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Does surgery induce angiogenesis in breast cancer? Indirect evidence from relapse pattern and mammography paradox

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Abstract A significant bimodal relapse hazard pattern has been observed in two independent databases for patients untreated with adjuvant chemotherapy. This implies there is more than one mode of relapse. The earliest and most closely grouped relapses occur 8–10 months after surgery for young women with node-positive disease. Analysis of these data using computer simulation suggested that surgery probably instigated angiogenesis in dormant distant disease in approximately 20% of cases for premenopausal node-positive patients. We explore if this could explain the mammography paradox for women aged 40–49: an unexplained temporary excess in mortality for the screened population compared to controls. Calculations based on our data predict surgery-induced angiogenesis would accelerate disease by a median of two years and produce 0.11 early deaths per 1000 screened young women in the third year of screening. The predicted timing as well as the magnitude of excess mortality agree with trial data. Surgery-induced angiogenesis could account for the mammography paradox for women aged 40–49 and the bimodal relapse hazard pattern. According to the proposed biology, removing tumors could remove the source of inhibitors of angiogenesis or growth factors could appear in response to surgical wounding. While this needs confirmation, this could be considered when designing treatment protocols particularly for young women with positive nodes. It reinforces the need for close coordination between surgical resection and ensuing medical intervention. Women need to be advised of risk of accelerated tumor growth and early relapse before giving informed consent for mammography.

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Introduction

Breast cancer is a worldwide major health concern. While there have been reductions in mortality in recent years, progress is far too slow. In the US in 2005 it is estimated that there will be 212,930 new cases of breast cancer and 40,870 deaths from the disease.[1] Therapy has proven to be only partially effective in reducing death rates with little optimism until recently that major improvements are possible. The great hope for 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 avoid a bias, analyses are done based on invitation to screening rather than those who are actually screened.[2] When we discuss screening vs. controls in this document, the proper interpretation should be invited to be screened vs. controls who are not so invited.

As reported by eight randomized trials of breast cancer screening initiated between 1963 and 1980, women aged 50–59 who are screened have an early appearing 20–30% mortality advantage compared to unscreened control subjects. However, when women aged 40–49 years are screened, there is either no advantage or a slight disadvantage for the first 6–8 years of all trials. After that, an advantage begins to appear.[3–12]

When these disturbing results were first reported, a mammographer was quoted to say: ''You start screening and you expect to provide a benefit, and suddenly people die at a higher rate. Now, hold it, we're not going out and killing women. This demands an explanation''.[13] Pursuing this line of thought, if more women died of breast cancer in the screened arms than in the control arms, the trials themselves must be spurious.

Since these trials covered the full range of the cancer experience from randomization of a great many (apparently) healthy subjects to ultimate death from cancer or (much more likely) from any other cause, there are many opportunities to introduce bias or other errors. It was easy to criticize these trials. These data are, however, all we have to modulate our biases.

Following the National Institutes of Health Consensus Development Conference on Breast Cancer Screening for Women Ages 40–49, where all trial data were presented, two different and contradicting reports were published.[14] A consensus panel voted that data do not support a universal recommendation of screening for all women aged 40–49 years and women need to be advised of risks and benefits. A minority report came to the opposite conclusion on the former and agreed with the latter. This was not well received. The director of the National Cancer Institute criticized the majority report and the US Senate voted 98-0 in a non-binding action against it. Fletcher described these events in a colorful comparison to Alice in Wonderland.[15]

The resultant controversy became even more complicated when a later paper raised doubts about the value of mammography screening for women of all ages.[16] Now, in the US, despite conflicting data, screening starts at age 40 or earlier. In most of Europe, it starts at age 50.

It is surprising that during this heated controversy, no attention was paid to the paradoxical breast cancer mortality surge for younger women invited to undergo screening.[11] Meta-analysis of trial data by Cox (shown in Fig. 1) indicates a mortality increase in the screening arms of up to 0.15 deaths per 1000 screened subjects. That begins in the third year (where it is maximum) and extends to the 11th year. While the possibility that random occurrence cannot be excluded, there is a significant excess mortality ratio of screened to unscreened at the 3 year point of 2.4 (1.1–5.4, 95% CI). No other individual years show statistically significant disadvantages as shown in Fig. 2.

Breast cancer is known as a heterogeneous disease. What is causing apparently healthy young women to die from breast cancer three years after the start of screening?

Rather than a controversy, we looked upon this situation as a scientific paradox and research opportunity in that data do not agree with current theories. The scientific method instructs us to reexamine the theory when theory and data disagree.

To help understand this paradox, we studied relapse patterns using a breast cancer database of 1173 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 approximately 1980.

Methods and patients

All patients who from 1964 through 1980 entered into three different clinical trials at the Milan

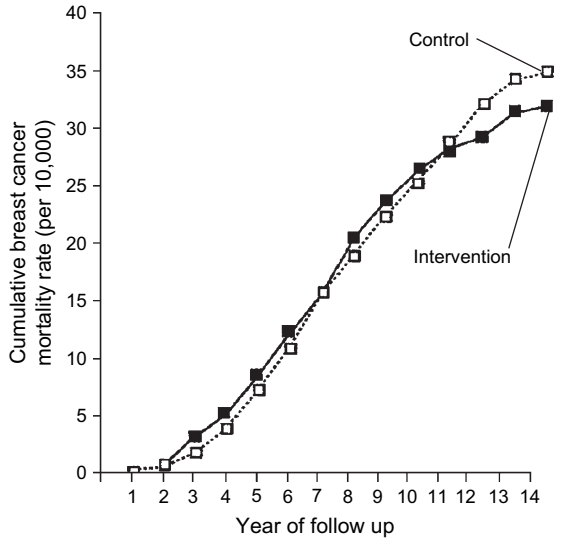

Figure 1 Meta-analysis data for six screening trials for younger women from Cox showing the cumulative breast cancer specific mortality per screened individual and the equivalent mortality per unscreened control. In five of these trials the age at entry was 40—49 years and it was 45—54 years in the other. 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 of approximately 0.15 deaths per 1000 screened young women is typical of results seen in all trials. In conjunction with data shown in Fig. 2, the significant disadvantage first appears 3 years into the trial where it is maximum. Modified from Cox.[11]

Cancer Institute, with mastectomy alone as primary treatment for operable breast cancer, were retrospectively evaluated. Before surgery all patients underwent standard staging: complete physical examination, X-ray study of chest, skull, spine, and pelvis, bilateral mammography, ECG, complete

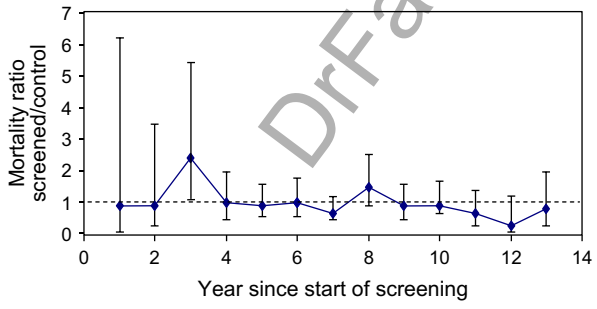

Figure 2 Yearly ratio of mortality in the screened arms to control arms for young women as described in the caption to Fig. 1. There are few events in the first two years accounting for the large error spread. The dashed line at 1.0 represents equal deaths among screened and unscreened controls in any year. The value at 3 years is the only point significantly different from 1.0. Data are from Cox.[11]

Table 1 Distribution within the Milan database 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

hemogram and routine biochemical tests. Primary tumor was treated by radical or modified radical mastectomy and no patient received postoperative radiotherapy or chemotherapy.

Menopausal status was defined as ''postmenopausal'' if one year was elapsed since the last menstrual period. The patients were clinical presentation cases, not screening detected. The number of patients included was 1173, and of these, 520 relapsed. Median age at diagnosis was 52 years with a range of 23—82. Distributions are shown in Tables 1 and 2. The representation of patients in the various tumor size and nodal groupings are similar between pre- and postmenopausal subjects.

Results

These data on 1173 untreated early stage breast cancer patients are mature since the follow-up is 16—20 years. Thus it can be assumed that nearly all relapse events have occurred.[17,18]

Surgical cure rates grouped by tumor size and grouped by the number of positive nodes are shown in Table 3. There is no statistical difference between pre- and postmenopausal patients in their long-term prognosis as grouped by tumor size or number of positive nodes. Thus, surgical cure rates were independent of menopausal status.

Relapse data are presented in Fig. 3 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

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

Table 3 Percentage of patients who eventually relapsed in the mature $N = 1173$ Milan database grouped by tumor size and by the number of positive lymph nodes for pre- and postmenopausal patients

	T1 (%)	T2 (%)	T3 (%)	$N = 0$ (%)	$N = 1-3$ (%)	$N > 3$ (%)
Premenopausal	41	60	70	30	66	84
Postmenopausal	38	56	62	25	66	84

From a difference of proportions hypothesis test, in each case and overall, there is no statistically significant difference between the two menopausal states in cure rates. Thus if a patient had x nodes positive and y tumor size, the long-term relapse probability was independent of menopausal status.

large bin sizes tend to mask structure. Ten-month bins were chosen to optimize the display of structure in the time dependent data.

The frequency of relapse has a double-peaked distribution. There is a sharp peak at 18 months, a nadir at 50 months and a broad peak at 60 months with a long tail extending to 15–20 years. Patients with larger tumors more frequently relapse in the first peak while those with smaller tumors relapse equally in both peaks. Specifically, for T1 tumors (<2 cm diameter) 50% of all relapses are in the first peak, for T2 tumors 75% of relapses are in the first peak, and for T3 tumors (>5 cm diameter) 83% are in the first peak.

When we compared these temporal relapse data between premenopausal patients and postmenopausal patients, the relapse pattern differed markedly but only in the initial period following resection and particularly so for patients with positive axillary lymph node involvement.[19] That is, the temporal relapse pattern had menopausal status dependent features. In premenopausal patients with node-positive disease, 20% relapsed within the first 10 months following resection. That is a far higher percentage than for any other grouping. For comparison, in that first 10-month period, the relapse rate was five times higher for node-positive patients as node-negative patients.

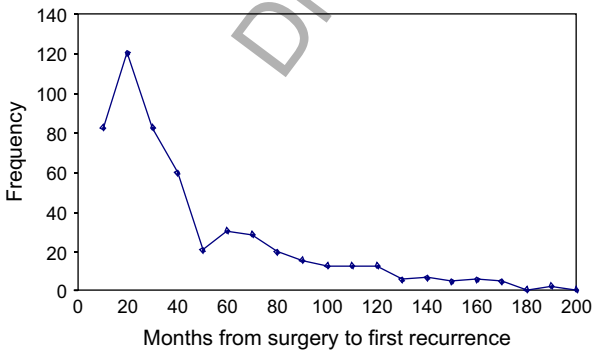

Figure 3 Milan database relapse frequency for distant plus local relapses. Data are grouped in 10-month wide bins.

Also in that same period, the relapse rate was twice as high for premenopausal as postmenopausal patients. So the high frequency of relapse in the first 10 months after surgery was mainly peculiar to premenopausal node-positive patients. See Table 4 for more details.

The Milan data are shown in Fig. 4 in the more usual disease-free-survival format. A subtle flattening at 4 years marks the nadir between the two peaks. That might explain why the bimodal pattern could be so often overlooked. While we have not conducted a thorough literature search, bimodal relapse patterns similar to what is seen in Figs. 3 and 4 have been identified in some (but not all) disease-free survival and hazard of relapse databases for untreated patients.[20–26] A recent study using a San Antonio database that is larger than the Milan database reported that a statistically significant bimodal relapse distribution is identified with similar features.[27] However, using a third database from Villejiuf, another analysis reported no such bimodal pattern.[28] All three databases were tested using different methodologies. From our perspective all these data are not too dissimilar. We have initiated a collaborative project to repeat these studies but with common methodologies.

Predictions from our previously reported computer simulation of the Milan bimodal relapse data are that breast cancer growth often includes periods of temporary dormancy. This is consistent with many reports.[29–38] The second peak is the

Table 4 Percentage of all distant relapses that occur in the first 10 months after surgery in Milan database

	0 nodes positive (%)	1–3 nodes positive (%)	>3 nodes positive (%)
Premenopausal	4	26	28
Postmenopausal	6	12	18

These very early relapses are associated with premenopausal status and positive nodes.

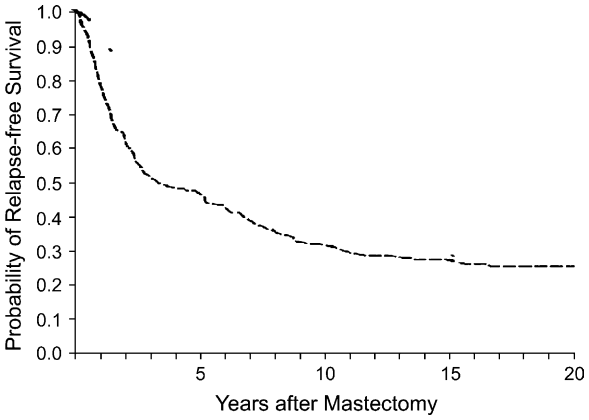

Figure 4 The same data as shown in Fig. 3 but presented in disease-free survival format. The 50-month nadir from Fig. 3 appears as a subtle flattening of disease-free survival before the relapses increase again at the 5-year point. Modified from Bonadonna et al.[59]

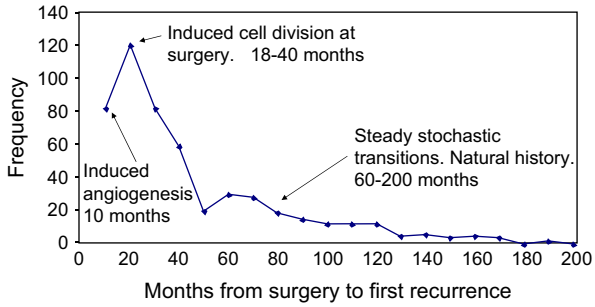

Figure 5 The Milan data from Fig. 3 are shown together with the interpretation resulting from the computer simulation. The main difference between premenopausal and postmenopausal patients is that surgery apparently stimulates angiogenesis of dormant distant disease for a significant fraction of premenopausal and node-positive patients, accelerating disease by a median of two years.

natural history of the disease. These relapses result from steady stochastic transitions from single cells (dormancy half-life of 1 year) progressing to an avascular micrometastasis (dormancy half-life of 2 years) to a growing lesion that eventually becomes detected as a relapse.

The top of the second peak (at 60 months) marks when the benefit of surgery is first seen. That is, the time that it takes a newly seeded malignant cell to become a detectable lesion is so long that the benefit of surgery, that stops the seeding process, does not appear as a reduction in relapses until 5 years have passed in a patient population. This process may be thought of as a metastatic pipeline that is so long that it is fully 5 years after the entrance spigot is turned off before the pipeline is depleted. The first peak is too sharp to be the result of steady stochastic transitions. Some breaking of dormancy had to occur at surgery to explain the first peak. The computer simulation results are shown in Fig. 5 superimposed on the data already shown in Fig. 3.

Two previously unreported surgery-accelerated relapse modes comprise the dominant first peak. This is consistent with some reports for animal models and human cancer.[36–41] In the first 10 months, there are relapses due to avascular micrometastases (preexisting 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 then must undergo a stochastic transition to an eventual growing metastasis. This mode is very common — occurring for 50–83% of relapsing patients increasing with tumor size but independent of age.

With this theoretical insight from the computer simulation studies, we turned our attention to the trials of early detection of breast cancer. Mammography screening was first studied in a large randomized controlled trial in New York (the Health Insurance Plan of Greater New York or HIP trial) in the 1960s[3] and was further assessed in other randomized trials (Malmo, Two-County, Stockholm, Goteborg) in Sweden in the 1970s and 1980s.[4–6] The Swedish trials (excluding a Kopparberg segment of the Two-County study) have been recently reviewed by an Overview Committee that confirmed fundamentally the results previously reported by the individual research groups.[42] Even the results of a UK trial (Edinburgh) were quite similar although this trial has been criticized for a randomization bias.[7,43] Trial results for the New York, Swedish overview and Edinburgh trials are shown in Figs. 6–8.

As already stated, computer simulation suggests that the removal of a primary breast tumor from premenopausal node-positive women triggers the growth of temporarily dormant distant micrometastases in approximately 20% of cases. Since the yield is relatively high at the initial screen in a previously unscreened population, such relapses would appear prominently in a screening trial within 1 year after the start of screening. However, we need to translate these relapse events into mortality events in order to compare to published data from all screening trials. Using published screening yield rates and knowing that survival after relapse is approximately 2 years, we have calculated that this putative surgery-induced growth could explain an additional 0.11 deaths

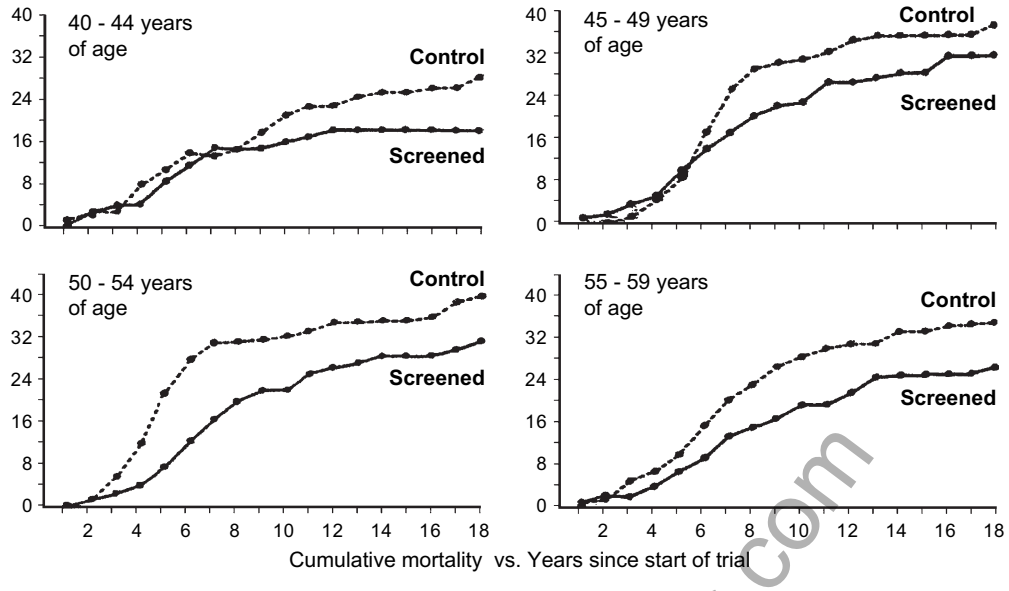

Figure 6 The Health Insurance Plan (HIP) of Greater New York was the first randomized clinical trial of mammography. These cumulative mortality data are modified from Shapiro.[3] The early appearing advantage of mammography for women aged 50—59 is seen together with the delayed advantage for women aged 40—49. A two-year shift to the right in the mortality curve for women aged 40—49 would provide early detection advantage very similar to the 20—30% advantage seen for women aged 50—59.

per 1000 screened women aged 40—49 that occurs in the third year after the start of screening.[19] This is approximately what is observed in trials as can be seen in Figs. 1,7, and 8. The HIP data (Fig. 6) are not published in a convenient format for this comparison, but the excess mortality is quantitatively the same as the other trials seen in Figs. 7 and 8.

While that excess mortality magnitude may seem small, it is comparable to the US age adjusted death rate from breast cancer of 0.24 per 1000 women.

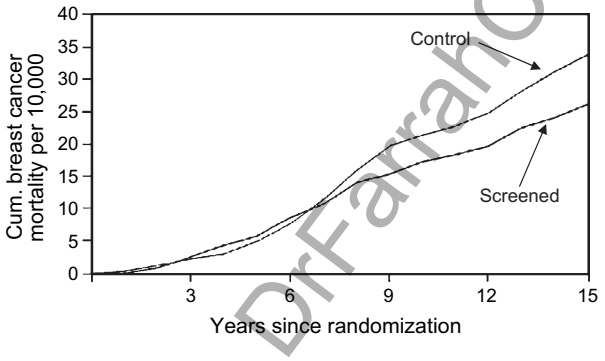

Figure 7 Five of the mammography trials were conducted in Sweden. These data are the combined results of these trials and constitute the bulk of the mammography data. Data for women aged 40—49 are shown. The early excess mortality for the screened population is apparent beginning in the third year and continuing until the seventh year when a clear advantage begins to appear. In the third year, the apparent disadvantage of screening is approximately 0.1 per 1000 screened women aged 40—49, in agreement with calculations. Modified from Larsson et al.[5] As in Fig. 6, a two-year shift to the right would produce 20—30% mortality advantage for women aged 40—49.

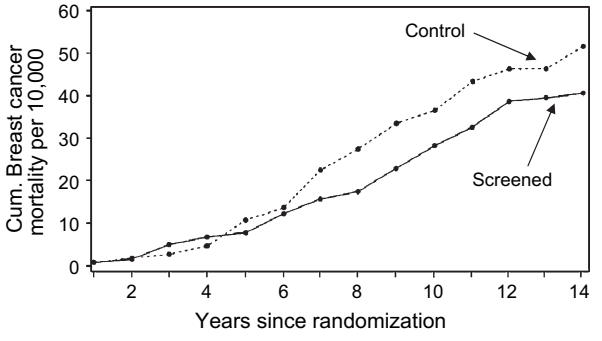

Figure 8 The Edinburgh clinical trial of mammography is shown. This trial has been criticized for a randomization bias. However, it still shows the same pattern as in the HIP (New York) trial in Fig. 6 and the Swedish overview in Fig. 7. The disadvantage to the intervention group is maximum in the third year and is approximately 0.1 per 1000 screened age 40—49 women. Modified from Alexander.[7] As in Figs. 6 and 7, a two-year shift to the right would produce 20—30% mortality advantage for women aged 40—49.

As an additional opportunity to compare the computer simulation with the trial data, we note that a two-year shift to the right of the age 40—49 screened population in Figs. 1, 6—8 would result in mortality advantage to screening similar to what is found in trials for women age 50—59. This is consistent with the previously mentioned two-year acceleration in disease due to termination of dormancy in avascular micrometastases.

We proposed that the biological mechanism of the surgical influence on the metastatic development could be a surge of angiogenesis resulting from the removal of inhibitors, the appearance of growth factors or other such effect. This would synchronize some patients to the time when screening begins — which might explain a subset with homogeneous behavior in a heterogeneous disease as seen in Fig. 2. This mechanism is proposed as an explanation of the paradoxical mammography data for women aged 40—49 and is consistent with the bimodal relapse pattern observed.

Conclusions

We have discussed a bimodal relapse pattern for untreated breast cancer patients and the mammography paradox for women age 40—49. Analysis of these data provides indirect evidence that surgery to remove a primary breast tumor can induce angiogenesis of dormant distant disease. Testing the hypotheses presented here should be a high priority. If they prove to be correct, various approaches could be taken to provide the full benefit of screening to women age 40—49.

Clinical trials could be designed to test whether premenopausal women given an antiangiogenic drug during the critical few days before and after surgery fared better. In addition, surgery-induced angiogenesis in breast cancer is very likely regulated by hormones since it occurs much more frequently in premenopausal patients than in postmenopausal patients. This strongly suggests that hormone related interventions, of which there are several possibilities, might prove very useful.[44—48] If there is concern that an antiangiogenic treatment after surgery could interfere with wound healing, a hormone-based method could be a good option.

An interesting off-topic speculation resulting from this study is a possible evolutionary based explanation of why there is dormancy of distant micrometastases in premenopausal women with primary breast tumors. Before the historical advent of surgical intervention in breast cancer,[49] this effect would allow a female of childbearing age with a primary breast cancer and this trait to live an extra two years and thus have more offspring than if she did not have that trait.

Another off-topic subject is that our conclusions might provide a scientific basis for the often-debunked myth that ''cancer spreads when the air hits it''.[50] The effect we describe would make it seem as though cancer spreads after surgery, while of course the cancer had already spread but only escapes long-lasting pre-angiogenic dormancy as a biological sequel of surgery.

Our results suggest that the biology of early detection is more complex than originally thought.[51,52] Early detection sometimes produces disappointing results as seen in large clinical trials[9] and community-based screening.[53]

The screened population is far from homogenous with regard to risk and benefit of early detection. In light of our findings, we suggest that until this is better understood and resolved, guidelines for early detection of breast cancer for young women be reconsidered. At the very least, women need to be advised of this information as part of an informed consent to mammography.[54] Well-intentioned sweeping this problem under the rug[15,55,56] has not been helpful.

More research is needed to confirm our findings. If true, in addition to the impact on early detection, a comprehensive treatment plan for breast cancer would probably need to take into consideration the possibility that surgery could stimulate tumor growth including inducing angiogenesis.[57,58]

Acknowledgement

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