Authors respond to controversy surrounding breast cancer study

We published a paper on September 13, 2005 in the International Journal of Surgery that discussed our research in breast cancer.1 As our work provided a new perspective and possible explanation of a subject steeped in controversy for a decade, the Journal issued a press release, as did the home institution of the lead author. This was widely reported in the medical and lay press including interviews and comments from one or more of the authors and, for balance in reporting, contrary views from scientists or physicians were often included (see Table 1). We want to take this opportunity to discuss the resulting favourable and unfavourable comments including the letters to the editor published in this issue of the IJS and to provide our own comments on this episode.

Much of the criticisms state that our paper does not prove its case. This is a very important issue as it involves the quality of the discussion from two points: the logic of our arguments and the level of understanding of these by the discussant. As for the first point, we believe that we should not be “interpreted” and that only our stated remarks should be attributed to us. We never argued that we were providing some “proof” of something. Our paper simply suggests a possible biology-based explanation of clinical observations, and no statements about “proven hypotheses” were reported.

Regarding the second point, we never tire of repeating what all researchers know:

It is virtually impossible to prove that a given model is true, models can only be disproved when they result in significant departure from observed findings.

We wish to affirm here that if our explanation will be proven unfounded (this might be done), we will reject it and we will accept a better one. This is the way by which science moves forward.

Critics frequently noted that breast cancer in young women is more aggressive and that is probably the reason for the early relapses among women aged 40–49 years. The point is not to deny that this “aggressiveness” occurs, the point is “Why?” And “Why premenopausal women?”. We suggested2–6 that “aggressiveness” is the putative result of surgery-induced angiogenesis. Since 20% of young women with node-positive disease would relapse within one year of surgery in absence of chemotherapy, that is certainly an expression of aggressive behaviour. We suggest that this is ordinary tumour growth but kick-started out of dormancy by surgery. Furthermore we suggested that it happens among premenopausal women because of their hormone milieu4,5 and that a further factor may play a role i.e., timing of surgery in the menstrual
Table 1  A table of the responses from researchers and clinicians published in the media

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<th>Person commenting</th>
<th>Publication/source</th>
<th>Their comments and authors reply (in italics)</th>
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<td>Michael O'Reilly, MD Anderson Centre, Texas, USA</td>
<td>Wall Street Journal, 13 September 2005</td>
<td>…animal data suggest that surgery-induced angiogenesis exists, and could be a factor in early relapse. But it still wasn’t clear whether the phenomenon worked the same way in every cancer, how to identify at-risk patients, or even whether surgery-induced angiogenesis was the only explanation. “It may explain the phenomenon in some patients but not all of them,” (These points are well taken. Dr. O’Reilly was lead author of the Cell 1994 paper documenting surgery induced angiogenesis in the Lewis lung model.)</td>
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<td>Robert Smith, American Cancer Society</td>
<td>WebMD Health, 13 September 2005</td>
<td>Don’t believe any of this. The idea that surgical interruption of the tumor bed will cause death this rapidly just does not make sense. The idea that women became worse after surgery may stem from the fact that their prognosis may have been poorer to start with since young women tend to get more aggressive cancers. Retsky et al. misread the trial data. Retsky et al.’s data are based on observations from long ago, when breast cancer screening was in its infancy. (In the editorial, we address some of the issues raised by Drs. Smith, Kopans, Borgen and Love.)</td>
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<td>Daniel Kopans, Massachusetts General Hospital, USA</td>
<td>Boston Globe, 13 September 2005</td>
<td>If we discourage women from getting breast cancer screening, significant gains that we have made will go down the tubes. (and from Wall Street Journal)... The number of cases... are too small to permit accurate analysis. The study is mostly theory and hypotheses that could scare people from getting mammograms out of fear that the treatment will kill them.</td>
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| Patrick Borgen, Memorial Sloan Kettering Cancer Center, USA | Boston Globe, 13 September 2005                          | "The idea that surgery could cause cancer to spread originated in animal studies that were first conducted about 15 years ago. Some of these studies suggested that cancer cells that have metastasized ... could begin to grow once the primary tumor is removed. Others suggested that surgery might even cause the spread of cancer. But what is true in animals is not always true in humans."

"...it’s impossible to say that the surgery itself was responsible for the recurrence and not some other factor, such as the timing of the surgery, hormone levels, if mammography detected the cancer, or whether treatment included chemotherapy and/or radiation. Also, it is well recognized that young women tend to have tumors with more aggressive characteristics than those that appear in older women, which could influence the findings as well. ...it is very critical that news stories make it clear that this particular study is pure conjecture. The last thing that I would want to hear is that women are not getting surgery to remove breast cancer tumors because they are afraid the surgery will cause the cancer to spread..."

Hazel Thornton, University of Leicester, UK          | Editorial in this issue of the IJS                    | Letter questions decision making process and the advisability of issuing a press release (We address these serious and valid questions below). |

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...one of the most explosive and controversial papers to appear in the medical literature in recent years ...
cycle might modulate the tumour–host relationship and ultimately the disease outcome. In other words, we suggested a biology-based conceptual model by applying to women some facts and mechanisms incontrovertibly demonstrated in animal models, such as tumour dormancy, surgery-driven tumour growth acceleration, and angiogenesis linked to sex hormone correlations. Even if humans are not mice and we are well aware that what is true in animals is not always true in humans, we are definitely persuaded that we share most of our biology with other mammals and that, as "Natura non facit saltus", it is perfectly justified to do this. Obviously, confirmatory data should be looked for and found in breast cancer patients. Anyway, corroboration of the general correctness of our hypotheses is to be seen in many recent publications. For example, persistency of breast cancer cells in bone marrow or in blood months and even years following primary tumour surgical removal have been documented. Angio-active molecules have been observed to wax and wane within each menstrual or estral cycle. Moreover, the failure of continuous growth to explain clinical findings, such as breast cancer local recurrences, and the need to assume some tumour growth interruption, were confirmed a few years ago.

About the possible explanation of the mammography screening paradox in younger women that we proposed, the first point is the occurrence of the phenomenon. Some have denied the occurrence of an early mortality excess for younger women and suggest that it represents a statistically insignificant artefact. We do not have a fidelistic attitude towards the p-value from either univariate or multivariate analysis but wish to emphasize the fact that the early mortality excess of invited women is documented consistently across screening trials, countries and time, supports its clinical and scientific significance. The second point is to agree that the surge in mortality at the third year is very difficult to explain if tumours are autonomous, even by recourse to the heterogeneity of breast cancer. We state that it would not be possible unless something synchronized screened young women and initiated sudden tumour growth. Our study of the Milan breast cancer database strongly suggested that something near the time of surgery induced angiogenesis in 20% of premenopausal women with node positive disease. With that...
assumption, we were able to calculate the result of this in a trial of early detection of breast cancer. That turned out to be 0.1 deaths per 1000 screened young women in the third year. That is the same value that is seen in the trials. This would be a temporary effect (concerning the trials — obviously not the affected individuals) and eventually it would appear that screening reduced mortality. This is also seen in the trials. We were very impressed with the meta-analysis data from Cox that were based on over 800,000 person-years of experience in both the intervention arm and the control arm. We called this indirect evidence but, based on our findings, that was a conservative statement and we think far stronger than pure conjecture.

Most criticisms came from physicians involved in mammography screening, who stigmatized any idea of reconsidering screening guidelines for young women by stating that the paper will frighten young women into avoiding mammography or, from bad to worse, into avoiding surgery to remove breast cancer. In the paper, we called for the reconsideration of guidelines for early detection of breast cancer and suggested that, at the very least, women need to be advised of the information presented. Obviously, we were not addressing this to lay persons but to specialists and we are very surprised at their foreclosures of any possible doubt about a subject that in the past had such a wavering course.

To reconsider does not mean to change, but only to take into account some other point of view to verify whether we are doing the right thing. In our opinion, as each man and woman is land lord of his or her own life, he or she is entitled to have all relevant elements to make decisions. The majority report and the minority report of the 1997 NIH Consensus Conference strongly disagreed on the key recommendations but both agreed that women needed to be advised of the risks and benefits of early detection. Anyway, after seeing the widespread publicity occurring, we took care to clarify that at present we are certainly not recommending any change in clinical practice but that this topic needs to be readdressed on a scientific level. We did this on our own volition. Our would-be censors are concerned that women will not understand these results and take inappropriate action. These criticisms are condescending to women implying that they are not capable of making appropriate informed decisions. We find these criticisms to be wrong but we are well aware of the technically challenging discussion and emotional climate surrounding this topic. However, we wonder, how should a scientific minority behave? Should it be silent? The minority opinion group at the 1997 NIH Consensus Conference was not. Is science a question of votes?

It is proper to address the question of the advisability of issuing press releases, mainly when the press shows the trend to sensationalize the conclusions and when errors in reporting cannot be avoided. We published papers in the past that discussed the possibility that surgery could induce angiogenesis, mostly in premenopausal patients with node positive disease, and that this would explain the mammography paradox. The hypotheses are testable and the risks of early detection can be eliminated with better understanding and research. But first they need to be discussed. We have been very patient waiting for this study to be debated and have not rushed into issuing press releases promoting our work.

One of us (MR) is a patient advocate on the Board of Directors of the Colon Cancer Alliance. From an advocate/researcher’s perspective, the mammography paradox or controversy is odorous and needs to be properly aired out in public. This was likewise consistent with our intention to fuel a debate about the merit of the scientific proposal. We might have been wrong. Yet, to affirm with certainty that it has been so, we wish to wait for the future scientific debate among oncology researchers.

References


