mammograms in the Canadian trial is on record as having been poor at the start of the trial", citing an independent review of mammography quality in the CNBSS that we published in 1990.<sup>5</sup> Such a statement could be made of every other breast-screening trial; however, only the CNBSS investigators have published an independent review.

Mammograms can also be evaluated by examining their outcomes. Fletcher and colleagues (*J Natl Cancer Inst* 1995; 85: 1664–66) pointed out that the sensitivity and specificity of CNBSS mammography were as good as those in any other trial, as were other indicators of performance. Indications that in practice our mammograms achieved adequate detection rates come from comparisons with rates published for routine (1990s) programmes in comparable age groups. In Ontario, Canada, for example, the

only provincial programme in Canada to use the full CNBSS approach of mammography plus physical examination of the breasts, shows that the detection rate on first screen for women aged 50–59 years in 1996–97 was 6.7 per 1000 (Ontario Breast Screening Programme Annual Report 1998–99) in the CNBSS it was 7.2.<sup>6</sup>

de Koning claims<sup>4</sup> that breast screening in the UK and the Netherlands has resulted in a reduction in breast-cancer mortality in the population. It is hard to determine the exact causes of mortality reductions, when more than one cause potentially operates. Mortality data for the UK show an unexplained increase before the recent fall, an increase not seen in North America (*J Natl Cancer Inst* 1999; 91: 750–52). de Koning is almost certainly correct in expecting there to be an interval of at least 9 years before any impact of an effective breast-screening programme can be seen in a population, in part because of the lag between initiation of screening and effect documented in all trials that appear to show an effect, but also because for some time after initiation of screening, most breast cancer deaths in the population will be in women with cancer diagnosed before the programme began. The recent reduction in mortality in North America is almost certainly attributable, not to screening, but to the widespread adoption of adjuvant chemotherapy or tamoxifen for node-positive disease in the 1980s. It therefore seems reasonable to assume that much, if not all, of the recent mortality reduction in the UK and the Netherlands is due to a similar effect. The lack of a reduction in breast-cancer mortality in Sweden, at least to 1995, despite population-based screening, seems to support this.

One benefit of a screening programme is to place women with breast cancer under surveillance and management; attention they would not have had in the absence of screening. Such a benefit is probably more evident in the UK than in North America. However, decreases in

mortality cannot be attributed to mammography screening per se.

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- 1 Gotzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? *Lancet* 2000; 355: 129–34.
- 2 Miller AB, Baines CJ, To T, Wall C, et al. Canadian National Breast Screening Study 1. Breast cancer detection and death rates among women aged 40 to 49 years. *Can Med Assoc J* 1992; 147: 1459–76.
- 3 Miller AB, Baines CJ, To T, Wall C, et al. Canadian National Breast Screening Study 2. Breast cancer detection and death rates among women age 50 to 59 years. *Can Med Assoc J* 1992; 147: 1477–88.
- 4 de Koning HJ. Assessment of nationwide cancer-screening programmes. *Lancet* 2000; 355: 80–81.
- 5 Baines CJ, Miller AB, Kopans DB, et al. Canadian National Breast Screening Study: assessment of technical quality of external review. *Am J Roentgenology* 1990; 155: 743–47.

Sir—Peter Gotzsche and Ole Olsen (Jan 8, p 129)<sup>1</sup> present an inaccurate summary of the evidence on breast-cancer screening, both in terms of its effect on breast-cancer mortality and its association with all-cause mortality. Their basic argument is that small imbalances in age have consequences for all-cause mortality in those randomised trials which found a benefit for screening. They infer either that the results of these trials can be ignored or that screening increases all-cause mortality. Both conclusions are wrong.

The Swedish Two-County Trial was criticised for age imbalance of 5 months (in a study population aged 40–74 years at randomisation) and for an alleged inconsistency in the reporting of the study population size. Both of these points were answered in 1989,<sup>2</sup> in a paper which Gotzsche and Olsen cite but seem not to have read fully. In that paper, we acknowledged that the study group was slightly older than the control group. Such imbalances are not guaranteed against, even in individually randomised therapeutic trials. As Harry de Koning points out (Jan 8, p 80)<sup>3</sup> this imbalance is likely to be conservative, leading us to underestimate the benefit

## CORRESPONDENCE

of screening, but we felt we should deal with it, as in therapeutic trials, by adjustment in the statistical analysis. Age for age, there was a significant 31% reduction in breast-cancer mortality and a non-significant 1% reduction (no increase) in details from all causes in the group invited to screening. Our critics assert that such adjustment is invalid because it was not planned at the time of the study design. Whether the analysis was designed or not is arguable, but if Gotzsche and Olsen are right, the analysis of all-cause mortality is similarly invalid.

We also explained in the 1989 paper that the 1985 analysis had excluded from the breast cancers and breast-cancer deaths all women who had had breast cancer diagnosed before the trial. Record linkage subsequently made it possible to extend this exclusion to the total population randomised, and from 1989 onwards we used this "clean" population (77 080 women in the invited group, 55 985 in controls) as our denominator. There is no "inconsistency".

Gotzsche and Olsen's paper has many other shortcomings. Here are some examples. They uncritically accept the adequacy of randomisation in the Canadian trial, despite evidence of bias in the most important dimension of all, prevalence of advanced cases at randomisation.<sup>4</sup> They describe that trial as the "best documented" but cannot find data on the age distribution in the Canadian trial—and then label our trial as inadequately randomised on the basis of an age imbalance, which we disclosed and dealt with. All large studies have potential flaws but Gotzsche and Olsen are selective about recognising them. Their methods for determining age differences and standard errors do not seem to take account of the discrete grouping, and the p values for the age differences may not be valid. They suggest that a 1999 paper by G Sjönell and L Ståhle also casts doubt on the reliability of mammography trials, despite the well-documented evidence that it is hopelessly flawed,<sup>5</sup> with shortcomings far worse than a tiny imbalance in age.

As scientists, we must be prepared to listen to and answer criticism, though we would prefer that criticism to have been better informed. Two other important populations are unfairly affected by this article, however. The morale of those who work hard to provide an effective mammographic screening service is needlessly damaged by high profile but inaccurate publications such as this. The second group is the millions of women faced

with the decision whether to attend for screening. To both populations we reiterate our finding that, age for age, screening yields a substantial and significant reduction in breast-cancer mortality and no increase in death from other causes. For both of these populations, the paper by Gotzsche and Olsen is not worth a moment's consideration.

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- 1 Gotzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? *Lancet* 2000; 355: 129–34.
- 2 Tabar L, Fagerberg G, Duffy SW, Day NE. The Swedish Two-County Trial of mammographic screening for breast cancer: recent results and calculation of benefit. *J Epidemiol Community Health* 1989; 43: 107–14.
- 3 de Koning HJ. Assessment of nationwide cancer screening programmes. *Lancet* 2000; 355: 80–81.
- 4 Mettlin CJ, Smart CR. The Canadian National Breast Screening Study: an appraisal and implications for early detection policy. *Cancer* 1993; 72: 1461–65.
- 5 Rutqvist LE. Naturalförloppet, grova metoder ledde till felaktigt om bröstcancer. *Läkarskrivningen* 1999; 96: 1210–11.

Sir—Peter Gotzsche and Ole Olsen<sup>1</sup> reject six screening mammography trials because of alleged bias, evidence for which is based on very small differences in mean age between the invited (for screening) and control groups. These small differences result from the cluster randomisation used in some of the trials.<sup>2</sup> Considerably larger differences in age (or any other risk factor) would be necessary to explain the effects on breast-cancer mortality. Cluster randomisation may be imperfect but to suggest, as Gotzsche and Olsen do, that a difference of less than 5 weeks in average age renders the randomisation so imperfect as to nullify the results of the study is not justified.

Two trials they judge to be unbiased. No data were available on age-distribution for the Canadian trial. The age difference between the groups for the Malmö trial (estimated from the Swedish overview results in a complicated fashion, using many assumptions) was similar to those for the Göteborg and Stockholm trials.

The Canadian trial, besides being underpowered, had a different design from the others in that it compared annual mammograms with physical examination. In the Malmö trial, 24% of controls had undergone mammography; this, together with the low take-up rate, considerably reduced the effective size of the trial.<sup>3</sup>

The claim that "exclusion of deaths from breast cancer in cases diagnosed before entry to the trial can lead to bias" is unjustified. Such cancers will have been diagnosed and confirmed before the invitation to screening and will not therefore be identified by the first round of screening.

The difference in all-cause mortality between the study and control groups in the Swedish overview disappears with adjustment for age. It is, therefore—contrary to Gotzsche and Olsen's suggestion—possible to believe that the Swedish trials are unbiased without accepting that screening for breast cancer with mammography causes more deaths than it saves.

Prevalent disease will heavily dilute the effect of screening seen in national statistics in the early years of screening. The study by Sjönell and Ståhle<sup>4</sup> examined mortality up to 1996 in programmes which started between 1986 and 1993. Other serious criticisms of that study have been made.<sup>5</sup>

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- 1 Gotzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? *Lancet* 2000; 355: 129–33.
- 2 Nyström L, Larsson L-G, Wall S, et al. An overview of the Swedish randomised mammography trials: total mortality pattern and the representativity of the study cohorts. *J Med Screening* 1996; 3: 85–87.
- 3 Cuckle H. Breast cancer screening by mammography: an overview. *Clin Radiol* 1991; 43: 77–80.
- 4 Sjönell G, Ståhle L. Hålsokontroller med mammografi minskar inte dödlighet i bröstcancer. *Läkarskrivningen* 1999; 96: 1050–51.
- 5 Rosen M, Rehnqvist N. No need to reconsider breast screening programme on basis of results from defective study. *BMJ* 1999; 318: 809–10.

Sir—Peter Gotzsche and Ole Olsen,<sup>1</sup> in referring to the study by Sjönell and Ståhle,<sup>2</sup> note "although that study can be criticised". This statement is astonishing, coming from two representatives of a Cochrane centre. The study is a disaster; its design makes it impossible to detect any effect of the intervention due to dilution.

Sjönell and Ståhle assume that the decrease in the breast-cancer mortality should be linear, starting when the intervention was implemented in 1987, but it takes several years before any effect is seen,<sup>3</sup> and the mortality trend could not be expected to change until 5–8 years after the start of a national screening programme. When

Allocation	Age range at entry, years	Mean age (median), years
<b>CNBSS1</b>		
Mammography plus physical breast examination	40–44	41.82 (42)
Usual care	40–44	41.82 (42)
Mammography plus physical breast examination	45–49	46.96 (47)
Usual care	45–49	46.95 (47)
<b>CNBSS2</b>		
Mammography plus physical breast examination	50–54	51.95 (52)
Physical breast examination alone	50–54	51.95 (52)
Mammography plus physical breast examination	55–59	56.78 (57)
Physical breast examination alone	55–59	56.80 (57)

Mean and median ages at entry by quinquennium in the CNBSS

## Critique:

- Methods of primary studies
- Interpretation by reviewers
- Personal slander
- Defence of programs
- Protection of women

Sir—Peter Gøtzsche and Ole Olsen (Jan 8, p 129)<sup>1</sup> present an inaccurate summary of the evidence on breast-cancer screening, both in terms of its effect on breast-cancer mortality and its association with all-cause mortality.

As scientists, we must be prepared to listen to and answer criticism, though we would prefer that criticism to have been better informed. Two other important populations are unfairly affected by this article, however. The morale of those who work hard to provide an effective mammographic screening service is needlessly damaged by high profile but inaccurate publications such as this. The second group is the millions of women faced with the decision whether to attend for screening. To both populations we reiterate our finding that, age for age, screening yields a substantial and significant reduction in breast-cancer mortality and no increase in death from other causes. For both of these populations, the paper by Gøtzsche and Olsen is not worth a moment's consideration.

# Cochrane review on screening for breast cancer with mammography

Ole Olsen, Peter C Gøtzsche

**In 2000, we reported that there is no reliable evidence that screening for breast cancer reduces mortality. As we discuss here, a Cochrane review has now confirmed and strengthened our previous findings. The review also shows that breast-cancer mortality is a misleading outcome measure. Finally, we use data supplemental to those in the Cochrane review to show that screening leads to more aggressive treatment.**

*Lancet* 2001; **358**: 1340–42

Sir—I wonder why reports such as that of Ole Olsen and Peter Gøtzsche<sup>1</sup> raise such a lot of angry criticism. It would be rather too pessimistic and cynical to believe that the criticism stems only from self-interest of radiologists, surgeons, managers, and so on, whose daily bread depends on the continuation of mammographic screening programmes. I think that such reports shake the very basis of intuitive logic and are, therefore, not palatable. But isn't the world frequently counterintuitive?

## CORRESPONDENCE

e-mail submissions to [correspondence@lancet.com](mailto:correspondence@lancet.com)

### Screening for breast cancer with mammography

I am concerned about some of Ole Olsen and Peter Gøtzsche's review (Oct 20, p 1340),<sup>1</sup> especially to their comments on the reviews of causes of death, cited by the investigators of the Insurance Plan (HIP) trial,<sup>2</sup> and related to the Canadian National Screening Study (CNBSS)<sup>3</sup> and its.<sup>4</sup>

One of the death reviewers for the trial, initiated the death review for the NBSS, and I chair the Death Review Committee for the Prostate, Lung, Colorectal and Ovary trial (PLCO).<sup>4</sup> The HIP trial was done in an era when the size of breast cancers was larger than became usual in the next two decades in North America. I recall no instance in which the allocation was biased. The major difficulty for reviewers was not whether the patient died of cancer, nor whether breast cancer had been diagnosed, but whether breast cancer was the cause of death when the patient had been diagnosed with another malignant disease. The decisions made were entirely masked, even after consultation between the reviewers for initial disagreement.

Lumpectomy was not practised, although radiotherapy was used frequently, especially for locally advanced disease. However, if an unrecognised consequence of radiotherapy was the cause of death, and was labelled as cardiovascular disease, such labelling would have been applied without bias as to treatment assignment.

Olsen and Gøtzsche comment that equal numbers of patients, by allocation, were reviewed, but that the numbers assigned to breast cancer as a cause of death were fewer in the screening group, and they cite this as evidence of bias. An alternative explanation is more plausible. If screening was truly effective, then the numbers of deaths from breast cancer in a reviewed series would be less in the screened group. It seems not to have occurred to Olsen and Gøtzsche that the equal numbers reviewed could have resulted from a deliberate attempt to ensure that equivalent numbers of

patients in the two groups were reviewed at the same time to avoid bias.

I am also concerned by Olsen and Gøtzsche's comments on the difference in numbers of women with breast cancer excluded from the two groups. This difference arose because, when women in the screened group attended for screening, previously diagnosed breast cancers were identified, but this was not possible for the controls. The 18-year follow-up, however, enabled all deaths from breast cancer to be identified in the two groups; identification of the date of diagnosis was then possible from hospital records. Patients diagnosed before randomisation were excluded.<sup>5</sup> Although this process did not eliminate the inequality in the numbers of patients with previously diagnosed breast cancers still living at 18 years who were not excluded, the small difference in person-years of observation is unlikely to have biased the results.

Therefore I believe the HIP trial results are valid, and the trial should not be dismissed as flawed.

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- 1 Olsen O, Gøtzsche PC. Cochrane review on screening for breast cancer with mammography. *Lancet* 2001; **358**: 1340–42.
- 2 Shapiro S, Venet W, Strax P, Venet L. Periodic screening for breast cancer: the Health Insurance Plan Project, 1963–1986, and its sequelae. Baltimore: Johns Hopkins University Press, 1988.
- 3 Miller AB, Baines CJ, To T, Wall C. Canadian national breast screening study, 1: breast cancer detection and death rates among women age 40–49 years. *Can Med Assoc J* 1992; **147**: 1459–76.
- 4 Miller AB, Yurgalevitch S, Weissfeld JL. Death review process in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trials. *Control Clin Trials* 2000; **21**: 400S–06S.

Sir—Ole Olsen and Peter Gøtzsche's review<sup>1</sup> concurs with the findings of their earlier report<sup>2</sup> that screening mammography programmes do not reduce breast-cancer mortality and lead to more aggressive treatment. In his Oct 20 Commentary, Richard Horton<sup>3</sup> agrees with their conclusion that

screening mammography programmes are not therefore justified. Conclusions could have a major impact on women's health care and deserve careful scrutiny.

Our primary criticism is that that a screening programme is justified only if it reduces mortality. Mortality is a very important and easily measured, and clinically outcome parameter for measurement is a common bias for clinical investigators. Outcomes such as quality of life are important to patients and cost screening programmes. Unfortunately such outcomes have been undervalued in the assessment of breast screening. Rather than assumptions about whether positive tests and earlier detection of breast cancer improves or hampers life, objective measurement of how mammography programmes affect quality of life, whether certain types of patients benefit more than others.

Olsen and Gøtzsche conclude that screening mammography leads to overly aggressive treatment. In fact, it is a condemnation of current practices, not of screening in general. An organisation is one of many ways of providing better education of patients, to lower the prevalence of unnecessarily aggressive treatment. The best solution to improving breast cancer care is better technology, education, training, along with communication between physicians and patients. These strategies deserve attention from the medical community before a decision is made to screen screening programmes that earlier diagnoses. There is no need to throw out the baby with the bathwater.

We are also concerned with the analysis itself. In six randomised trials (including extended Malmö trial<sup>4</sup>) and Olsen and Gøtzsche, a reduction in breast-cancer mortality was observed with the use of screening mammography. We recommend caution in rejecting these findings, especially when incorporated data from hundreds of thousands of patients, on the one meta-analysis.

# CA

*A Cancer Journal for Clinicians*

## The Mammographic Screening Trials: Commentary on the Recent Work by Olsen and Gotzsche

Stephen W. Duffy, László Tabár and Robert A. Smith  
*CA Cancer J Clin* 2002;52:68-71

## The benefit of population screening for breast cancer with mammography

Gezondheidsraad

Health Council of the Netherlands

## Editorial

### Global summit on mammographic screening

Forty years of clinical trials, the contribution of hundreds of scientists and health workers and the dedication of hundreds of thousands of women to participate in studies lasting for decades has resulted in adequate evidence to support the efficacy of mammographic screening for breast cancer, which now allows its transfer to the arena of public health policy. Doctors and women can be assured that participation in organised screening programmes, with rigorous quality assurance standards implemented, is of benefit, provided appropriate diagnostic investigation and treatment is available. Special efforts should be made to encourage screening among the more deprived members of society. It is important not to overemphasise the benefit of screening, and to appreciate that this is but one step in the total management of women with the disease. Women should, however, be informed clearly of the level of benefit and of potential risks and costs.

## CLINICAL GUIDELINES

### Breast Cancer Screening: A Summary of the Evidence for the U.S. Preventive Services Task Force

Linda L. Humphrey, MD, MPH; Mark Helfand, MD, MS; Benjamin K.S. Chan, MS; and Steven H. Woolf, MD, MPH

**Purpose:** To synthesize new data on breast cancer screening for the U.S. Preventive Services Task Force.

**Data Sources:** MEDLINE; the Cochrane Controlled Trials Registry; and reference lists of reviews, editorials, and original studies.

**Study Selection:** Eight randomized, controlled trials of mammography and 2 trials evaluating breast self-examination were included. One hundred fifty-four publications of the results of these trials, as well as selected articles about the test characteristics and harms associated with screening, were examined.

**Data Extraction:** Predefined criteria were used to assess the quality of each study. Meta-analyses using a Bayesian random-effects model were conducted to provide summary relative risk estimates and credible intervals (Cris) for the effectiveness of screening with mammography in reducing death from breast cancer.

**Data Synthesis:** For studies of fair quality or better, the summary relative risk was 0.84 (95% CrI, 0.77 to 0.91) and the number needed to screen to prevent one death from breast cancer

after approximately 14 years of observation was 1224 (CrI, 665 to 2564). Among women younger than 50 years of age, the summary relative risk associated with mammography was 0.85 (CrI, 0.73 to 0.99) and the number needed to screen to prevent one death from breast cancer after 14 years of observation was 1792 (CrI, 764 to 10 540). For clinical breast examination and breast self-examination, evidence from randomized trials is inconclusive.

**Conclusions:** In the randomized, controlled trials, mammography reduced breast cancer mortality rates among women 40 to 74 years of age. Greater absolute risk reduction was seen among older women. Because these results incorporate several rounds of screening, the actual number of mammograms needed to prevent one death from breast cancer is higher. In addition, each screening has associated risks and costs.

*Ann Intern Med.* 2002;137:347-360.

[www.annals.org](http://www.annals.org)

For author affiliations, see end of text.

See related article on pp 344-346 and editorial comments on pp 361-362 and pp 363-365.

## PLAIN LANGUAGE SUMMARY

### Screening for breast cancer with mammography

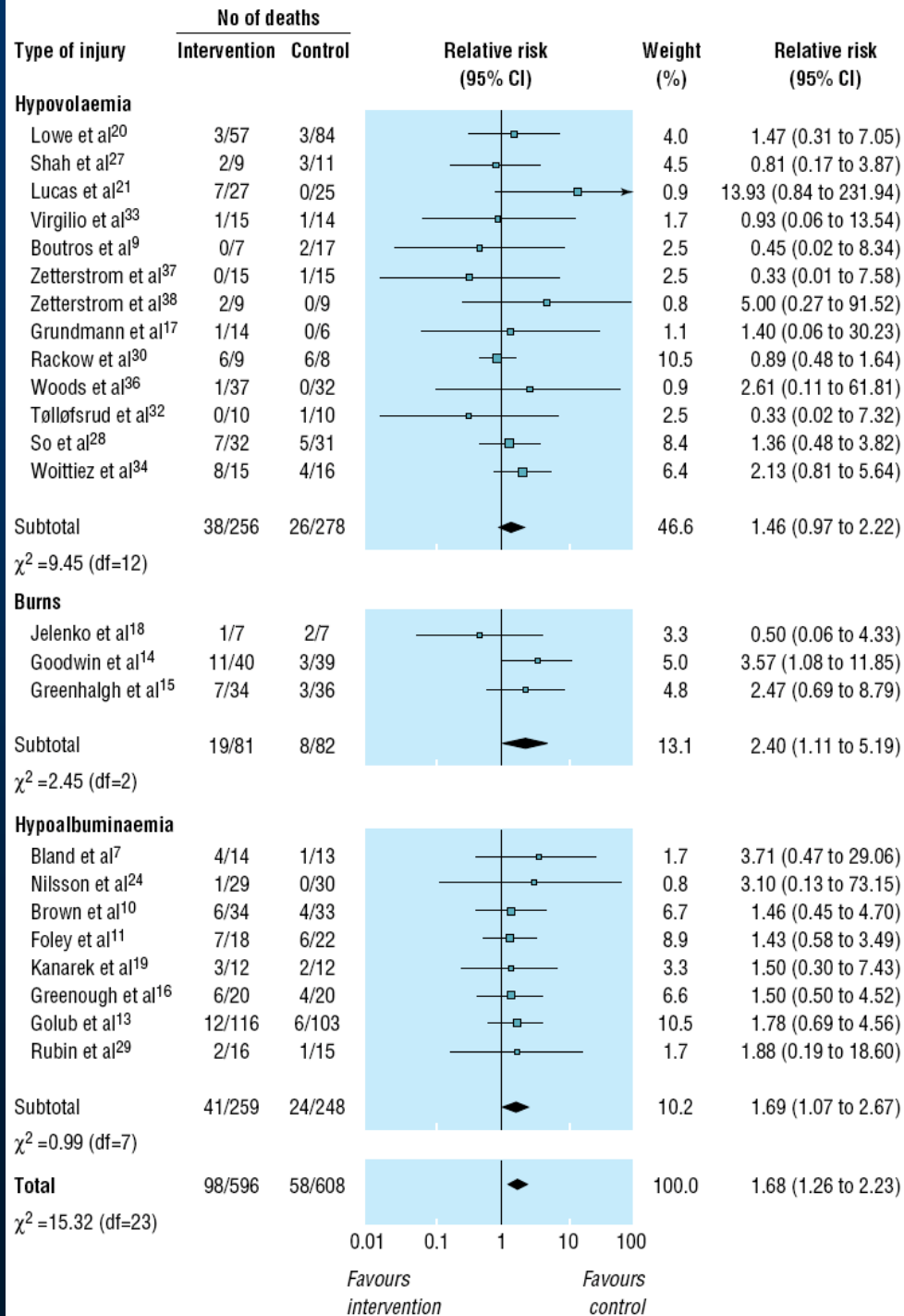
Screening uses a test to check people who have no symptoms of a particular disease, to identify people who might have that disease and to allow it to be treated at an early stage when a cure is more likely. Mammography uses X-ray to try to find early breast cancers before a lump can be felt. Many countries have introduced mammography screening for women aged 50 to 69. The review includes seven trials involving a total of half a million women. The review found that mammography screening for breast cancer likely reduces breast cancer mortality, but the magnitude of the effect is uncertain and screening will also result in some women getting a cancer diagnosis even though their cancer would not have led to death or sickness. Currently, it is not possible to tell which women these are, and they are therefore likely to have breasts and lumps removed and to receive radiotherapy unnecessarily. Based on all trials, the reduction in breast cancer mortality is 20%, but as the effect is lower in the highest quality trials, a more reasonable estimate is a 15% relative risk reduction. Based on the risk level of women in these trials, the absolute risk reduction was 0.05%. Screening also leads to overdiagnosis and overtreatment, with an estimated 30% increase, or an absolute risk increase of 0.5%. This means that for every 2000 women invited for screening throughout 10 years, one will have her life prolonged. In addition, 10 healthy women, who would not have been diagnosed if there had not been screening, will be diagnosed as breast cancer patients and will be treated unnecessarily. It is thus not clear whether screening does more good than harm.

*Cochrane Review (updated 2006)*

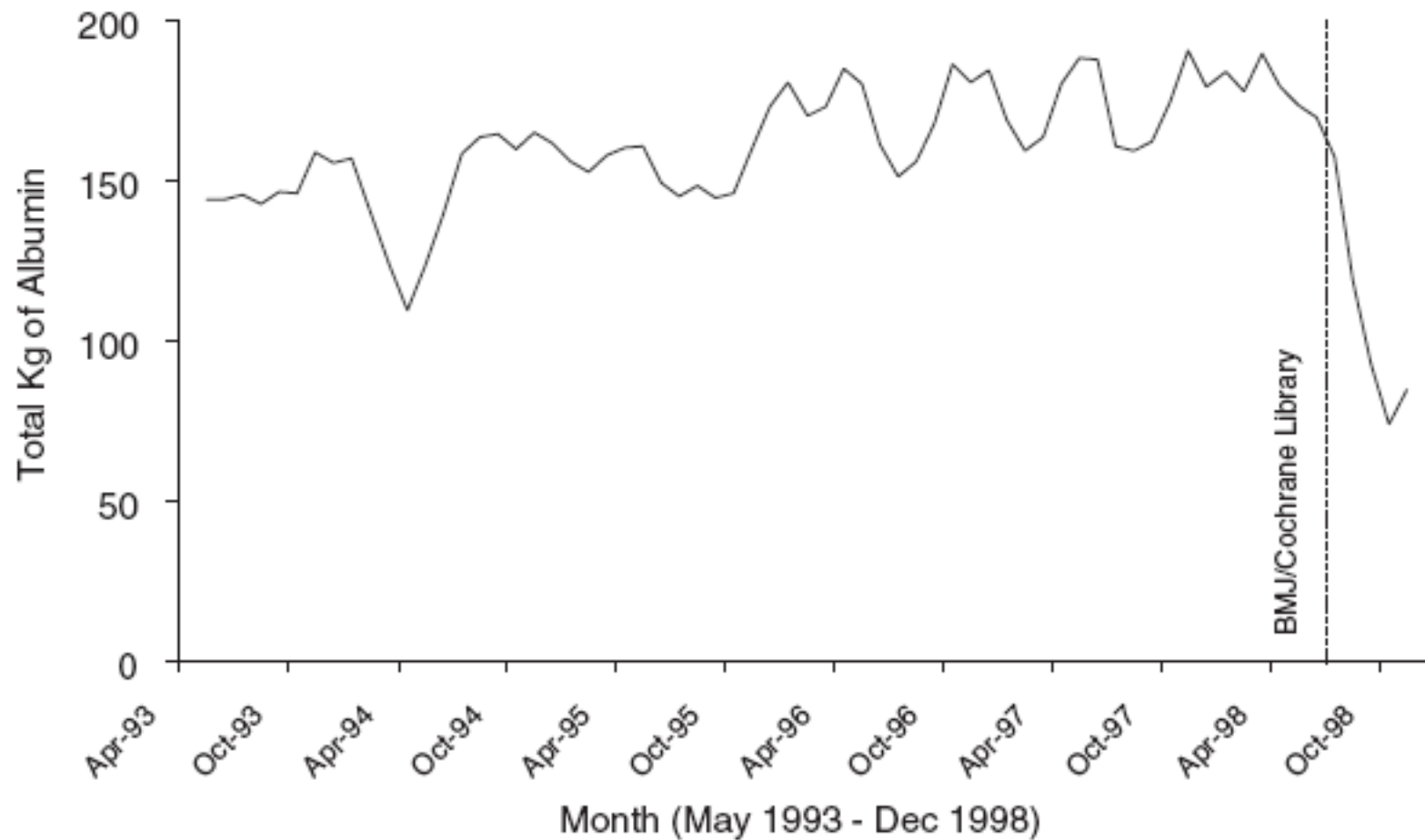
# Albumin



- Plasma protein solution given to patients needing fluids in ICU
- Large protein molecules encourage fluid to stay in the circulation longer than crystalloids



Cochrane Injuries Group  
Albumin Reviewers,  
*BMJ* 1998



**Figure 1: Albumin Sales in Scotland and Northern Ireland Before and After Publication of Systematic Review on Human Albumin Administration in Critically Ill Patients**

## Responses:

- Disbelief
- Denial
- Personal attacks through letters pages

than patient-centered outcomes.

The conclusion that albumin could increase the risk of death<sup>2</sup> led to responses ranging from policies to limit albumin use, to claims that this interpretation was tendentious, to academic and industry counter-detailing, and to confusion at the bedside. Recognition that meta-analyses of small, older trials may yield findings that are discordant

ORIGINAL ARTICLE

## A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

The SAFE Study Investigators\*

### ABSTRACT

#### BACKGROUND

It remains uncertain whether the choice of resuscitation fluid for patients in intensive care units (ICUs) affects survival. We conducted a multicenter, randomized, double-blind trial to compare the effect of fluid resuscitation with albumin or saline on mortality in a heterogeneous population of patients in the ICU.

#### METHODS

We randomly assigned patients who had been admitted to the ICU to receive either 4 percent albumin or normal saline for intravascular-fluid resuscitation during the next 28 days. The primary outcome measure was death from any cause during the 28-day period after randomization.

#### RESULTS

Of the 6997 patients who underwent randomization, 3497 were assigned to receive albumin and 3500 to receive saline; the two groups had similar baseline characteristics. There were 726 deaths in the albumin group, as compared with 729 deaths in the saline group (relative risk of death, 0.99; 95 percent confidence interval, 0.91 to 1.09;  $P=0.87$ ). The proportion of patients with new single-organ and multiple-organ failure was similar in the two groups ( $P=0.85$ ). There were no significant differences between the groups in the mean ( $\pm$ SD) numbers of days spent in the ICU ( $6.5\pm 6.6$  in the albumin group and  $6.2\pm 6.2$  in the saline group,  $P=0.44$ ), days spent in the hospital ( $15.3\pm 9.6$  and  $15.6\pm 9.6$ , respectively;  $P=0.30$ ), days of mechanical ventilation ( $4.5\pm 6.1$  and  $4.3\pm 5.7$ , respectively;  $P=0.74$ ), or days of renal-replacement therapy ( $0.5\pm 2.3$  and  $0.4\pm 2.0$ , respectively;  $P=0.41$ ).

#### CONCLUSIONS

In patients in the ICU, use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days.

The Saline versus Albumin Fluid Evaluation (SAFE) Study is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group, the Australian Red Cross Blood Service, and the George Institute for International Health. The writing committee (Simon Finfer, M.B., B.S., Rinaldo Bellomo, M.B., B.S., M.D., Neil Boyce, M.B., B.S., Ph.D., Julie French, R.N., John Myburgh, M.B., B.Ch., Ph.D., and Robyn Norton, Ph.D., M.P.H.) takes responsibility for the content of this article. Address reprint requests to Dr. Finfer at ANZICS CTG, Level 3, 10 levers St., Carlton, VIC 3053, Australia, or at [ctg@anzics.com.au](mailto:ctg@anzics.com.au).

\*The Saline versus Albumin Fluid Evaluation (SAFE) Study investigators are listed in the Appendix.

N Engl J Med 2004;350:2247-56.

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# Evidence & decision-making

- Evidence is important but one of several drivers in decision-making
- Clinical practice:
  - Best evidence – Experience & judgment – Patient values
- Policy-making:
  - Many stakeholders
- ‘Hidden’ drivers of opinion & behaviour

# Dealing with Dissonance

- If it's the evidence itself – can we improve it?
- If it's other factors – can there be more constructive ways than we have witnessed in these examples?
- Therefore need to acknowledge & clarify source of dissonance

# *Validity of evidence*

“Should I believe the evidence?”

- Design and quality of primary research
- Methods and quality of a review
  
- Currency of the research
- Theoretical basis underpinning the research

# *Applicability & relevance of evidence*

“Is it relevant to me and my jurisdiction?”

- Similarity of patients
- Similarity of contexts
- Feasibility of the intervention
- Important outcomes of the intervention
- Alternatives

# *Implications of evidence*

“What are the likely consequences of agreeing with or acting on the evidence?”

- Professional
- Socio-political
- Medico-legal
- Financial

# Questions

- Do I have a problem with this research?
- Does the problem relate to validity of the research?
- Does the problem relate to applicability or relevance of the research?
- Does the problem relate to the implications of the research?