Karrison et al. (1) retrospectively studied 1547 patients with breast cancer operated on during the period from 1945 through mid-1987 to evaluate the limit of breast cancer dormancy. In the report, the authors stated that they “did not see evidence for a second peak in the hazard curve as reported by Demicheli et al.” (2) and drew evidence for tumor dormancy from the elevation of mortality rates out to 20 years after primary tumor removal and from the detection of new recurrences even after this time. While we agree with the authors’ conclusions about the occurrence of tumor dormancy, we wish to focus on the question of why they did not observe a two-peaked hazard curve, as has been confirmed by other reports (3–5).

In our opinion, the fact that two peaks were not observed could be due to both the chosen end point and to the characteristics of their data base. While the events “first recurrence” and “death from breast cancer” reliably identify patients who are not cured, the combined event “first recurrence or death from breast cancer” is not a useful end point for study of the time-dependent structure of the hazard of each of the two events. First recurrence and death may have different time distributions, and the use of the combined end point may obscure the fine structure of the hazard curve of each event. Moreover, since Karrison et al. showed that an association existed between the time from mastectomy to first recurrence and the subsequent residual survival time, such an association may affect the hazard curve of “first recurrence or death from breast cancer.” Even more confounding noise, masking the time dependence of hazard function, may have resulted from the possible inadequate reliability of their event dating. Indeed, the examined time
period, during which patients underwent their surgical treatment, presumably outside clinical trials, is quite long. Moreover, about half of the patients had some local or systemic treatment in addition to surgery. Last, data were obtained indirectly. We are aware of difficulties encountered when time to recurrence is to be accurately identified or when cause of death has to be labeled. These difficulties even occur for patients entering controlled clinical trials and undergoing direct follow-up in a single institution.

There are other issues to be considered, however. We analyzed the mortality data reported in Table 1 by Karrison et al. (1). To reduce the uncertainties involved in assigning causes of death, we used the life-table method (6) to estimate the yearly discrete hazard for time to death from all causes—i.e., the conditional probability of death within each 1-year interval, given that the patient is alive at the beginning of the interval. Similar analysis was performed for the 1173 patients who underwent mastectomy in the Milan study (2), a population whose first treatment failure was reported to be double peaked. The results are reported in Fig. 1. The quantitative and qualitative similarity in pattern between the Karrison et al. and Milan data is impressive, and the difference in early mortality could reasonably be thought to depend on the absence of American Joint Commission on Cancer stage III (7) patients in the Milan series.

Both curves display an initial, wide peak at about 3 to 4 years and a second, narrower peak at 8 years.

We conclude that: 1) the findings of the study by Karrison et al. (1) should not be considered as contradicting our findings, and, in addition, 2) not just the recurrence hazard curve, but also the death hazard curve might be double peaked.

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REFERENCES


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RESPONSE

Demicheli et al. are quite correct that the vast majority of patients in our series were not enrolled in a clinical trial and that the time period under consideration, from 1945 through mid-1987, was long. Consequently, ascertainment of the timing of recurrences was probably not as reliable as in their series of patients, all of whom were enrolled in clinical trials in Milan between 1964 and 1980. In fact, we noted that in our cohort, 146 of the 647 patients who died of breast cancer did so without a previously detected recurrence. (Presumably such cases were rare or nonexistent in the Milan dataset.) We were, therefore, left with little choice but to define failure as the combined event “first recurrence or death from breast cancer,” and we agree that this combination could have obscured a second peak.

We are likewise impressed by the similar patterns seen in the hazard rates for all-cause mortality between the two studies displayed in Fig. 1. In this case, there is no ambiguity in the timing of events, and both series provide evidence for a second peak in the hazard curve. Clearly, the two series are far more consistent with one another than they are contradictory.

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Fig. 1. Yearly discrete hazard for time to death from all causes for breast cancer patients from the Karrison et al. (1) study (1547 patients) and from the study by Demicheli et al. (2) (1173 patients).