

Breast cancer screening: controversies and future directions

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Purpose of review

Recent criticisms of the mature breast cancer screening trials claimed that there is no evidence that screening saves lives. This has developed into a major public controversy, causing physicians, women, and policy analysts to rethink and debate mammography-screening guidelines. We have studied this subject from a different perspective – using computer simulation to fit a simple growth model to clinical data. We can thus provide another viewpoint of the screening controversy that may help elucidate the underlying biology and aid policy makers in devising sound screening guidelines.

Recent findings

We agree with some reviewers that there is partial validity to the criticism. Based on our studies, we have arrived at a new explanation of why screening has not lived up to expectations.

Summary

Our fundamental hypothesis is that breast cancers often undergo periods during which they are temporarily dormant. In addition, surgical intervention to remove primary tumors can interrupt this dormancy. Therefore screening finds smaller tumors with fewer positive lymph nodes, which is beneficial. But then the resulting extirpation accelerates the growth of dormant distant micrometastases, and results in earlier relapses than in women who have not been screened. This partly offsets the early detection advantage. One hypothetical mechanism proposed to explain this biology is that surgical wounding, particularly for premenopausal node-positive patients, can trigger the angiogenesis of dormant avascular micrometastases.

Keywords

breast cancer, mammography, screening controversy, early detection, surgery, angiogenesis, dormancy, computer simulation

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Abbreviation

HIP New York State Health Insurance Plan (trial)

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Introduction

Breast cancer is a major health concern in the United States. Although there have been reductions of a few percent per year in mortality in recent years, progress is far too slow. In 2001 there were 193 700 new cases of breast cancer and 40 200 people died from the disease [1]. Therapy has proved to be only partly effective in reducing death rates, with little optimism until recently that major improvements are possible. The great hope for an immediate meaningful reduction in breast cancer mortality was early detection, which is known to facilitate the discovery of breast tumors at a smaller size and with fewer positive nodes. The probability of cure for a 1 cm or smaller tumor and no lymph nodes involved is approximately 90%. With the reasonable probability that screening would detect more and more cancers in that or similar very early states, it was expected that mammographic screening would result in a major reduction in breast cancer deaths.

To determine the value of screening mammography, seven randomized controlled trials were undertaken. Results were quite variable, demonstrating little or no overall benefit to as much as a 60% mortality reduction [2,3,4–5].

Recent criticisms of the trials

Gotzsche and Olsen [6,7] reviewed all screening trials using the Cochrane evidence-based results concept. They graded trials according to the following criteria: (1) were study arms comparable after proper randomization? (2) were there any important exclusions after randomization? (3) was there any early contamination (mammography within the control arm)? and (4) was the cause of death unbiased (for example by independent panels who were blinded to whether the patient was screened or control)? Of the seven trials, two were called fair (medium quality) – Canadian and Malmo – and did not find any benefit of screening over controls. All other trials had one or more areas of concern and were defined as poor (Two County, Stockholm and Gothenburg) or even flawed [New York State Health Insurance Plan (HIP) and Edinburgh]. The authors concluded that there is no reliable evidence that screening for breast cancer reduces mortality. Moreover, they stated that all-cause mortality was a better index of benefit compared with breast cancer mortality, and that screening leads to more aggressive treatment.

The Gotzsche and Olsen statements raised immediate and harsh criticism in the invited commentary accom-

panying the first paper, in a following volley of letters among which only a few lukewarm supporting notes may be read, and in further papers [8–19]. Most of the critical remarks disputing methods, results and conclusions came from researchers directly involved in breast cancer mammography screening, and mainly in the trials that were defined as poor quality or flawed. The discussion fragmented into a series of disputes about single issues and no conclusions were reached.

The controversy was further complicated because the Cochrane Collaboration did not endorse the first paper [6] and, since, in the subsequent Cochrane-accepted review [7**], the Gotzsche and Olsen statements are a little different and fairly less categorical. The breast cancer screening controversy has political and economic connotations, and is intertwined with the individual personalities of opponents and their biases. Reactions and commentary in the literature and public domains have been extensive [20,21*–31*,32**,33**,34*–36*,37**,38*,39**,40*–43*,44**,45*–49*,50**,51*,52*,53**,54*,55,56*–59*,60**,61**,62,63,64*–68*,69**]. Judging from these papers, it will be difficult to reach a general consensus. We accept that the Edinburgh trial is flawed (inadequate randomization) as claimed by Olsen and Gotzsche but not that the HIP is flawed. Based on our independent review, we are convinced that, overall, screening mammography modestly decreases mortality from breast cancer (21% reduction in the last Swedish overview [32**]) and, importantly, this benefit is dependent upon the age of the screened women.

Breast cancer screening paradoxes

Looking beyond the current controversy, breast cancer screening results raised some important scientific questions that may be posed as individual paradoxes serving to deconstruct the screening controversy. At the 1997 National Institutes of Health Consensus Development Conference on breast cancer screening for women aged 40–49 years [70], data were presented that challenged the fundamental breast cancer treatment paradigm – that therapies are most effective when cancer is diagnosed early. There were four trials in Sweden, so the Swedish overview data [71] comprise much of the available screening data. Beginning in the third year and lasting until the sixth year there are more deaths among the intervention arm than among controls. In the Edinburgh trial (the randomization bias should not be important here), a short surge in mortality is seen at years 3 and 4 of the trial [72]. For HIP patients, there are more deaths among the screening group at various times from year 2 to year 7 [73]. Canadian data [3**] show an excess of breast cancer deaths among the screened population from years 3 to 11.

In summary, randomized controlled trial data for younger women showed a surprising mortality disadvantage for the screened group compared with the unscreened or usual care controls in the first 6–8 years of all trials. The magnitude of the excess is approximately 0.15 deaths/1000 individuals according to a meta-analysis by Cox [74] shown in Figure 1. An advantage to the screened population eventually developed in the later years for all trials. These data were unexplained.

In the meta-analysis, a statistically significant excess of breast cancer deaths among the screened group compared with the control group was found at the 3-year point, with a ratio of 2.4 (1.1–5.4 95% confidence interval) as shown in Figure 2. Even if a chance finding cannot be excluded, as Cox pointed out, the occurrence is very suggestive.

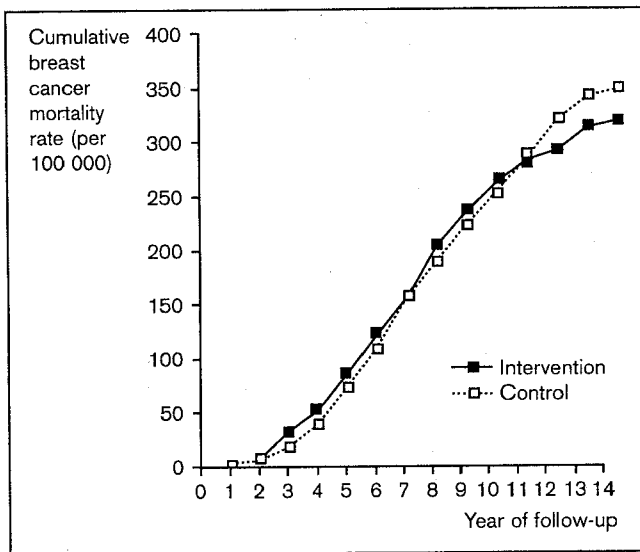
Therefore, we can conclude that, paradoxically, the early detection of breast cancer provided by screening mammography seems to be harmful for some women aged 40–49 years, at least for 6–8 years after the beginning of screening. What is causing the third-year mortality surge in the screened group with an unexpected death rate inversion, and why does it disappear later on? Breast cancer is well known to be a heterogeneous disease. What is causing apparently healthy young women to die from breast cancer 3 years after the start of screening?

The Canadian trial [3**] was the only one of the trials specifically designed to evaluate the benefit of screening women aged 40–49 years. It included 25 000 subjects per arm, and there was a high expectation that it would show a clear benefit to screening young women when it was designed in the late 1970s. When this did not happen, suspicion was cast on a highly unusual excess of patients diagnosed in the screened arm with more than three positive lymph nodes in the first year (25 versus seven for controls). The Canadian trial with more subjects, modern treatment and a Cochrane-approved trial design and conduct showed even worse end results than the other screening trials, thus deepening the paradox. Moreover, it raised a further question (a further paradox): if one supposes that findings about node positivity do not occur by chance, how can screening worsen the breast cancer stage at diagnosis?

Hypotheses to explain paradoxes

We analyzed relapse data from the Milan National Cancer Institute that included 1173 untreated early-stage patients with a 16–20 year follow-up [75]. These data showed a remarkable double-peaked relapse pattern. There was a sharp first peak at 1.5 years, a nadir at 4 years, and a broad peak at 5–6 years that extended to 15–20 years. Baum has identified this same pattern in a UK

Figure 1. Meta-analysis data for six screening trials for younger women from Cox showing the cumulative breast cancer-specific mortality per screened individual and the equivalent mortality per unscreened control.



In five of these trials the age at entry was 40–49 years, and in the other trial the age was 45–54 years. This figure is based on over 800 000 person-years of experience in each of the screened and control arms. The early disadvantage to screened young women is typical of results seen in all trials. In conjunction with data shown in Figure 2, the significant disadvantage to screening younger women first appears 3 years into the trial.

Reproduced from Cox [74], with permission of the *Journal of the National Cancer Institute*.

database [76–78] and we have also observed it in five additional independent databases [79–83].

To help understand this pattern, we used a computer simulation to fit a simple growth model to the Milan data. The model had two possible dormant phases (single-cell and avascular micrometastasis) and two growth phases (avascular growth and a growing vascularized lesion) as shown in Figure 3. Model details and both clinical and experimental data supporting it were published in 1997 [84,85]. Holmgren *et al.* [86] found dormancy frequently before tumor angiogenesis. Klauer-DeMore *et al.* [87•] and Naumov *et al.* [88••] published new supporting findings on dormancy in human breast cancer and breast cancer models.

According to the computer simulation of this model [89••,90••], the second peak results from steady stochastic transitions from one phase to the next. To fit these data, the half-life of the transition from the single cell to an avascular micrometastasis was determined to be 1 year. Likewise, the half-life of the transition from the avascular micrometastasis to the growing vascularized lesion was estimated to be 2 years. The top of the second peak corresponds to the eventual depletion of

new metastasis seeding as a result of the surgical removal of the primary tumor 5–6 years earlier. That is, the metastatic pipeline is so slow that the benefit of surgery is not observed until 5–6 years later. The first peak is too sharp to be the result of only stochastic processes, and it may reasonably represent transitions triggered by surgery. Events in the first peak result from single dormant cells that were induced to divide as a result of surgery and then vascularize stochastically. This occurs for patients of all ages, increasing with the tumor size. Also included in the first peak, mainly in its early phase, are events following the stimulation of angiogenesis in avascular micrometastases at surgery. This relapse mode is only important for premenopausal node-positive patients. These are shown in Figure 4.

We have, of course, not proved here that angiogenesis is stimulated at surgery to produce the early relapses, or that the 18-month peak is caused by induced single-cell division at surgery. However, we can say with confidence that some states of dormancy are broken at surgery, synchronizing patients, and that induced single-cell division and induced angiogenesis are numerically consistent with all the data we have examined.

Hofer *et al.* [91] reported that tumor outgrowth after surgery has long been observed, and also that there is commonality between some tumor growth factors and some growth factors that promote wound healing after surgery.

We think these surgery-induced events are at least partly responsible for the modest results of mammography and the age dependency. As a result of screening, cancers are found at an earlier stage than would be found without screening, which is favorable, but then surgical intervention to remove the primary tumor accelerates metastatic growth, offsetting the early detection advantage. In other words, screening and control arms have different surgery timing distributions, resulting in an early recruitment of unfavorable events for screened women [90••,92•].

Why was the premature interruption of tumor dormancy less often observed for older women? The balance between benefit from early detection downstaging and harm from unfavorable events synchronization may be different in women under or over 50 years. The most obvious difference between the two age groups is menopausal status. Peculiar conditions relevant to tumor growth, such as menstrually waxing and waning levels of angiogenesis active factors, may be characteristics of premenopausal women [93].

It is also well accepted that downstaging less commonly occurs in young women in comparison with older women,

Figure 2. Yearly ratio of mortality in the screened arms to control arms for young women as described in the caption to Figure 1

There are few events in the first 2 years accounting for the large error spread. The dashed line at 1.0 represents equal deaths among screened and unscreened controls in any year. The value at 3 years is the only point significantly different from 1.0.

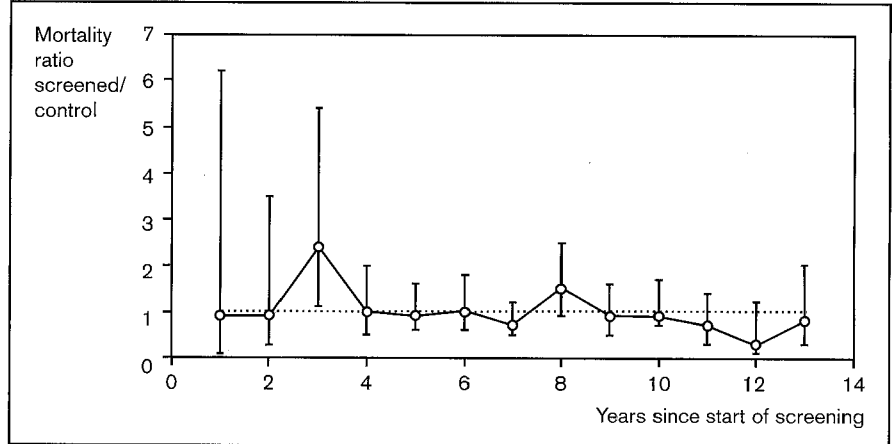


Figure 3. Elementary model of metastatic tumor development was fitted to the Milan database using computer simulation

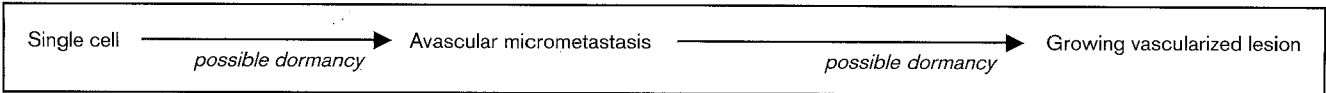
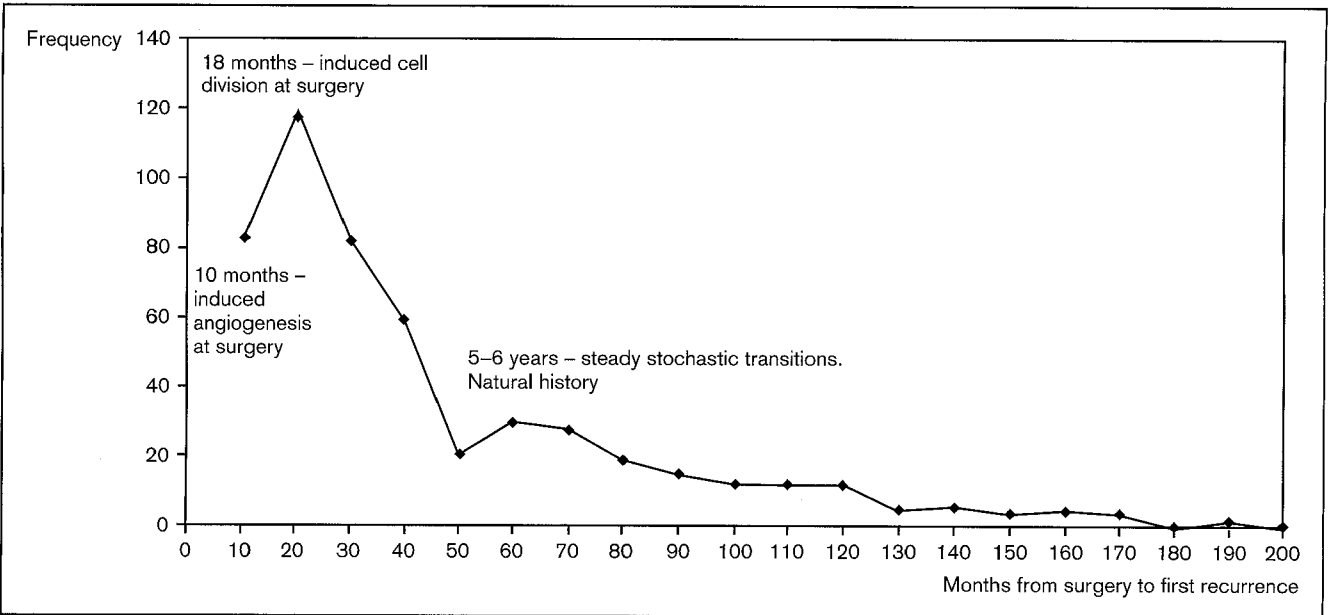


Figure 4. Relapse events in the Milan data grouped in 10-month bins



Relapses are combined distant and local. The nadir at 50 months is significantly below a smooth curve drawn through the other points. Two distinct relapse peaks are seen. As described in the text, the second peak is the natural history of the disease. Two previously unreported relapse modes comprise the first peak. In the first 10 months, there are relapses caused by avascular micrometastases (pre-existing at primary tumor detection) that are stimulated to vascularize at surgery. This mode is prominent only for premenopausal node-positive patients, in which case over 20% of patients relapse in this manner. The remainder of events in the first peak are single cells that are dormant at primary detection and are induced to divide as a result of surgery. These must then undergo a stochastic transition to an eventual growing metastasis. This mode is very common – occurring for 50–80% of relapsing patients depending on tumor size but independent of age.

as a result of the diminished effectiveness of mammography in this group [41*,45*]. On the basis of these and other known differences in the biological behavior of breast cancer in pre- and postmenopausal women, we do not consider it surprising or unreasonable that there is an age dependence of benefit from screening.

As stated, we observed that early relapses are more frequent in premenopausal node-positive patients, and occur in the first year. Moreover, the median survival time after relapse was 2 years. Therefore, even if death events do not strictly parallel the corresponding recurrence events, we may estimate the order of magnitude of the mortality surge putatively induced by surgery-related interruption of dormancy. From the relapse surge in the first 10 months of the Milan data, we calculated that 0.11 deaths per 1000 screened individuals would be expected in the third year of screening trials. This estimate is similar to the Cox meta-analysis finding. Reasonably similar values are seen in the Swedish overview, HIP and the Edinburgh data. Although this may seem small, the age-adjusted US yearly death rate from breast cancer is 0.24 deaths per 1000 women – not much larger.

We interpret the statistically significant excess of deaths in the third year for the screened population aged 40–49 years as seen in Figure 2 as a ‘smoking gun’ for the interruption of tumor dormancy.

The paradoxical worsening of the breast cancer stage at diagnosis in the screening arm of the Canadian trial may also be surgery related. In the first year of that trial there were three times as many biopsies for screened subjects than for controls. Because the breast is rich in lymphatics, the wounding associated with a false-negative biopsy might upregulate the secretion of growth factors and induce lymphangiogenesis within the tumor. This explanation could seem quite caviled, but it is a further extension of the concept that surgery may change the tumor–host balance. The lack of screening benefit in the Canadian study could be explained if as few as 18 (or roughly 3%) of the extra 550 biopsies performed in the first year in the intervention arm showed false-negative results and caused lymphangiogenesis and stage progression (e.g. from 0–3 to >3 positive lymph nodes). This effect is small enough that it would escape detection in anything other than a large screening trial of premenopausal women.

An alternative and simpler explanation is that there was an ascertainment bias because screen-detected cancers were assigned to more specialized units who performed more careful axillary dissections. This is probably the correct explanation because recent trial data show that

47% of node-negative diagnosed patients in the control group died of breast cancer, whereas a more reasonable 28% of node-negative patients in the mammography arm died [3**].

The picture that we are trying to paint is even more complicated in reality. It was proposed by Hrushesky *et al.* in 1989 [94] that breast cancer surgery should be performed in the luteal phase of the menstrual cycle for premenopausal women to diminish the probability of recurrence and death rates – a controversy in its own right [95].

Conclusion

Even if breast cancer screening *per se* is not necessarily detrimental, the resulting interventions produce a worsened situation for a significant fraction of young women. Screening is not, therefore, the benign process commonly thought. If our explanation is correct, breast cancer grows in a manner that includes various periods of dormancy, and surgical interventions can accelerate residual tumor growth. This non-linear growth is most prominent in the premenopausal woman, in whom the concentrations of a multitude of central and peripheral hormones and growth factors vary during the menstrual cycle. Baines *et al.* [96] showed that the number of false-negative mammograms may be decreased by 50% in premenopausal women by optimally timing the screening test within the menstrual cycle.

The biology of tumor–host relationships is probably the underlying explanation for why screening has not lived up to expectations. In our opinion, screening for breast cancer may be a valid concept even in women aged 40–49 years, but it should take into account many factors, some of which are still poorly understood; otherwise, the result will be more harm than good.

There is some interest in starting new screening trials, perhaps using all-cause mortality as an endpoint. However, from our research, trial results depend on the treatments used. Screening trials started now will thus not be relevant in 10 years when different adjuvant treatments will be the norm.

What is the interaction among (putative) induced angiogenesis at surgery, (putative) benefits of timing of surgery within the menstrual cycle and adjuvant chemotherapy? For example, does adjuvant chemotherapy blunt surgery-induced tumor angiogenesis? Are there more angiogenic-specific therapy choices? If so, what would be a reasonable screening protocol for countries where no adjuvant therapy is available? Perhaps the timing of surgery would be very effective in those societies.

Finally, we urge testing of our hypotheses by looking for confirmatory or contrary findings. We believe that a further detailed examination of databases of the already performed screening trials from the perspective provided here will be useful for a better understanding of breast cancer biology in pre- and postmenopausal women and for drawing up sound early detection guidelines.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

- 1 Greenlee RT, Hill-Harmon MB, Murray T, Yhun M. Cancer Statistics, 2001. *CA Cancer J Clin* 2001; 51:15–36.
- 2 Tabar L, Vitak B, Chen HH, et al. Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality. *Cancer* 2001; 91:1724–1731.
Comment in: *Cancer* 2001; 91:1699–1703; *Cancer* 2002; 94:578–579, discussion 581–583; *Cancer* 2002; 94:578, discussion 581–583; *Cancer* 2002; 94:579–580, discussion 581–583; *Cancer* 2002; 94:580–581, discussion 581–583.
- 3 Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study 1: breast cancer mortality after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years. *Ann Intern Med* 2002; 137:305–312.
An important, finely detailed review of the Canadian trial for young women. The authors also discuss why there were more patients diagnosed with many nodes in the mammography group compared with the control group. They also address the need to understand the mortality surge at 3 years of screening in young women.
- 4 Humphrey LL, Helfand M, Chan BK, Woolf SH. Breast cancer screening: a summary of the evidence for the US Preventive Services Task Force. *Ann Intern Med* 2002; 137:347–360.
An important summary of all trial data and US Preventive Services Task Force conclusions.
- 5 Sox H. Screening mammography for younger women: back to basics. *Ann Intern Med* 2002; 137:361–362.
A discussion of the update on the Canadian trial by Miller et al. [3••] and the report from the US Preventive Services Task Force by Humphrey et al. [4••].
- 6 Gotzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? *Lancet* 2000; 355:129–134.
- 7 Olsen O, Gotzsche PC. Cochrane review on screening for breast cancer with mammography. *Lancet* 2001; 358:1340–1342.
This is the Olsen and Gotzsche paper as sanctioned by the Cochrane Breast Group. The full review is on the Web as is the original 2000 paper at the Lancet website (lancet.com). The review is available at <http://image.thelancet.com/lancet/extra/fullreport.pdf>.
- 8 de Koning HJ. Commentary – assessment of nationwide cancer screening programmes. *Lancet* 2000; 355:80–81.
- 9 Rozenberg S, Liebens F, Ham H. Screening mammography re-evaluated. *Lancet* 2000; 355:751–752, discussion 752.
- 10 Baum M. Screening mammography re-evaluated. *Lancet* 2000; 355:751, discussion 752.
- 11 Leung GM, Lam TH, Hedley AJ. Screening mammography re-evaluated. *Lancet* 2000; 355:750–751, discussion 752.
- 12 Cates C, Senn S. Screening mammography re-evaluated. *Lancet* 2000; 355:750, discussion 752.
- 13 Law M, Hackshaw A, Wald N. Screening mammography re-evaluated. *Lancet* 2000; 355:749–750, discussion 752.
- 14 Hayes C, Fitzpatrick P, Daly L, Buttner J. Screening mammography re-evaluated. *Lancet* 2000; 355:749, discussion 752.
- 15 Nystrom L. Screening mammography re-evaluated. *Lancet* 2000; 355:748–749, discussion 752.
- 16 Moss S, Blanks R, Quinn MJ. Screening mammography re-evaluated. *Lancet* 2000; 355:748, discussion 752.
- 17 Duffy SW, Tabar L. Screening mammography re-evaluated. *Lancet* 2000; 355:747–748, discussion 752.
- 18 Miller AB, Baines CJ, To T, Wall C. Screening mammography re-evaluated. *Lancet* 2000; 355:747, discussion 752.
- 19 Cady B. Screening mammography: the continuous dilemma. *Breast J* 2002; 8:185–186.
- 20 Horton R. Screening mammography – an overview revisited. *Lancet* 2001; 358:1284–1285.
- 21 Mammography: what's a woman to do? *Johns Hopkins Med Lett Health After* 2002; 14:4–5.
A good summary of how the different professional and policy groups have responded to the controversial situation.
- 22 van Veen WA, Knottnerus JA. Screening mammography. *Lancet* 2002; 359:1701.
The Netherlands will continue to screen women older than 50 years of age.
- 23 Saul H. Mammography: consensus in sight? *Eur J Cancer* 2002; 38:1035.
Thoughtful comments in interviews of Baum and de Wolf.
- 24 Burton A. Europe continues breast screening despite doubts. *Lancet Oncol* 2002; 3:258.
Various European countries react differently to uncertainty.
- 25 Baum M. Screening – a cruel deception. *Practitioner* 2002; 246:293.
Baum discusses whether women are provided proper information on the benefits and risks of screening. Surgeon, researcher and social-medical historian, Baum's opinions should not be taken lightly.
- 26 Lee CH. Screening mammography: proven benefit, continued controversy [Review]. *Radiol Clin North Am* 2002; 40:395–407.
The viewpoint of screening controversy from an academic diagnostic radiologist.
- 27 Hoey J. Does mammography save lives? *Can Med Assoc J* 2002; 166:1187–1188.
The author reviews a paper published in 2002 in the *Lancet* by Miettinen et al., and makes suggestions for screening women aged 55 years and older.
- 28 Arnold K. Mammography guidelines in the national spotlight again. *J Natl Cancer Inst* 2002; 94:411–413.
A news feature. An interesting background and interviews especially with Barron Lerner on the polarization of viewpoints on controversy.
- 29 Rodger A. Is it worth screening women over 70 for breast cancer – or indeed any women? *Med J Aust* 2002; 176:247–248.
The author on the Cochrane Breast Group discusses the paper by Barratt et al. [30*].
- 30 Barratt AL, Les Irwig M, Glasziou PP, et al. Benefits, harms and costs of screening mammography in women 70 years and over: a systematic review. *Med J Aust* 2002; 176:266–271.
An interesting comparison of the effectiveness and costs of screening women at different ages in Australia.
- 31 Gelmon KA, Olivotto I. The mammography screening debate: time to move on. *Lancet* 2002; 359:904–905.
A thoughtful letter suggesting that it is time to move on from screening to questions of molecular diagnosis, optimizing therapies and improving survival of women.
- 32 Nystrom L, Andersson I, Bjurstam N, et al. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet* 2002; 359:909–919.
An important update of all Swedish trials excluding Kopparberg – one of the Two County Trials.
- 33 Duffy SW, Tabar L, Smith RA. The mammographic screening trials: commentary on the recent work by Olsen and Gotzsche. *CA Cancer J Clin* 2002; 52:68–71.
A criticism of the Olsen and Gotzsche thesis. The case for mammography screening is presented by steadfast advocates. Their arguments are not always persuasive in our opinion.
- 34 Editorial. Confusion over mammography screening intensifies. *Lancet Oncol* 2002; 3:127.
A good summary concluding with a recommendation for new, strictly controlled, high-quality trials.
- 35 Feig SA. Current status of screening mammography. *Obstet Gynecol Clin North Am* 2002; 29:123–136.
In our opinion, this is an overoptimistic viewpoint of the value of screening.
- 36 Juffs HG, Tannock IF. Screening trials are even more difficult than we thought they were. *J Natl Cancer Inst* 2002; 94:156–157.
Editorial comments on the paper by Black et al. [37••].
- 37 Black WC, Haggstrom DA, Welch HG. All-cause mortality in randomized trials of cancer screening. *J Natl Cancer Inst* 2002; 94:167–173.
This important paper discusses problems encountered when screening trials use breast (or other) cancer-specific mortality as an endpoint. On the basis of this analysis, the Edinburgh trial had inadequate randomization as Olsen and Gotzsche claimed.

- 38 Cochrane Breast Cancer Group Editors. Screening mammography: setting the record straight. *Lancet* 2002; 359:439-440, discussion 440-442. A discussion of why there are two slightly different versions of the Gotzsche and Olsen documents.
- 39 Goodman SN. The mammography dilemma: a crisis for evidence-based medicine? *Ann Intern Med* 2002; 137:363-365. A very good editorial, especially on the burden required when eliminating data from consideration.
- 40 Wells J, Marshall P, Crawley B, Dickersin K. Newspaper reporting of screening mammography. *Ann Intern Med* 2001; 135:1029-1037. A discussion on the influence of newspaper reporting on mammography.
- 41 Shen Y, Zelen M. Screening sensitivity and sojourn time from breast cancer early detection clinical trials: mammograms and physical examinations. *J Clin Oncol* 2001; 19:3490-3499. Statisticians compare the importance of physical examination and mammography.
- 42 Norton L. Letter to editor. *New York Times*, 3 Feb 2002.
 • In an extraordinary public letter, the President of the American Society for Clinical Oncology urges women to continue following current screening guidelines.
- 43 Kopans DB. Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality. *Cancer* 2002; 94:580-581, discussion 581-583. This author has long been an unwavering and vocal advocate of mammography.
- 44 Smith RA, Cokkinides V, von Eschenbach AC, et al. American Cancer Society guidelines for the early detection of cancer. *CA Cancer J Clin* 2002; 52:8-22.
- 45 Keith LG, Oleszczuk JJ, Laguens M. Are mammography and palpation sufficient for breast cancer screening? A dissenting opinion. *J Womens Health Gender Based Med* 2002; 11:17-25. The authors discuss the variability of interpretation and other limitations of mammography, especially for women with dense breasts. They advise including thermal detectors as another modality.
- 46 von Eschenbach AC. NCI remains committed to current mammography guidelines. *Oncologist* 2002; 7:170-171. The NCI Director cites Begg [47*] and stays with the recommendation that screening start at the age of 40 years, with mammograms every 1-2 years.
- 47 Begg CB. The mammography controversy. *Oncologist* 2002; 7:174-176.
 • A statistician does not find genuine substance in the Olsen and Gotzsche papers.
- 48 Dixon-Woods M, Baum M, Kurinczuk JJ. Screening for breast cancer with mammography. *Lancet* 2001; 358:2166-2167, discussion 2167-2168. The authors are critical of UK informed consent information on screening.
- 49 Vaidya JS. Screening for breast cancer with mammography. *Lancet* 2001; 358:2166, discussion 2167-2168. We should stop talking about early detection and instead think about learning how to live with dormant cancers, according to this author.
- 50 Duffy SW, Tabar L, Smith RA. Screening for breast cancer with mammography. *Lancet* 2001; 358:2166, discussion 2167-2168. The Olsen and Gotzsche paper is riddled with misrepresentation, inconsistency, and errors according to this letter. Gotzsche replies to these comments.
- 51 Thornton H. Screening for breast cancer with mammography. *Lancet* 2001; 358:2165, discussion 2167-2168. This letter criticizes the Cochrane Breast Cancer Review group for interfering with the scientific freedom of Olsen and Gotzsche.
- 52 Lee JH, Zuckerman D. Screening for breast cancer with mammography. *Lancet* 2001; 358:2164-2165, discussion 2167-2168. Concern is expressed about the use of meta-analysis (which has its own biases) to make important health policy decisions.
- 53 Miller AB. Screening for breast cancer with mammography. *Lancet* 2001; 358:2164, discussion 2167-2168. The author, a co-Principal Investigator of the Canadian trial and who also worked on the 1964 era HIP trial, defends HIP trial against criticism by Olsen and Gotzsche, stating that HIP is not flawed. On the basis of our previous communications with this author, we accept this information. The original Principal Investigator of HIP, Sam Shapiro, died several years ago.
- 54 Senn S. Screening for breast cancer with mammography. *Lancet* 2001; 358:2165, discussion 2167-2168. The author defends the cluster method of randomization as used in the Edinburgh trial, and is critical of the statistical software package used by the Cochrane Collaboration.
- 55 Cimons M. Experts at odds over mammography. *Nat Med* 2002; 8:202.
- 56 Breen N, Wagener DK, Brown ML, et al. Progress in cancer screening over a decade: results of cancer screening from the 1987, 1992, and 1998 National Health Interview Surveys. *J Natl Cancer Inst* 2001; 93:1704-1713. Documentation on screening utility.
- 57 Tabar L, Smith RA, Duffy SW. Update on effects of screening mammography. *Lancet* 2002; 360:337. An interesting comparison of individual trial results with the percentage of cancers found with node-positive disease.
- 58 Nystrom L, Andersson I, Bjurstram N, et al. Update on effects of screening mammography. *Lancet* 2002; 360:339-340. Authors' reply to Tabar et al [57*].
- 59 Goodman NW. Screening mammography: but how do women decide? *Lancet* 2002; 360:171. The author argues to have patience and await clearer answers.
- 60 US Preventive Services Task Force. Screening for breast cancer: recommendations and rationale. *Am Fam Physician* 2002; 65:2537-2544. The US Preventive Services Task Force statement has changed - now includes women aged 40-49 years, but downgrades evidence from level A to level B.
- 61 PDQ on the National Cancer Institute website cancer.gov. [accessed August 2002]
 • Reflecting the uncertainty around the world, even organizations within the National Cancer Institute do not agree on guidelines for screening. This useful site is closely associated with Donald Berry, a highly regarded biostatistician and frequently quoted critic of mammography.
- 62 McTiernan A. Recent controversies in mammography screening for breast cancer. *Medscape Womens Health* 2002; 7:3.
- 63 Royak-Schaler R, Klabunde CN, Greene WF, et al. Communicating breast cancer risk: patient perceptions of provider discussions. *Medscape Womens Health* 2002; 7:2.
- 64 Wilcken N. Mammography screening. *Lancet Oncol* 2002; 3:268.
 • A member of the board of the Cochrane Breast Group discusses whether academic freedom was jeopardized when the group decided against publishing the original Olsen and Gotzsche paper.
- 65 Vacek PM, Geller BM, Weaver DL, Foster Jr RS. Increased mammography use and its impact on earlier breast cancer detection in Vermont, 1975-1999. *Cancer* 2002; 94:2160-2168. Good information on the effect of mammography on the percentage of women detected with small tumors and negative nodes in one state.
- 66 Chamot E, Perneger TV. Misconceptions about efficacy of mammography screening: a public health dilemma. *J Epidemiol Commun Health* 2001; 55:799-803. A survey conducted in Geneva shows perceptions of breast cancer risk and the utility of mammography.
- 67 Walter LC, Eng C, Covinsky KE. Screening mammography for frail older women: what are the burdens? *J Gen Intern Med* 2001; 16:779-784. The authors determine the value of mammography in a nursing home setting.
- 68 Mayor S. Row over breast cancer screening shows that scientists bring 'some subjectivity into their work'. *BMJ* 2001; 323:956. Internal politics at the Cochrane Breast Cancer Group.
- 69 Smith RA, Cokkinides V, von Eschenbach AC, et al. American Cancer Society guidelines for the early detection of cancer. *CA Cancer J Clin* 2002; 52:8-22. A yearly update of the American Cancer Society screening guidelines.
- 70 J Natl Cancer Inst Monogr 22. (1997 Consensus Conference) On the web at www3.oup.co.uk/jnci/cancerspectrum/monographs/monograph_22/.
- 71 Larsson L-G, Anderson I, Bjurstram N, et al. Updated overview of the Swedish randomized trials on breast cancer screening with mammography: age group 40-49 at randomization. *J Natl Cancer Inst Monogr* 1997; 22:57-61.
- 72 Alexander F. The Edinburgh randomized trial of breast cancer screening, NIH consensus conference on breast cancer screening for women ages 40-49. *J Natl Cancer Inst Monogr* 1997; 31:31-36.
- 73 Shapiro S. Periodic screening for breast cancer: the HIP randomized controlled trial. *Health Insurance Plan. J Natl Cancer Inst Monogr* 1997; 22:27-30.
- 74 Cox B. Variation in the effectiveness of breast screening by year of follow-up. *J Natl Cancer Inst Monogr* 1997; 22:69-72.
- 75 Demicheli R, Abbattista A, Miceli R, et al. Time distribution of the recurrence risk for breast cancer patients undergoing mastectomy: further support about the concept of tumor dormancy. *Breast Cancer Res Treatment* 1996; 41:177-185.
- 76 Holmberg L, Baum M. Work on your theories! *Nat Med* 1996; 2:844-846.
- 77 Baum M, Badwe RA. Does surgery influence the natural history of breast cancer? In: *Breast cancer: controversies in management*. Wise H, Johnson HJ (editors). Armonk, NY: Futura; 1994. pp. 61-69.
- 78 Baum M, Chaplain M, Anderson A, et al. Does breast cancer exist in a state of chaos? *Eur J Cancer* 1999; 35:886-891.

- 79 Fisher ER, Sass R, Fisher B. Pathologic findings from the National Adjuvant Project for breast cancers (protocol no. 4). *Cancer* 1984; 53 (Suppl. 3):712-723.
- 80 Veronesi U, Marubini E, Del Vecchio M, et al. Local recurrences and distant metastases after conservative breast cancer treatments: partly independent events. *J Natl Cancer Inst* 1995; 87:19-27.
- 81 Fortin A, Larochelle M, Laverdiere J, et al. Local failure is responsible for the decrease in survival for patients with breast cancer treated with conservative surgery and postoperative radiotherapy. *J Clin Oncol* 1999; 17:101-109.
- 82 Bedwinek J. Adjuvant irradiation for early breast cancer. An on-going controversy. *Cancer* 1984; 53 (Suppl. 3):729-739.
- 83 Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. *J Clin Oncol* 1996; 14:2738-2746.
- 84 Retsky MW, Demicheli R, Swartzendruber DE, et al. Computer simulation of a breast cancer metastasis model. *Breast Cancer Res Treatment* 1997; 45:193-202.
- 85 Demicheli R, Retsky M, Swartzendruber D, Bonadonna G. Proposal for a new model of breast cancer metastatic development. *Ann Oncol* 1997; 8:1075-1080.
- 86 Holmgren L, O'Reilly MS, Folkman J. Dormancy of micrometastases: balanced proliferation and apoptosis in the presence of angiogenesis suppression. *Nat Med* 1995; 1:149-153.
- 87 Klauber-DeMore N, Van Zee KJ, Linkov I, et al. Biological behavior of human breast cancer micrometastases. *Clin Cancer Res* 2001; 7:2434-2439.
- Evidence of dormant micrometastases and growing macrometastases in human breast axilla.
- 88 Naumov GN, MacDonald IC, Weinmeister PM, et al. Persistence of solitary mammary carcinoma cells in a secondary site: a possible contributor to dormancy. *Cancer Res* 2002; 62:2162-2168.
- This paper, featured on the cover of *Cancer Research*, documents single-cell dormancy in a mouse breast cancer model. We cite this paper as experimental evidence for the role of single-cell dormancy to explain the modest benefit of early detection.
- 89 Retsky M, Demicheli R, Hrushesky W. Premenopausal status accelerates relapse in node positive breast cancer: hypothesis links angiogenesis, screening controversy. *Breast Cancer Res Treatment* 2001; 65:217-224.
- An hypothesis to explain the age 40-49-years mammography controversy is described.
- 90 Retsky M, Demicheli R, Hrushesky W. Wounding from biopsy and breast cancer progression. *Lancet* 2001; 357:1048.
- A discussion of excess breast biopsies and possible stage progression. There are small numerical differences between this letter and the review text. The text is accurate.
- 91 Hofer SO, Molema G, Hermens RA, et al. The effect of surgical wounding on tumour development. *Eur J Surg Oncol* 1999; 25:231-243.
- 92 Retsky M, Demicheli R, Hrushesky W. Breast cancer screening for women aged 40-49 years: screening may not be the benign process usually thought. *J Natl Cancer Inst* 2001; 93:1572.
- The letter summarizes recent findings regarding surgical and biopsy interventions and the possible adverse impact on screening benefit
- 93 Heer K, Kumar H, Speirs V, et al. Vascular endothelial growth factor in premenopausal women - indicator of the best time for breast cancer surgery? *Br J Cancer* 1998; 78:1203-1207.
- 94 Hrushesky WJM, Bluming AZ, Gruber SA, Sothorn RB. Menstrual influence on surgical cure of breast cancer. *Lancet* 1989; 338:949-952.
- 95 Hortobagyi GN. The influence of menstrual cycle phase on surgical treatment of primary breast cancer: have we made any progress over the past 13 years? *J Natl Cancer Inst* 2002; 94:641-643.
- 96 Baines CJ, Vidmar M, McKeown-Eyssen G, Tibshirani R. Impact of menstrual phase on false-negative mammograms in the Canadian National Breast Screening Study. *Cancer* 1997; 80:720-724.