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

Curr Opin Obstet Gynecol 15:1–8. © 2003 Lippincott Williams & Wilkins.

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Current Opinion in Obstetrics and Gynecology 2003, 15:1–8

Abbreviation

HIP New York State Health Insurance Plan (trial)

1040-872X

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••–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-

DOI: 10.1097/01.gco.0000051562.77832.a9

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.

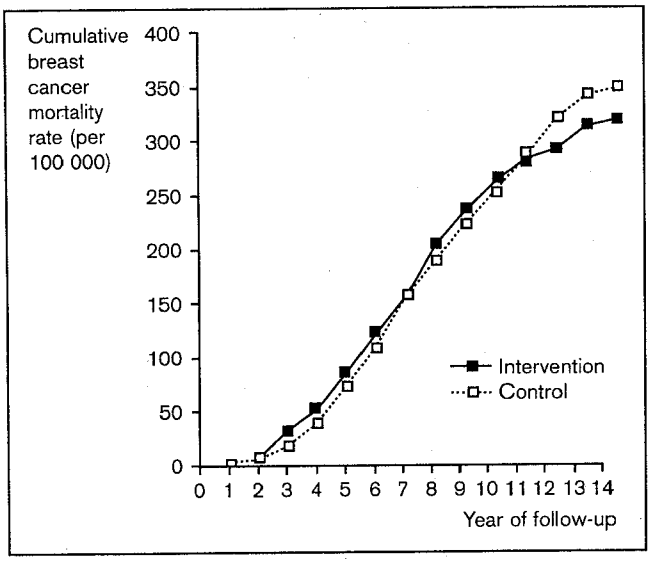
Therefore, we can conclude that, paradoxically, the early detection of breast cancer provided by screening mammography seems to be harmful for some women aged 40–49 years, at least for 6–8 years after the beginning of screening. What is causing the third-year mortality surge in the screened group with 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. Klauber-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.

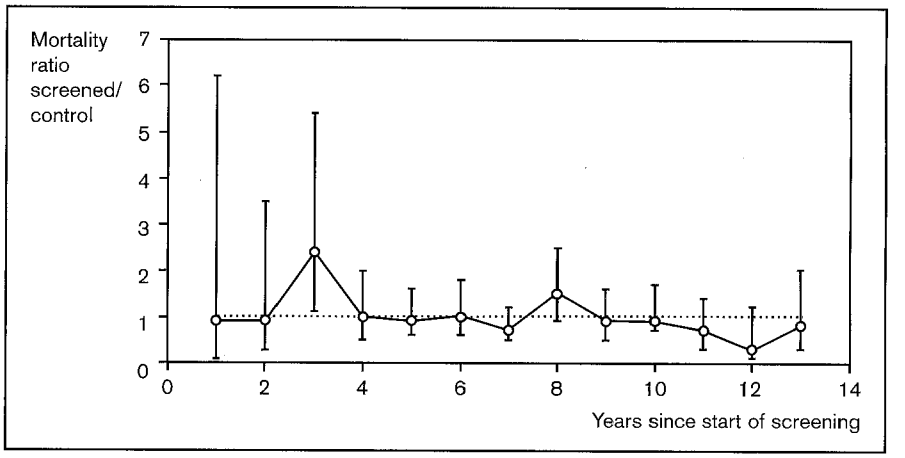


Figure 3. Elementary model of metastatic tumor development was fitted to the Milan database using computer simulation

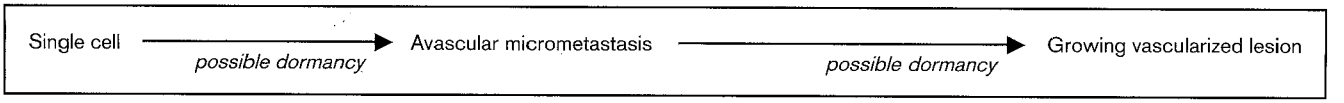
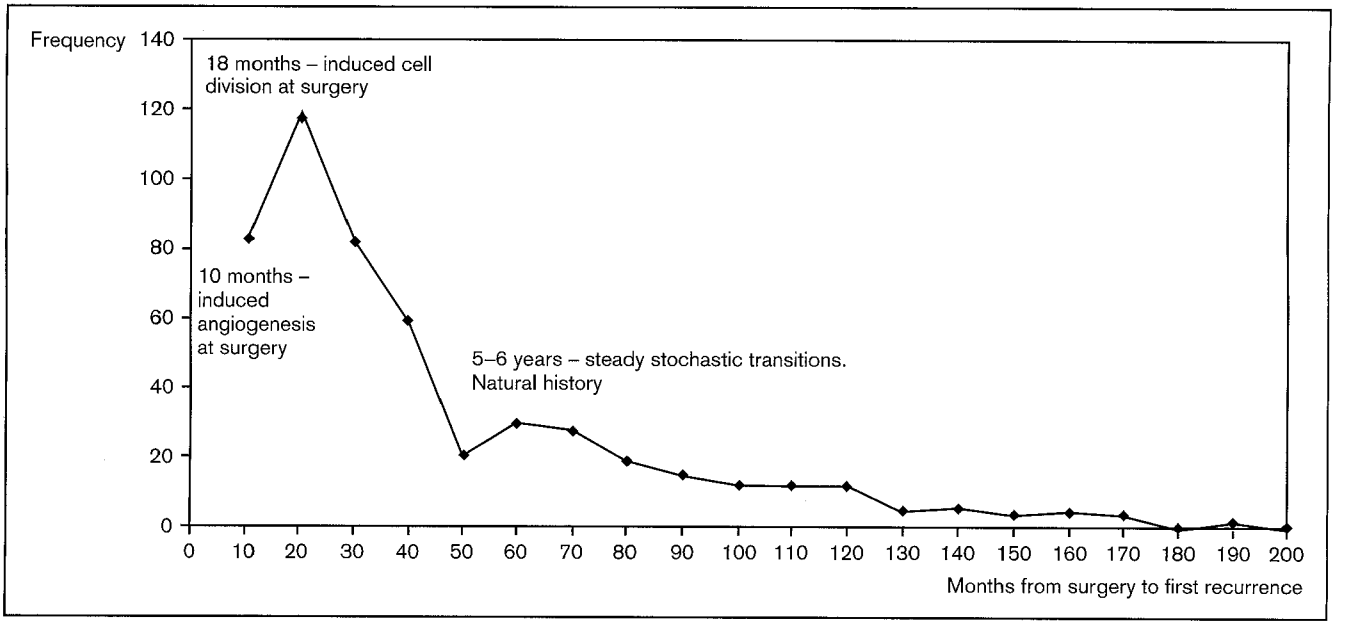


Figure 4. Relapse events in the Milan data grouped in 10-month bins



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

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- • of special interest
- •• of outstanding interest

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