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COMMENTARY



RE: Reflections on screening mammography and the early detection of breast cancer

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I welcome this opportunity to comment on the piece by Dr. Steven Narod in this issue of *Current Oncology*. His commentary systematically responds to, and rebuts, the near-hysterical reactions to the recent publication of the 25-year follow-up results of the Canadian National Breast Cancer Screening Study[1]. I admire his restraint in the face of criticisms that go way beyond the boundaries of polite scientific disputation.

Much of the criticism the authors of the trial have faced goes so far as to accuse them of being guilty of scientific misconduct and fraud. Those charges are libellous, but I'm sure that Narod *et al.* are wise enough not to resolve their differences in a court of law, but simply to open their books to scientific scrutiny, in a way that fair-minded clinicians can judge who are the real culprits. Narod has achieved precisely that end in his timely and measured response. My only criticism is minor ... in that he doesn't go far enough. For example, it could easily be pointed out that the results of the National Breast Cancer Screening Study sit comfortably within the confidence intervals of a Cochrane Collaboration overview of the screening trials, with no hint of heterogeneity[2]. If anything, the trial in that overview that is closest to being an outlier is the Swedish two-county trial, whose authors are the shrillest of all the critics[3].

The debate is so polarized that, leaving aside possible conflicts of interest, the only assumption that can be made is that the clash is one of ideology rather than scientific discourse. In other words, the true believers in the screening dogma will never be persuaded of the error of their ways by data alone, and so when facts don't fit their prejudice, they resort to *ad hominem* attacks.

I was one of those who established the first screening centre in London and South East England in 1988, but as an open-minded clinical scientist, I allowed the emerging new data to change my mind. With all due modesty, that is what is called an expression of scientific integrity. Of course, as Narod points out, the prolonged and futile debate merely inhibits real progress on the subject. The importance of breast screening programs lies not in their success, but in their failure. As Huxley put it, "The tragedy of science is the slaying of a beautiful hypothesis by an ugly fact."

The national breast screening programs around the world have provided us with a natural experiment of the greatest historical importance, not because of their success in reducing breast cancer mortality, but because of the observations that have emerged concerning overdiagnosis of the disease[4,5]. About two hundred years ago, cancer was defined by its microscopic appearance. With the discovery and use of the modern microscope, the nineteenth century saw the birth of scientific oncology. Rudolf Virchow, often called the founder of cellular pathology, provided the scientific basis for the modern pathologic study of cancer[6]. As earlier generations had correlated autopsy findings observed with the unaided eye with the clinical course of cancer one hundred years earlier[7], so Virchow correlated the microscopic pathology of the disease. However, the material he was studying came from the autopsies of patients *dying* from cancer. In the mid-nineteenth century, pathology correlations were performed either on cadavers or on living subjects presenting with locally advanced or metastatic disease who were almost always predetermined to die in the absence of effective therapy. Since then, and without pause for thought, the microscopic identification of cancer according to those classical criteria has been associated with the assumed prognosis of fatal disease in the absence of treatment.

A syllogism at the heart of the diagnosis of cancer therefore runs like this: People frequently die from malignant disease. Under the microscope, this malignant disease has many histologic features that we will call "cancer." Ergo, anything that looks like "cancer" under the microscope will kill you. The screening debacle therefore suggests that some of the earliest stages of "cancer," if left unperturbed, will not progress to a disease with lethal potential. Those pathologic entities might have microscopic similarity to true cancers, but their appearances alone are insufficient to predict a life-threatening disease.

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Conventional mathematical models of cancer growth are linear or logarithmic—in other words, completely predictable at the outset. They predict transition from *in situ* phases to early invasive, and from early invasive to late invasive over time. Most natural biologic mechanisms are nonlinear or are better described by chaos theory[8]. Prolonged latency followed by catastrophe should not be all that surprising. We accept the case for prostate cancer, because we know that most elderly men will die *with* prostate cancer *in situ* and not *of* prostate cancer. In fact, the United Kingdom's national prostate-specific antigen screening trial (PROTECT) is predicated on that fact, with two *a priori* outcome measures defined: deaths from prostate cancer, and the number of cancers over-detected and treated unnecessarily[9].

Next, it is worth noting that, contrary to all common-sense predictions, the increased detection rate of ductal carcinoma *in situ* has led to an *increase* in the mastectomy rate for the screened population[4,5]. Up to 45% of women with a screen-detected case of ductal carcinoma *in situ* end up undergoing mastectomy because of the multicentricity of the disease[10]. And yet the paradox is that clinically detected multicentric invasive breast cancer is relatively uncommon[11]. Surely that is proof enough that at least half the foci of ductal carcinoma *in situ* will regress if left alone; of course, determining which half remains the problem.

In conclusion, then, it can be stated with a great deal of conviction that a large proportion (on the order of 50%) of screen-detected (preclinical) foci of breast cancer are not programmed to progress if left unperturbed. That observation is of seismic importance and could set the agenda for breast cancer research into the next decade. The choice to ignore those observations, either because they do not support personal prejudice or because of some sleazy political agenda, will result in our community missing an opportunity of a lifetime—and that would be unforgivable.

Narod is to be congratulated for his systematic and robust rebuttal of the unjustified attempts to destroy the credibility of the Canadian trial by a small group of vociferous critics who provide a background noise so loud that it nearly drowns out the true signal of the 25-year experiment of population screening for breast cancer.

"There's non so blind as those that will not see."
— Jonathan Swift, *Polite Conversation*

CONFLICT OF INTEREST DISCLOSURES

I have no financial conflicts of interests to declare, but some might judge that, as a long-time critic of mammographic screening, I might look upon Narod's commentary with favour.

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