Does trauma or an intercurrent surgical intervention lead to a short-term increase in breast cancer recurrence rates?

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Background: Several lines of evidence suggest that cytokines released as a result of wound healing might reactivate dormant breast cancer metastases. To test this, we examined if accidental trauma or surgery, unrelated to the original cancer, might stimulate the growth of dormant micrometastases and be related to an increase in the recurrence rate in the period after the event.

Methods: To test this hypothesis, we used data from the ATAC [Arimidex (anastrozole), tamoxifen alone or in combination] trial and coded the data for women who have experienced trauma or surgical procedures unrelated to the cancer. For the initial analysis, we considered recurrences occurring 2–24 months after the traumatic event and also between 2 and 12 months after trauma. In a secondary analysis, we also looked at recurrences in the first 2 months after event.

Results: The hazard ratio (HR) for recurrence 2–24 months after event was 0.96 [confidence interval (CI) 0.86–1.07, $P = 0.48$]; for 2–12 months, it was 0.96 (CI 0.82–1.11, $P = 0.58$) and for 0–2 months, the HR was 0.87 (CI 0.54–1.38 $P = 0.87$).

Conclusion: Trauma was not associated with an increased rate of breast cancer recurrence in the 24-month window after the event in this large study.

Key words: breast cancer, dormant metastases, surgery, trauma
**introduction**

In spite of undoubted progress in treating breast cancer over the past century and a 30% fall in age-adjusted mortality in the UK since 1984, the year of the first world overview of adjuvant systemic therapy, we are still faced with 1.4 million cases and 500 000 deaths from breast cancer worldwide [1], and both incidence and mortality are increasing rapidly in the developing world [1]. Breast cancer is curable for the majority of cases at the early stage of the disease, but much remains to be done before it becomes a fully curable disease.

The treatment of breast cancer has improved as our conceptual understanding of the disease has evolved. Adjuvant therapy has had a major impact on survival and indicates that many treatment failures are due to occult micrometastases that were present at the time of diagnosis. This perception has also led to less aggressive surgical procedures and greater reliance on local excision and now sentinel node biopsies as opposed to full mastectomy and axillary clearance.

Nevertheless, there are major gaps in our understanding of the natural history of this disease. Breast cancer is characterised by a long natural history, especially when the tumour is estrogen receptor positive, where recurrences remain at a 2%–2.5% annual rate for 20 years, despite use of chemotherapy and long-term endocrine treatment [2]. The conventional model of the disease, with micrometastases that grow according to exponential or Gompertzian dynamics, cannot possibly explain this late recurrence rate and adjuvant chemotherapy regimens modelled on these assumptions of actively growing micrometastases have not lived up to their promise.

Another unexplained phenomenon is the high rate of distant recurrence that occurs within 2 years of diagnosis, despite a low rate of metastatic disease at the time of initial diagnosis [3]. The amplitude of this peak depends on the characteristics of the primary tumour, being more pronounced in node-positive and high-grade tumours, but the time of its occurrence appears unaffected by these factors.

Both of these observations suggest that the act of surgery may have an impact on the seeding of new disease or outgrowth of metastatic disease that is already present.

However, achieving local control is important and a meta-analysis examining the effects of radiotherapy and the extent of surgery for early breast cancer on local recurrence and 15-year survival [4] found that for every four local recurrences avoided, one death from breast cancer was prevented. Of interest is one of these studies in which women over the age of 70 were randomly assigned to surgery plus tamoxifen or tamoxifen alone [5]. In this study, there was a much higher early recurrence rate in those who did not receive surgery, which translated into a poorer long-term survival. Of course, there are many possible explanations for this apart from those related to wound healing, such as dissemination of local tumour cells.

A biological model that can explain these observations while accounting for the successes of the past has been developing over the last decade [6]. Stated simply, it proposes that at the time of diagnosis, occult micrometastases are not in an actively proliferating state but in a state of dormancy or dynamic equilibrium [6].

The underlying pathophysiology of this theory (trauma stimulating growth of micrometastases), as elaborated on by Retsky et al. [7], is dependent on two mechanisms: the stimulation of angiogenesis and the stimulation of proliferation. The stimulation of angiogenesis could be due to either the down-regulation of angiogenic factors or the up-regulation of pro-angiogenic growth factors. Both of these effects could then result in the temporary vascularity of dormant micrometastases that would enable them to enter a rapid growth phase [7]. Murthy et al. [8] tested this theory by looking at 1065 women with operable breast cancer, to see if there was any correlation between delayed wound healing and the development of systematic recurrence with a focus on tumour necrosis factor-α, vascular endothelial growth factor, epidermal growth factor, fibroblast growth factor, platelet-derived growth factor and inflammatory cytokines such as interleukins 1 and 6. They found a statistically significant increase of developing systemic recurrence in patients with wound problems compared to those without [hazard ratio (HR) = 2.87 [95% confidence interval (CI) 1.97–4.18]]. Further support was provided by Adelson et al. [9] who compared the effect of fluid from a mastectomy wound with that of fluid from abdominal wounds on the growth of cells. They found that the fluid from the mastectomy wounds stimulated the growth of cancer cells, whereas the fluid from the abdominal wounds did not.

Additionally, Coffey et al. [10] combined clinical evidence from 10 different studies (5 of which were on breast cancer) that indirectly support the theory that tumour removal adversely alters residual neoplastic disease. However, the confounding factors associated with manipulating the primary tumour would not apply once it has been removed and therefore, an examination of recurrence rates following incidental trauma unrelated to the primary treatment would provide a more critical test of the wound healing hypothesis. Here, we examine such data.

**methods**

For the current study, we used data from the ATAC [Arimidex (anastrozole), tamoxifen alone or in combination] trial [11]. The ATAC randomised trial is a large study that compared tamoxifen with anastrozole alone or the combination of anastrozole plus tamoxifen for 5 years in 9366 postmenopausal patients with early breast cancer [11]. The combination arm was terminated after the 33-month analysis when no benefit over tamoxifen was seen [12] and follow-up of this arm was discontinued at that time. Patients were assessed every 6 months for 5 years and then annually for another 5 years. At each visit, the patients were asked if they had experienced any adverse events and details of all medical interventions were recorded.

We searched the trial database to identify women who had experienced trauma or had surgical procedures and computed the HR for breast cancer recurrence in 2- to 24-month and 2- to 12-month windows after a traumatic event. All three arms of the trial were included. This file included all interventions undertaken on all women from the start of the trial in 1999 until 2007, including surgical or accidental trauma. We first excluded all interventions that consisted only of use of drugs and then coded the remaining interventions according to the severity of trauma (major, minor, none). To avoid any confounding with surgery relating to the disease process, we omitted any breast surgery, except for breast reconstructions, which were clearly of cosmetic intent. As there was no precedent for such
a classification, the coding was based on general medical knowledge and surgical experience. The initial assessment by one author (ZA) was cross-checked by a second author (MB) and in most circumstances were in broad agreement. It was decided in advance that those cases of accidental trauma or surgical trauma that required either prolonged general anaesthetic or the risk of measurable blood loss would be categorised as major trauma; cases carried out under local anaesthetic or brief period of sedation and requiring a skin incision or the use of diathermy as minor trauma and all other interventions as non-traumatic. The most common ‘major trauma’ were hip or knee replacements (N = 322), hysterectomy or bilateral salpingo oophorectomy (N = 197) and breast reconstruction (N = 134), while the most common ‘minor traumas’ were non-breast biopsy (N = 295) and diathermy and curettage (N = 231).

The a priori hypothesis tested was based on the assumption that the time lag between the trauma and the peak incidence of recurrence would be the same as seen between primary surgery and the first peak of recurrence seen between 12 and 24 months after diagnosis.

### statistical methods

The data were initially left censored at 2 months after trauma and right censored 24 months after trauma to create a 22-month window in which recurrences were evaluated. A smaller 2- to 12-month window was also examined. The left censoring was to allow time after the occurrence of the trauma for the cancer to develop and become detectable. An interval of 24 months was felt to be a reasonable time for any recurrence of cancer as a result of the trauma experienced, based on the peak hazard for recurrence after the original surgery. As a subsequent exploratory analysis, we also looked at the 1- to 60-day post-trauma window.

The comparisons made were as follows:

- any trauma versus no trauma
- major trauma versus minor or no trauma

Recurrence was modelled using the Cox proportional hazards model with trauma considered as a time-dependent internal binary covariate [12] that was only positive during the post-trauma window. All CIs are at the 95% level and all P values are two sided. All calculations were carried out using STATA (version 10).

### results

In total, there were 14 683 recorded non-drug interventions and 4571 of the 9366 women in the trial had at least one non-drug intervention. A total of 1689 major and 2672 minor traumatic events were identified in 777 (8.3%) and 1188 (12.7%) of the women, respectively (Table 1).

We first compared any trauma (i.e. major and minor) with no trauma and then compared major trauma with minor and no trauma combined.

The results are summarised in Table 2. The HR for major and minor trauma grouped together compared with no trauma was 0.98 (95% CI 0.83–1.15) at 2–24 months after trauma and 0.99 (95% CI 0.80–1.23) for a 2- to 12-month window. The 95% CIs in both cases were relatively narrow and included unity. When major trauma was compared with minor or no trauma, the HRs were 0.90 (95% CI 0.69–1.16) and 0.82 (95% CI 0.57–1.18) at 24 and 12 months, respectively. In addition, no effect was seen in the 1- to 60-day interval (HR = 1.12), but the 95% CIs were wider (0.58–2.15) in this instance.

Similar results were seen when restricted to the higher-risk node-positive patients [HR = 1.03 (95% CI 0.83–1.38)] for any versus no trauma in the 2- to 24-month window. Also, no evidence of an increased recurrence rate was seen if only breast reconstruction was considered as the traumatic event (vs no trauma) (HR = 0.70, 95% CI 0.26–1.86 for 2- to 24-month window), albeit the number of events was small, so CIs are wide.

### discussion

The prediction that trauma might kick-start the rapid outgrowth of dormant micrometastases was derived from a combination of clinical anecdotes, biological reasoning [8–10, 13], and a study in mice that concluded that breast cancer cells can lie in dormancy but can be stimulated to grow by trauma [14]. One study also reported a higher early distant recurrence rate following surgery compared with tamoxifen alone [5]. However, all the above-mentioned evidence is indirect and none of the clinical studies mentioned looked at the effect of trauma per se. In addition, most of the studies reviewed by Coffey et al. [10] compared survival of patients who underwent surgery versus those who did not and looked at the negative effect of surgery on survival, in the context of tumour removal, as opposed to our study, which looked at surgery unrelated to the cancer. The detrimental effects of surgery for the breast cancer could be attributed to several other factors, including dissemination of tumour cells and alteration of the biological properties of the residual tumour cells.

A strength of our study is its size, long follow-up period (9283 women, 1679 major trauma events, 100-month median follow-up) and resulting statistical power. Another strength is the detailed reporting of all adverse events during the active 5-year treatment period and reports of all severe adverse events
and fractures for an additional 5 years. No significant differences were seen in either of these two periods.

The issue of breast reconstruction is an important question and we have separated it from breast biopsies that might have been related to disease status. A recent paper has suggested a long-term higher recurrence rate after delayed large flap reconstruction [15]. In our study, a total of 134 breast reconstructions were recorded, and although there was a non-significantly lower recurrence rate in the 2- to 24-month window after reconstruction, the number of events is too small to be certain about this.

These results indicate that the rate of breast cancer recurrence in the period 2–24 months after trauma is similar to that predicted if the trauma had not occurred. In addition, the CIs were all small and indicating no clinically relevant association between post-treatment trauma and breast cancer recurrence in this window of observation. Thus, other explanations need to be sought for the continuing high recurrence rate in breast cancer patients for up to 20 years after diagnosis. The hypothesis of outgrowth of dormant micrometastases is still attractive, but our data suggest that stimulation as a result of factors associated with wound healing is not likely to be the explanation, and some other trigger is responsible. Another option is that the initial cancer only reflects a small portion of a field of partially transformed cells and late recurrences reflect additional mutations in these partially transformed cells.

conclusions

There was no association between incidental trauma either major or minor and the appearance of recurrent breast cancer in the 2- to 24-month period after major trauma, and so the primary hypothesis of our study cannot be supported.

Thus, the proposal by Folkman [16] that the surgical removal of the tumour might be responsible for the reactivation of micrometastases via a general effect from cytokines associated with wound healing after surgery is not supported by this study, although it is still possible that surgery for the primary cancer could have a detrimental effect in some other way, such as increasing the dissemination of new tumour cells or some other mechanism involving an equilibrium between the primary tumour and micrometastatic cells.

disclosure

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references


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