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Editorial

The Usefulness of Screening Data for Studying the Biology of Breast Cancer

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IN THIS issue of the *European Journal of Cancer*, Norden and associates describe biological characteristics of breast cancer which they have inferred from data from the Uppsala screening programme (pages 624–628). Their conclusions seem, at first glance, to support the advocates of breast cancer screening, exemplified in the recent discussion on the cost benefit analysis of breast cancer screening in this Journal [1]. However, the comparison made in the Norden study is not between screened and unscreened populations, but rather a comparison of screen-detected cancers and clinical cancers detected in a screened population. Therefore, the pros and cons of screening cannot be directly examined from this material, and it is correct that the authors focus on biological inference. They conclude that lymphatic spread frequently occurs in the late preclinical period, which certainly does suggest, indirectly, that breast cancer screening may be beneficial.

The patients included in this study were those diagnosed during the first period of a structured screening programme, so that the category of 'clinical cases' was a heterogeneous group composed of real interval cancers, clinical cancers in non-respondents, and clinical cancers in those who had yet to be invited for screening (the latter comprising a substantial number of women). The complexity of the structure of the groups that are compared should be borne in mind in order to prevent misinterpretation of the presented data.

That the screen-detected breast cancer cases in this study, when compared with the clinical cases, were smaller in size, with fewer cases having lymph node metastases, is a logical finding. The correlation of tumour size and nodal status is almost an axiom in cancer biology.

The interesting finding in the paper is the significant reduction of node-positive cases for tumours detected by screening, even when the size of the tumour (and other less important, prognostic factors) were corrected for in the multivariate analysis. The fact that more cases with negative lymph nodes than expected were detected by the screening is a stimulating finding. Many node-negative patients can be cured with appropriate treatment, but if the tumour is left untreated, it may ultimately disseminate and lead to death. Early detection prior to dissemination is crucial.

Node-positive cases, even the few ones with small tumours detected in screening programmes, do relatively poorly.

The important finding of the increased number of node-negative cases within the screen-detected group (after correction for size) will not necessarily lead to lower mortality. It is possible that the excess group of node-negative cases are of a non-aggressive sub-type which does not disseminate even when diagnosed clinically.

The authors suggest a number of factors which may help to explain the extra increased number of node-negative cases in the screen-detected group

(1) A more benign biology with only late node metastases is related to easy visualisation on the mammogram. Moreover, some mammographically occult lesions may be more aggressive with early regional (and distant) spread; such cases will only appear in the clinical case group, increasing relatively the rate of node-negatives in the screen-detected group.

In my opinion, these points have to be treated with caution. Size measurement (essential in this study) can be confusing: tumours with Extensive *In Situ* Component (EIC), which are usually easily detectable by mammographic screening, are frequently reported to be larger than the part of the tumour with metastatic potential. Also, size measurement in the radiologically occult lesions is difficult. Therefore, less or even no excess of node-negative cases might be found in the screen detected group, if calculations are based on revision changed sizes.

(2) Length bias may play some role, with slow growing tumours (the group that is found specifically in screening) metastasising later than fast growing tumours. However, the authors' previously published data show that interval cancers (the group that includes many fast growing tumours) do not have such a poor prognosis.

(3) It is mentioned by the authors that a few patients with small tumours may still present with symptomatic axilla metastases, resulting in more node-positive cases in the clinically detected group, even when corrected for size.

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However, this might explain only a small proportion of the excess number of node-negative cases in the screen-detected group.

An interesting finding by the authors (albeit based on very small numbers) was the increased number of node-negative patients (corrected for tumour size) to be especially evident within those under the age of 50 years, with also an increased detection of ductal carcinoma *in situ* (DCIS). They, of course, realise that this does not support the introduction of screening for this younger age group, since the study also showed that few cases were detected in this age group by the screening programme. Even with a relatively large gain of node-negative cases in the screen-detected group, the benefit of screening for the younger group would still be marginal. The cost–benefit analysis will probably also be negatively influenced by tumour induction by repeated irradiation.

The authors are aware that their conclusions, particularly those related to the extra increase in node-negative cases detected by screening in those under the age of 50 years, lack strong statistical backing. The numbers are small and chance findings in the subgroup analysis are possible. Others have also hinted at similar findings for the younger age category [2, 3].

The study of the Uppsala group is intriguing, and stimulates investigations in similar data sets of other screening programmes.

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