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Report

Premenopausal status accelerates relapse in node positive breast cancer: hypothesis links angiogenesis, screening controversy

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Summary

Much attention has been given to determining the benefit of mammographic screening to reduce breast cancer mortality. Eight randomized clinical trials have been conducted in four countries: the US, Canada, Scotland and Sweden. Trials report an early and stable 30% reduction in breast cancer mortality for women aged 50–59. For women under 50, unexpectedly, the early years of screening produce a disadvantage to the screened population. Only in later years does an advantage appear. To help understand this, we studied relapse patterns using a breast cancer database of 1,173 pre- and postmenopausal, node negative and positive patients treated with surgery only and having 16–20 years of follow-up. This approach is relevant since at least five of the eight screening trials began before the widespread use of adjuvant chemotherapy in the 1980s. Surgical cure rates were independent of menopausal status. However, a major difference in early relapse rate was found. In premenopausal and node positive patients, 27% of all distant relapses occurred within the first 10 months following resection. This is twice the early relapse frequency of any other clinical group. Using computer simulation, we interpret that these early relapses probably result from a disadvantage induced at surgery. A disinhibition or surgery/wounding induced angiogenic surge might be responsible. Disinhibition is known to occur in animal models such as Lewis lung where lung metastases are avascular and dormant until the primary is removed. Sudden outgrowth of tumor after wounding has been observed for a century. According to the simulation, in breast cancer this induction apparently accelerates inevitable relapses by a median of two years. This is offset in later years with a balancing reduction in relapses. These data suggest that the angiogenic switch may be upregulated more frequently among premenopausal women, perhaps depending upon the sex hormones. The acceleration would cause 0.11 deaths per 1,000 screened aged 40–49 subjects in years 2–3, a value comparable to the early year excess mortality in trials of a significant 0.15 deaths per 1,000 subjects. Equal screening advantage is predicted for node negative (but not node positive) pre- and postmenopausal patients. The acceleration of relapse after surgery may explain the paradoxical effect of mammographic screening for women under 50.

Introduction

The first and apparently simplest decision after the diagnosis of early stage breast cancer is whether to remove the primary tumor. Theoretically, however, the situation is not so clear. Fisher and Fisher demonstrated conclusively that laparotomy alone can induce tumor growth in animal models [1]. Gunduz et al. and De Wys reported that tumor removal in animals resulted in stimulation of cell proliferation in metastatic foci. [2, 3]. Resection of the primary tumor may be accompanied by the release of growth enhancing factors by the act of surgical wounding, as well as by inducing a profound albeit temporary cellular immune paralysis [4–8].

In addition, it is known that circulating antiangiogenic factors such as angiostatin and endostatin result directly or indirectly from the presence of the primary tumor. These factors compete with proangiogenic factors such as basic fibroblastic growth

factor (bFGF) and vascular endothelial growth factor (VEGF) to at least partially control angiogenesis of existing dormant micrometastatic tumors [9]. According to the angiogenesis concept, upon removal of the primary tumor, inhibition ceases, angiogenesis is switched on and previously dormant micrometastases begin to grow. This effect is well documented in the Lewis lung animal model where angiostatin was first identified by O'Reilly et al. [10]. In this model, lung metastases develop but they remain avascular and dormant while the primary tumor is in place. When the primary tumor is removed, the lung metastases vascularize and begin to grow. Similar effects are also suspected to take place in human melanoma and primary pulmonary cancer [11, 12]. From these and other observations it must be considered that removal of a primary breast tumor could unintentionally produce the undesired result of stimulating metastatic cancer growth causing early relapse and death.

These negative effects of surgical resection may be visible in the results of trials to determine the survival benefits of mammographic screening. Eight randomized clinical trials of mammography have been conducted in the United States (Greater New York State Health Insurance Plan or HIP), Sweden (Kopparberg, Ostergotland (sometimes combined with Kopparberg), Malmo, Stockholm, and Gothenburg), UK (Edinburgh) and Canada [13–18]. There is a stable 30% survival advantage that appears within a few years from the start of mammographic screening. While this has recently been challenged by a Danish report [19] and the Canadian study failed to show an advantage of mammography over regularly scheduled physical exam [20], it is generally accepted. However, for women in their 40 s, the early years of screening produce an unexpected early disadvantage to the screened population [21–23]. At 10 years, a slight (about 6%) cumulative advantage over unscreened controls becomes apparent. Cox has suggested that there is a biological difference in the effect of screening between pre- and postmenopausal women. Fletcher suggested that there might be a stage shift caused by screening in younger women. Clearly, however, this negative effect of screening upon breast cancer mortality remains unexplained. It is noteworthy that five of the eight clinical trials of screening started before the widespread use of adjuvant chemotherapy for node positive premenopausal patients. In two other trials (Gothenburg and Stockholm) it is unknown if chemotherapy was used for all node positive premenopausal patients. In the Canadian trial virtually all such patients received adjuvant chemotherapy.

This lack of clear-cut benefit of screening for young women has produced considerable consternation over the past decade. With access to the same data, some authorities have recommended screening for women in their 40 s while others have come to the opposite conclusion. The 1997 National Institutes of Health (NIH) Consensus Panel concluded that the data currently available do not warrant a universal recommendation for mammography for all women in their 40 s [24]. Each woman should be informed of the risks and benefits and decide for herself whether to undergo screening mammography. Young women are, however, not routinely warned that screening and resection may accelerate breast cancer mortality.

Representative of the opposite viewpoint, Kopans believes the randomized studies show that screening mammograms are as important for women aged 40–49 as for women aged 50 years old and above [25]. He blames the controversy on improper use of retrospective, unplanned, sub-group analysis. Furthermore, he feels that separating women into those two groups was arbitrary and led to the incorrect conclusion that the age of 50 is a significant break point when it is not. Although it is hard to imagine that menopausal physiologic status, which transforms approximately at age 50, represents an arbitrary division, Kopans claims that no data demonstrate parameters of screening change abruptly at that age.

This highly charged situation has been well summarized by Maranto [26]:

> "Physicians, radiologists, statisticians and public health officials have made claims and counterclaims and with sometimes startling emotion – have accused one another of misreading or misrepresenting data, of performing faulty analyses and of perpetuating myths that have dire consequences for women. Some specialists, as well as cancer societies, women's health advocates and manufacturers of mammography machines, have argued that mass screening saves lives; others on the clinical front lines and in policy-setting roles have contended that evidence from a number of randomized controlled trials does not support such a claim".

Faced with such inconsistent screening recommendations from various authorities and organizations, most women in their 40 s are opting for screening, expecting that to be the safe alternative [27].

While we do not imagine that mammographic screening *per se* confers a disadvantage or advantage, we began to think of the consequences of the next more invasive steps after detection of an abnormality: biopsy and surgical extirpation.

A comprehensive biologic understanding of what happens when a primary tumor is removed is lacking. We hypothesized that an in-depth analysis of the dynamics of the post resection relapse pattern differences among pre- and postmenopausal patient subsets in women treated with mastectomy could provide insight. We reasoned that a better understanding of tumor growth shortly after surgery and without the additional complications of adjuvant therapy might help explain the puzzling mammographic screening data. Thus, we began by reexamining data on 1,173 pre- and postmenopausal, node negative and node positive breast cancer patients that were utilized in a previous report on a multi-peaked recurrence risk [28]. In the present study we focus on surgical cure rates, early relapse risks and the ability of a new model of metastatic development to explain the findings [29, 30].

Patients

The data used were provided by the Milan National Cancer Institute. All patients from January 1964 through 1980 who entered into three different clinical trials at the Cancer Institute, with mastectomy alone as the primary treatment for their operable breast cancer, were retrospectively evaluated. The patients were clinical presentation cases, not screening detected. The number of patients included was 1,173, and of these, 520 relapsed. Median age at diagnosis was 52 years with a range of 23 to 82. Distributions are shown in Table 1 and 2. The representation of patients in the various tumor size and nodal groupings are similar between pre- and postmenopausal patients.

Relapse data are presented as the raw number of distant relapse events grouped in serial bins of 10-month duration. The *a posteriori* choice to use 10 months as bin size resulted from a comparison of using bins sizes of 6, 10, 14, and 18 months. Small bin sizes show excessive noise while large bin sizes tend to mask structure. Ten-month bins were chosen to optimize the display of structure in the time dependent data [30].

Table 1. Distribution of tumor size among the subsets for T1 (<2 cm diameter), T2, and T3 (>5 cm diameter)

	T1 (%)	T2 (%)	T3 (%)	All
Premenopausal	222 (43)	264 (51)	30 (6)	516
Postmenopausal	237 (36)	364 (55)	56 (9)	657
All patients	459 (39)	628 (54)	86 (7)	1173

Table 2. Distribution of nodal status among the subsets

	$N = 0$ (%)	$N = 1$–3 (%)	$N > 3$ (%)	All
Premenopausal	265 (51)	158 (31)	93 (18)	516
Postmenopausal	333 (51)	184 (28)	140 (21)	657
All patients	598 (51)	342 (29)	233 (20)	1173

Results

This is a mature patient database. Thus, it can be assumed that nearly all relapse events have occurred. There is no statistical difference between pre- and postmenopausal patients in their long-term prognosis, grouped by tumor size as shown in Figure 1A or grouped by the number of positive nodes as indicated in Figure 1B. The fraction of node positive patients not cured by surgery is 0.73 for premenopausal and 0.74 for postmenopausal. However, the dynamics of the relapse pattern differ markedly-especially in the early years following resection.

For pre- and postmenopausal patients, relapse frequency is grouped by time after surgery for all patients (Figures 2A, 2B) and patients with >3 positive nodes (Figures 3A, 3B). To illustrate the manner of data presentation, of the 263 distant relapses among premenopausal patients, 44 relapses occurred >0 and <10 months after surgery. Therefore, the first bin in Figure 2A has the value 44.

As can be seen by comparing Figures 2 and 3, there are distinct differences between the menopausal groups in the first few bins of the relapse histograms. The fraction of all relapses that occur in the first 10 months is plotted versus the number of positive nodes in Figure 4. It is observed that a trend is apparent both for pre- (Figure 4A) and postmenopausal (Figure 4B) patients. However, this trend is approximately twice as strong for the premenopausal group. The fraction of all distant relapses that occur within the first 10 months for node negative patients is 2/46 or 0.04 ± 0.03 for premenopausal patients and 4/60 or 0.07 ± 0.03 for postmenopausal patients ($p > 0.05$). For node positive patients, the fraction of all distant relapses that occur

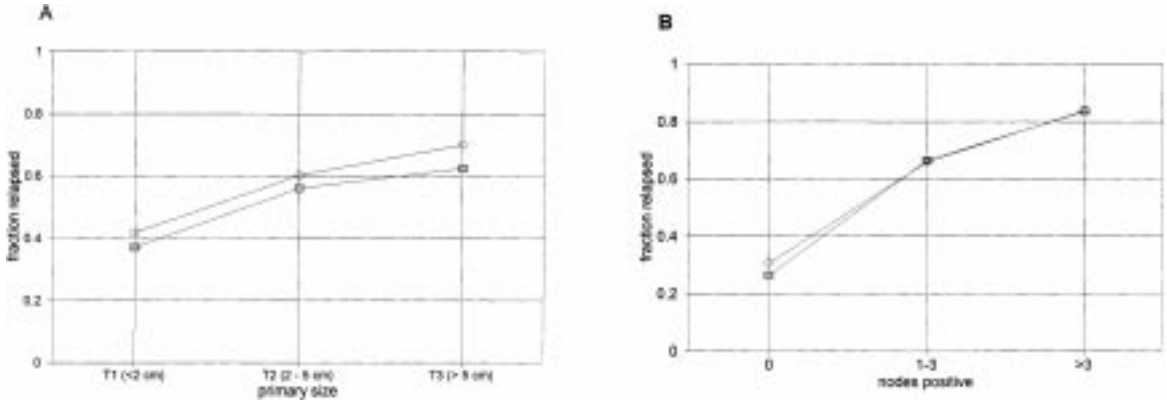

Figure 1. Fractions of patients who relapsed in the $N = 1{,}173$ Milan data base grouped by primary tumor size (A) and by number of positive axillary nodes (B) shown for premenopausal (open circles) and postmenopausal (shaded squares). There is no significant difference between the two menopausal states in either (A) or (B). These data show the probability of surgical cure is the same for premenopausal and postmenopausal patients. That is, if a patient had x nodes positive and y tumor size, the long-term relapse probability was independent of menopausal status.

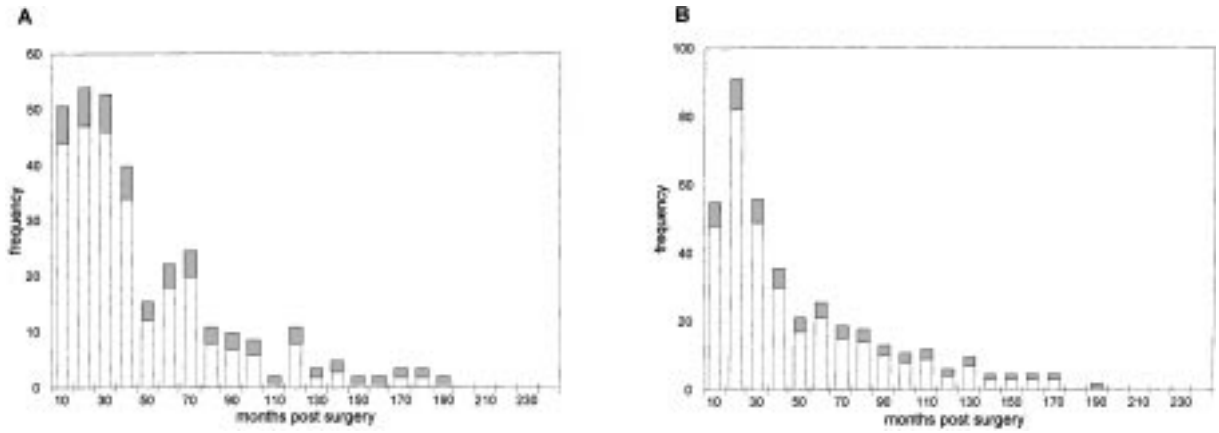

Figure 2. Histograms showing frequency of distant relapse events that occur in 10-month wide time periods measured from surgery. Shown are all premenopausal (A) and all postmenopausal (B) patients. Shaded areas are standard deviations. An early peak and a later peak appear in all subsets, more obvious with more patients in the subsets. There is a relatively sharp peak at 18 months and another peak at 60 months with a long tail which are more apparent in (B). A nadir at 50 months separates the peaks.

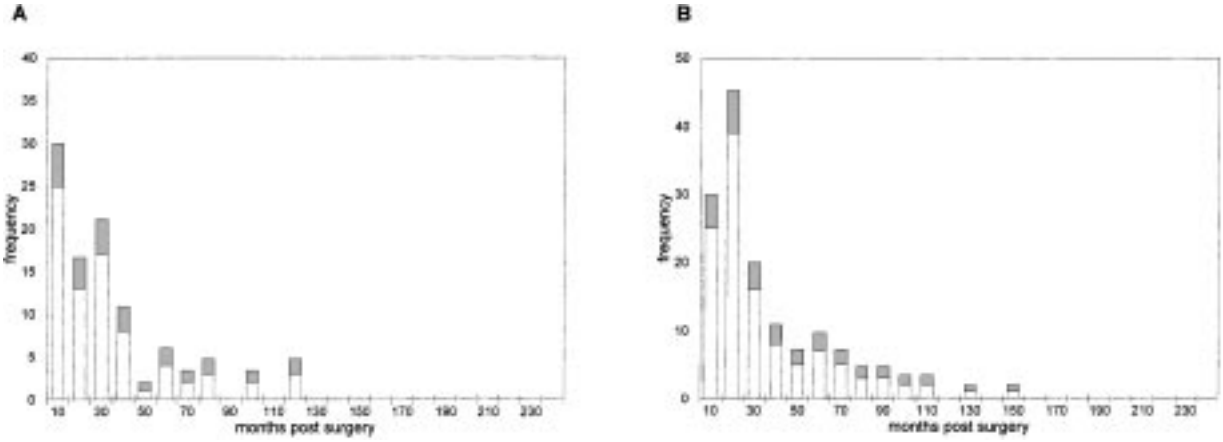

Figure 3. Histograms as in Figure 2 but only including patients with >3 positive nodes. The prominent surge in relapses just after surgery for premenopausal patients stands out as fine structure in the first peak (A). While this may appear to be a 'blip', it is significant and approximately the amount needed to explain the screening data. No such surge appears for postmenopausal women (B).

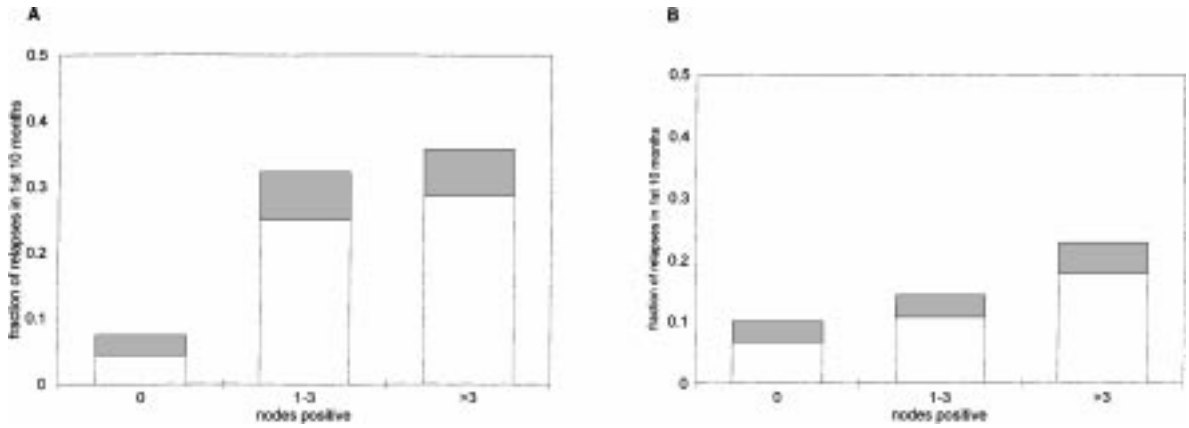

Figure 4. Milan relapse data showing the fraction of all distant relapses that occur in the first 10 months after surgery for premenopausal (A) and postmenopausal (B) patients. The shaded areas are standard deviations. These very early relapses are associated with positive nodes (compared to negative nodes by approximately 5:1) and premenopausal patients (compared to postmenopausal patients by approximately 2:1).

within the first 10 months is 28/104 or 0.27 ± 0.05 for premenopausal patients and 22/157 or 0.14 ± 0.03 for postmenopausal patients ($p < 0.05$).

Discussion

While the overall long term prognosis (ultimate apparent cure frequency) is very similar for pre- and postmenopausal patients as shown in Figure 1, there is a clear difference in the temporal dynamics characterizing relapse for the node positive subsets as shown in Figures 3 and 4. Specifically, in the first 10 months after surgery for node positive disease there is a surge of relapses for premenopausal patients that does not occur for postmenopausal patients.

The tumor/host interactions responsible for this very early relapse mode can be interpreted using a previously determined computer simulation of these same data [30]. Relapses that occur within the first 10 months after surgery are apparently due to dormant micrometastases that are stimulated by surgery, perhaps by the throwing of an angiogenic switch. Without this stimulation, the normal half-life of this state would be 2 years. Thus, such transitions induced at surgery could accelerate the disease by a median of 2 years.

Menopause usually occurs by age 50 so, as an approximation, aged 50–59 patients can be considered postmenopausal and aged 40–49 to be premenopausal. The menopausal status dependency of this tumor biology is likely to mean that the sex hormone milieu, in part, determines the angiogenic balance between host and cancer at the time of surgery [31]. As to why this seems to be relevant only for node positive patients, computer simulation predicts that the existence of avascular micrometastases prior to surgery is common for node positive patients but rare for node negative patients. That is consistent with these data.

Even though screening finds small tumors, a significant percentage of these patients have positive nodes. Considering an average of several screening trials, 24% of diagnosed patients had positive lymph nodes at the initial screen and 20% at rescreens. An overall goal proposed for screening is to detect fewer than 30% cancer patients with positive nodes [32]. For comparison, the Milan data (which did not involve screening) show 49% incidence of positive nodes. Cancer detection rates are 2.4 per 1,000 at initial screens and 2.0 per 1,000 at rescreens for women aged 40–49, again taking an average of several trials.

Since our data show that 27% of distant relapses among node positive premenopausal patients occurred within 10 months of primary tumor removal, the early relapse rate due to the suggested surgically induced acceleration in a screening trial can be calculated. These data imply that 0.24×0.27 or 6% of premenopausal women whose cancer was detected by the initial screening will relapse approximately 2 years earlier than their undetected (and for this reason not operated on) counterparts. If diagnosis were made at a subsequent screening, there would be 0.20×0.27 or 5% of such earlier relapses.

Since mammographic screening of premenopausal women find cancers at smaller size and fewer screening detected patients have positive nodes, according

to Figure 1, it provides long-term gain. This average benefit however, will be offset in some measure by the earlier relapses caused by screening, detection and removal before the control population tumors would have been detected and removed. The early year acceleration will be followed in later years by a balancing favorable effect.

There are separate implications for individual patients and for interpretation of clinical trials of screening. For individual women under age 50 there is a potential long-term advantage of finding smaller tumors with fewer positive lymph nodes. However, of these patients who are destined to relapse, 5–6% will do so several years prematurely as an indirect result of screening. For that minority of patients, screening is not safe.

For screening trials, the implications are complex because of the summed contribution of numerous individuals diagnosed at various times in the trials. However, it is possible to test our hypothesis using extant data.

The first test is to follow the patients detected at the initial screen of these trials for younger women. Initial screens find 2.4 cancers per 1,000 screened subjects. Of these patients, 24% have positive nodes. Of those, 73% will not be cured by surgery. Furthermore, 27% of these will have accelerated relapse. Thus a surge of $(2.4/1000) \times 0.73 \times 0.27 \times 0.24$ or 0.11/1000 early relapses, followed by deaths a predictable span after introducing the trial, should stand out of the background if the data are inspected in a way that will allow this to be seen. Survival after relapse has a median of approximately 2 years. Therefore, if our hypothesis is correct, 2 to 3 years after the onset of a screening trial there should be a surge of up to 0.11 deaths per 1,000 screened premenopausal subjects as a result of the initial screen (and subsequent operation). This prediction can be compared to available data. Cox combined results from six of the screening trials for younger women. Cox's data, seen in Figure 5, show a statistically significant surge in mortality of the screened population compared to controls of magnitude 0.15/1000 at 3–4 years.

As a second test, published data from the Swedish randomized trials can be used to determine if there is an early surge in mortality for screened subjects compared to unscreened controls for women aged 40–49 and not for women aged 50–59 [33]. This information is shown in Figure 6. As can be seen, there is a mortality surge for women aged 40–49 in the 3–4 year period after start of the trials, similar to the results of Cox. No

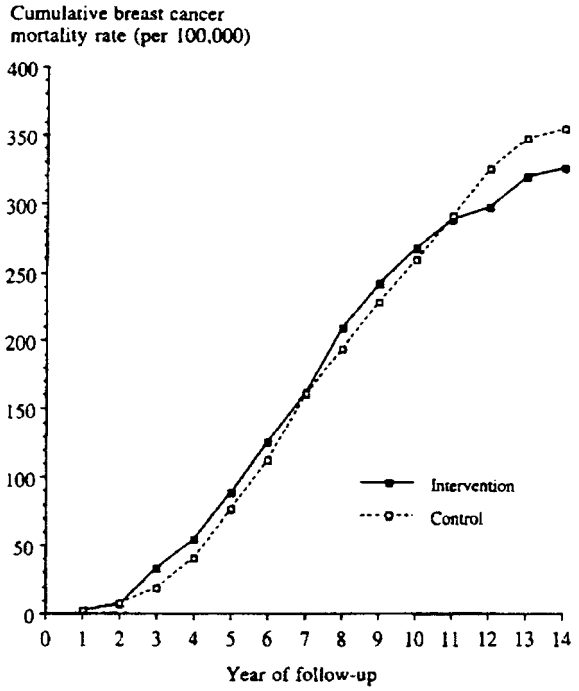

Figure 5. Meta-analysis data for six screening trials from Cox showing the cumulative breast cancer specific mortality per screened subjects and equivalent mortality per unscreened controls. In five of these trials the age at entry was 40–49 and in the other trial the age was 45–54. This figure is based 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 6, the significant disadvantage to screening younger women first appears 3 years into the trial. The early disadvantage to screening is approximately 0.15 mortalities per 1,000 screened subjects. A lateral translation of two years in the screened mortality curve would provide approximately 30% survival advantage to that population over controls or what would be similar to that which is reported for women 50–59. Reproduced from Cox [21] with permission of Journal of the National Cancer Institute.

such surge is seen in these data for women aged 50–59. The Swedish data are smoothed by the use of a running average technique. The timing and magnitude of trial mortality data are reasonably consistent with our prediction.

While according to our hypothesis, breast cancer mortality is accelerated only 6%, this effect is clearly observable. This is because early in a screening trial there are few other mortal events as the subjects are determined to be cancer free as an entry qualification, and second, the initial screening followed shortly by surgical resection apparently synchronizes these events. (It is interesting to observe that breast cancer that is well known for heterogeneity can act in a homogeneous fashion under certain conditions).

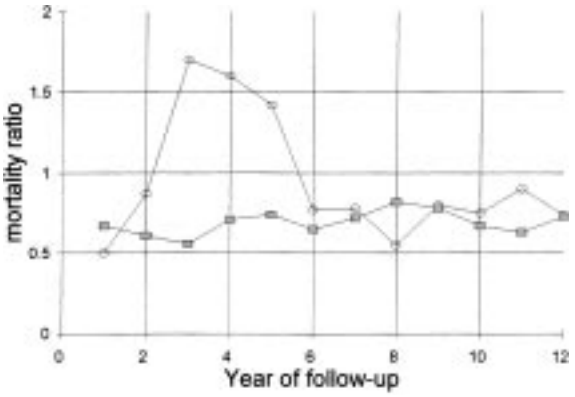

Figure 6. Published data from the Swedish screening trials were used to show the year to year excess mortality ratio for screened compared to unscreened controls. Data are shown separately for women aged 40–49 (open circles) and for women aged 50–59 (shaded squares). Considering 2-year average survival time after relapse, the timing is right for the surge at 3 years to be the accelerated result of the high yield and more node positive cancers detected at the initial screens.

We hypothesize that the failure to demonstrate a screening benefit for premenopausal women is explainable by a synchronized burst of tumor angiogenesis initiated at surgery for premenopausal node positive patients. As to why this would be prominent only for premenopausal patients, perhaps a primary breast tumor produces more endostatin or angiostatin in a premenopausal woman than in a postmenopausal woman. On the other hand, maybe the angiogenic switch is upregulated more often in premenopausal patients. This is consistent with data showing that VEGF varies as progesterone fluctuates during the menstrual cycle [31]. Perhaps the cyclic variation of VEGF within the menstrual cycle provides an angiogenesis-based mechanism that can explain the dependence of survival upon the timing of surgery within the menstrual cycle that has been verified by some investigators and disputed by others [34, 35].

Our results suggest that 5–6 % of premenopausal women diagnosed with breast cancer from mammographic screening will relapse and die approximately two years earlier than their unscreened counterparts due to the acceleration effect. Thus, it is not that screening women less than 50 causes higher mortality than not screening. Rather, our data suggest that such screening causes fewer mortal events just as it does for women over 50. However, for the node positive subset of premenopausal women, a significant percentage of these mortal events occurs several years earlier than would be the case without screening.

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