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Breast Cancer is Usually Described as Uncontrolled Cellular Growth However Recent Research Suggests That is not Accurate – At Least before Primary Surgery

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Abstract

In 1993 my colleagues and I were confronted with data that showed a bimodal pattern for relapse after surgery to remove primary breast cancer. This was quite unexpected since tumor growth was considered to be steady and continuous. Starting with a simple tumor growth model we proceeded to develop a computer simulation that might explain these data. We determined that over half of all relapses in breast cancer are accelerated by something related to primary surgery. These findings have also been used to explain a number of clinical features of breast cancer that were previously thought to be unrelated. This information has been published several times and for full discussion the reader is referred to our reviews. What has not been discussed previously is why we felt confident that these data were of sufficient high quality that we could make such dramatic conclusions. That is, there were literally hundreds of previous reports of breast cancer relapse that did not cite a bimodal relapse. Why is one found in the Milan database and why did we feel confident enough to make strong and counterintuitive conclusions? As final remarks, at risk of pontification, the cancer research community is advised that instead of cancer being categorized as uncontrolled cellular growth, it is mostly quiescent at least before primary surgery. The cancer research community's emphasis on discovering cancer growth pathways and how to block these pathways may be misdirected. Thus it is recommended that cancer research be redirected towards understanding why and how cancer is restrained before surgery and how that state may be retained for indefinite periods of time to avoid relapse.

Introduction

In 1993 my colleagues and I were confronted with data from two countries that showed a bimodal pattern for relapse after surgery to remove primary breast cancer. This was quite unexpected since tumor growth was considered to be steady and continuous. Indeed, the prevailing theory was that tumor growth started exponentially and gradually slowed as the tumor enlarged as mathematically described by the Gompertzian equation. The bimodal relapse pattern that we observed was not explainable with a continuous growth theory.

Relapse data from the Milan National Cancer Institute which we have analyzed in detail may be seen in our reviews [1,2] especially the 2008 document. One of my colleagues Romano Demicheli MD, PhD has long been associated with that group. Also discussed in our reviews is how these data can explain a variety of clinical observations. These reviews are available free online so there is no need here to repeat that discussion. Rather what I prefer to discuss in this document are general comments about quality in breast cancer databases and how a researcher might decide if a particular database is accurate enough to analyze in detail and follow up any anomalous findings to their conclusion even if these findings are unexpected. Finally, at the risk of pontification, I will conclude with recommendations to the cancer research community.

Methods and Materials

Since relapses in breast cancer have been studied for many years by many groups and these Milan data were so contrary to expectations, it is a fair question to ask how reliable these data are. Why did a bimodal relapse pattern present itself in these data and not in any of the literally hundreds of previously published relapse data? I don't want to mention names to embarrass anyone but I have seen breast cancer database problems that at the least waste investigator's time and money and at worst produce errors or turn what should be arguments about the biologic interpretation of data into arguments about whether trials conducted years ago were flawed. With this in mind, what can go wrong and what can be said of the Milan database?

Results

Since the patients were first treated in Milan over 20 years ago, these data were under the control of Pinuccia Valagussa. The clinician who directed the therapy was Gianni Bonadonna, MD. I have heard both of them speak to large and appreciative audiences at major oncology conferences. I have also visited their organization on a number of occasions and personally know all the professionals involved. There are many complex steps in the diagnosis and treatment of a cancer patient and thus many opportunities for imbalances or errors to appear in different arms of a trial. The Milan database manager impresses me that she would be the first person to know of a potential problem and get on a phone or get on a train to investigate and resolve the problem.

There are errors that can creep into a database that can produce less than reliable data for a disease that runs its course in several decades. As can happen, patients will relocate, physicians will retire, database managers and workers will change jobs or computer systems,

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patients will not completely obey physician directives, and patients will change doctors. The patients in that part of the world rarely change residences so they are less often lost to follow-up and also they are often characterized as being compliant with physician directives.

To illustrate what problems can happen with breast cancer databases I will relate some illuminating personal experiences. I was Visiting Professor at University of Texas – San Antonio for about 6 months in 1988 in the late William McGuire's department. I was there alternate weeks and would return home to my family in Colorado Springs, Colorado and my office at University of Colorado – Colorado Springs. My project in Texas was to make a computer simulation of breast cancer data that included the effect on tumor growth and relapse events from progesterone and estrogen receptors. They had a 57,000 patient database that they had developed over years of effort. It was a very valuable resource since frozen specimens were available and it was justifiably carefully controlled. Naturally enough they were concerned that their database could be passed on to other groups who might be competitors in pursuing grants. Thus they did not provide the entire database to me. Rather one person was directed to give me a sub-file with only the information I needed to conduct my project. This was done and I had a file with 57,000 patients and only the necessary times and clinical data. I had access to a Cray supercomputer at the University of Texas main campus in Austin. I worked diligently for a number of months but was not getting good results. The error rate between predictions of relapse events and actual outcomes was over 10% which was poor in everyone's opinion – mine included. One day by accident we discovered that there was a far better correlation of the patient relapse events with the identifying number of the patient in the database. In pursuing this unexpected result, we eventually determined that one of the columns provided to me was mislabeled. One column title was "date of relapse" when it should have been "date of last visit to physician". With the correct column label, the error rate in the next simulation using the Cray supercomputer was about 2%, a much more satisfying value.

Simultaneously, while in San Antonio, I wanted to learn more about "nitty-gritty" details of how a breast cancer database is built and maintained. I spent time with the 5-6 young women who were doing data entry. This was a lowly lighted room with each person sitting in front of a computer and using a telephone to call physician offices to obtain clinical data for each of the 57,000 patients who were all over the US. Each of the women was very dedicated and they knew how important their data were in Dr. McGuire's projects. Each person had a number of sticky notes pasted on the wall in front of her reminding her to call such and such a physician's office on such a date to get some needed data. In talking to the women it was apparent that they were not paid well and were mostly wives of soldiers stationed at Fort Sam Houston. There was steady turnover as husband-soldiers were transferred to different posts. It was impressed upon me how easily things could slip through the cracks with such a system despite workers' best intentions and dedication.

Let's contrast that experience with the Milan data. When I was initially studying the data from Milan, I noticed some apparent anomalies such as a few patients had died a short time before they are listed as having a relapse. I inquired about this and an answer was received (by fax in those days) very shortly thereafter. Ms. Valagussa's explanation was that the death dates were taken from hospital records while the relapse events were taken from clinician's records. This was understandable and furthermore told me she was very familiar with these data and that no one had gone over them sanitizing them and removing data that in their opinion were in error. These were raw and reliable data which was exactly what I wanted. I was quite convinced that these data could be used with confidence to conduct analysis.

Since these data were inconsistent with Gompertzian kinetics, Dr. Demicheli and I naturally were curious what other mathematical description would better describe breast cancer growth. I had used computer simulation in the past to study some problems in oncology and in physics which was my formal educational background. Dr. Demicheli in addition to having an MD also had a PhD in physics. His early background in the medical field was to study growth of tumors in animal models. We intended to develop a computer simulation of tumor growth using these data that might help us understand how breast cancer grows in patients. At one meeting in 1994 or 1995 in Milan shortly after Ms. Valagussa placed a 3.5 inch computer disk with the Milan data in my hand, Dr. Demicheli and I discussed what general form tumor growth we should consider as possible. We were not thinking of how a normal cell becomes malignant but rather once that transformation happens what would happen afterwards. We decided that the most general form would be that a single cell might not immediately begin dividing. It could remain in that state for a variable length of time before it divides. When this growth occurs it can proceed until the micro-deposit needs a blood supply to deliver essential molecules and remove waste products. We were fully aware of the angiogenesis studies of Judah Folkman at Harvard.

According to Folkman's research the initial formation of a blood supply to a cancer deposit may not be immediate. It was known that micro metastases of a mm or so in diameter consisting of approximately 1,000,000 cells could remain at that size for a variable period of time with balanced division and cell death resulting in a more or less stable configuration. Once vascularization occurs, growth is unlimited.

The results of these simulations have been reported a number of times previously so there is no need to list all details. Rather I will briefly summarize the findings and then, providing some new information, indicate how these may help explain one clinical feature of breast cancer.

The bimodal relapse pattern has now been identified in 20 separate databases from US, Europe and Asia. There is a broad peak in relapse hazard centered at about 5 years post surgery and extending to 15-20 years. There is an early wave of relapses in the first four years. Under careful examination, the early wave consists of two separate groupings at 10 months and at 30 months. The simulations showed that the late relapses were the result of steady stochastic transitions from single cells to avascular micro metastases and then to growing lesions. The 30 month events were cells that were not growing prior to surgery and were induced somehow into division by something related closely in time with surgery. They then progress through angiogenesis stochastically and growth until detection as metastatic relapses. The 10 month events were mostly confined to premenopausal patients with lymph nodes positive for cancer. These earliest relapses were apparently dormant avascular micro metastases that were induced into angiogenesis by something timed very close to surgery.

In terms of relative quantity of each of these events, the early relapses were over 50% of all relapses and this percentage increased

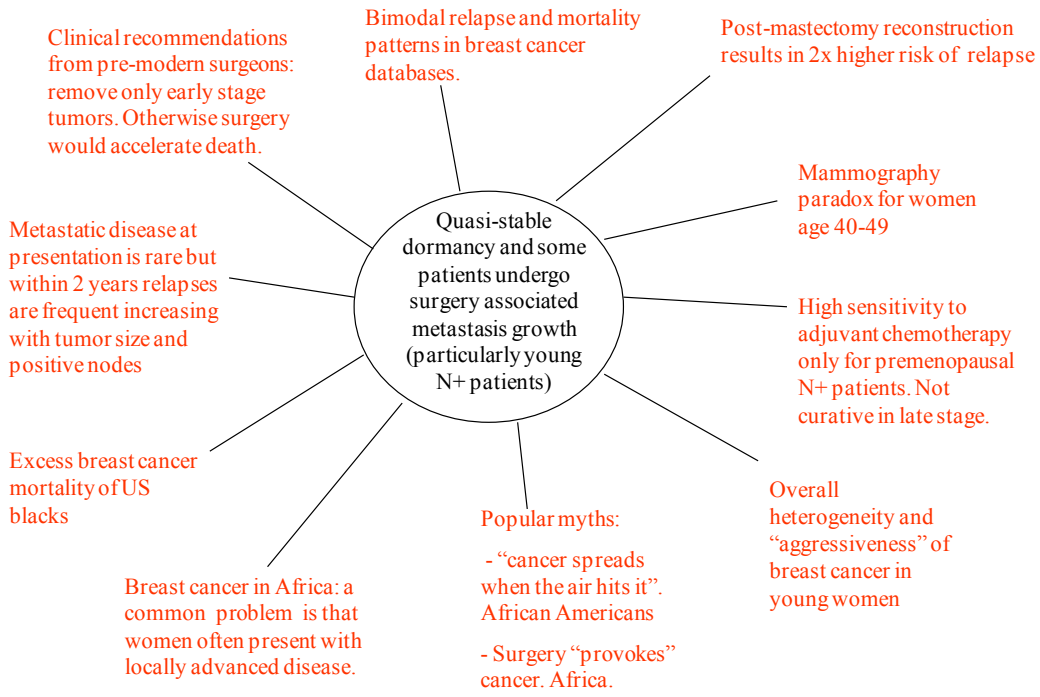

Figure 1: We have suggested that surgery kick-starts growth of dormant micro metastases. This effect increases with primary tumor size and in particular surgery induces angiogenesis in 20% of premenopausal node-positive patients. This one hypothesis seems to explain a variety of previously unconnected effects in breast cancer (1).

with tumor size. For the worst prognosis patients with many positive nodes and large tumors, 80-90% of relapses are in the 4 years or less category. The 10 month events were approximately 20% of all relapses for premenopausal node positive patients and were 2:1 premenopausal to postmenopausal and 5:1 node positive to node negative.

The clinical features that we have been able to correlate to these relapse patterns are shown in Figure 1. See our previously published reviews for detailed discussion of this figure. In this report, I will only discuss a possible relation between the use of adjuvant chemotherapy and the bimodal relapse hazard presented above. When adjuvant chemotherapy was first used in order to prevent metastatic relapse, it was found beneficial for premenopausal node positive patients. The 1980 and 1985 NIH consensus conferences recommended adjuvant chemotherapy for premenopausal node-positive patients. Later careful analysis showed some but less benefit for other patient categories. Quantitatively, the curative benefit of adjuvant chemotherapy is 12% for premenopausal node-positive patients and 2-6% for all other categories [3].

According to Luo et al. [4], "The two mainstay treatment options for cancer today—chemotherapy and radiation—are examples of agents that exploit the enhanced sensitivity of cancer cells to DNA damage. Despite all of our knowledge, however, we still do not have a clear molecular understanding of why these agents work to selectively kill tumor cells and, conversely, why they eventually fail." So it may be stated that molecular biology might need to study tumor kinetics to augment their other scientific tools.

From the perspective of the bimodal relapse patterns discussed here, it is reasonable to consider that since adjuvant chemotherapy by and large interferes with DNA replication for cell division, it would only be effective if cancer cells were actively dividing. We have noted that micrometastatic tumor growth is most pronounced after surgery for premenopausal node positive patients as a result of surgery-induced angiogenesis. Just post surgery is when adjuvant chemotherapy was empirically found to be most effective. The correlation is strong and quantitatively consistent. This information is presented to emphasize the importance of knowing how tumors grow when conducting cancer research.

Breast cancer is widely considered to be uncontrolled cellular growth. Thus, cancer research currently is mostly focused upon identifying growth pathways and then developing therapies that can block these growth pathways. This strategy assumes tumors are always growing and if that growth could be stopped, patients will benefit. But that assumption is wrong at least prior to surgery according to what I report here. Prior to detection and removal of primary tumor, metastatic disease is mostly quiescent and would be quite non responsive to therapies that interfere with cell division. It is only after primary removal that growth is uncontrolled. The main point I wish to make in this paper is that much of cancer research may be misdirected and working on the wrong problem. Breast cancer research should instead be redirected towards understanding why and how cancer is restrained before surgery and how this quiescent state may be retained for extended periods of time to avoid relapse. As an indication of what may be a more productive path, consider our most recent development [5].

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