Our series of patients covers a long calendar period and seems to confirm a tendency towards conservative treatment which has gone up to 81% in the past 2 years. Postoperative radiotherapy has also increased to 61%. Although axillary dissection has not given any contribution diagnostically or therapeutically, it was performed in 50% of the cases. This is probably due to the wish to avoid a second operation in the cases when the final histological examination of the lesion indicated the presence of infiltrating cancer. However, our experience also demonstrates that this choice is not correct [7].

The histopathological study of our cases shows a substantial prevalence of mixed forms (39%) and confirms the high percentage of multifocal (60%) and multicentric cases (22%) [11]. The frequency of nuclear grade 3 is particularly marked (76%) in the comedo histological type. The outcome of treatment does not seem to show elements, excluding axillary dissection, that might indicate a different behaviour in the future. Negative events are so few that an actuarial evaluation of the results would not mean anything. Survival does not seem to be affected by the type of surgery performed initially. The local control of the disease is worse after conservative treatment (10 vs. 2.9%). It should be noted that in all cases recurrence was infiltrating.

As regards conservative treatment, contrary to reports from other authors, our experience, owing perhaps to the limited number of cases, is not able to indicate significant elements of risk of local recurrence with reference to the histological type [2–3] or to the use of radiotherapy associated with conservative surgery [5–15]. Our indications as to conservative surgery are, at the moment, strictly related to the size of the lesion and to the possibility of performing a wide excision with free margins with good cosmetic result. Our data do not seem to indicate that the histological type can affect the choice of surgery, while in the use of radiotherapy there may have been a certain selection particularly in the last few years. Surgery without irradiation was advised for patients over 60 years of age, with tumours under 2.5 cm in size, free margin and breast favourable for mammographic examination. This might explain why we have more or less the same number of recurrences in conservative treatment with or without radiotherapy.

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Do Screening-detected Invasive Breast Cancers Have a Natural History of their Own?

L. Holmberg, A. Ekbom and M. Zack

INTRODUCTION

WOMEN WITH screen detected breast cancer have repeatedly been shown [1–7] to have a lower case fatality rate (CFR) than women with breast cancers detected in an ordinary clinical setting. The question here is whether the prognosis of screen detected breast cancer also differs from that of a clinically detected cancer after correction for the length of time by which diagnosis is brought forward by screening (lead-time bias) [8]. Such differences might come about through several mechanisms: (1) periodic screening picks up slower growing tumours more easily than the faster growing tumours; (2) breast cancers with mammographic signs that lead to the detection in screening might correspond with breast cancers with certain favourable histopathological characteristics; (3) the histopathological distinction between malignant and benign may be very difficult for the very small and never before thoroughly studied lesions detected in a screening program; (4) in women with breast cancers detected very early, a substantial proportion may not

yet have a tumour burden large enough to develop clinically important distant metastases; (5) breast cancers detected before they cause symptoms might not have had time to develop as many malignant properties as symptomatic breast cancers; (6) participants in screening programs might have more favourable prognostic characteristics than non-participants; (7) a well-organised screening program may offer treatment programs substantially better than those for patients diagnosed clinically.

We have chosen to discuss these seven different mechanisms separately, since they all involve theories about screening commonly discussed. However, some of them are clearly closely related, and lead to similar predictions. Mechanisms 1 and 2 deal with the logistics of a screening program and how mammography detects lesions. Mechanism 3 deals with the histopathological definition of cancer. Mechanisms 4 and 5 pertain to the tumour biology of cancers detected and treated during their preclinical (but mammographically detectable) phase. Mechanism 6 relates to whether screening participants have one or more prognostically favourable host or other characteristics than non-participants if they acquire a breast cancer. Mechanism 7 postulates that a well-organised follow-up of screening findings at screening could enhance the prognosis for screen-detected cancer patients.

DISCUSSION

1. *Length-biased sampling*

Periodic screening tends to select slower growing cancers, since they stay in a preclinical detectable phase for a comparatively longer period [8]. If length-biased sampling explained the lower CFR in screen detected cancers, the cancer growth rate would have to be directly related to prognosis so that slower growing cancers would be inherently more benign. Theoretically, even cancers that never would have surfaced clinically during the patient's lifetime could be diagnosed. A larger number of cases than expected in the same population without screening would therefore be detected in the screening process ("overdiagnosis"). Furthermore, interval cancer cases, which would contain faster growing cancers would have a more malignant clinical course.

However, overdiagnosis—in spite of being a major theoretical concern—has so far been shown to be of limited importance [19]. The prognosis for interval cancer cases resembles that of cancers detected clinically outside a screening program in most studies [1, 10, 11], thus contradicting the assumption that growth rate directly parallels the biological aggressiveness of the cancer. In one study [5], however, women with interval cancers carried a high risk of dying from their cancer compared with cancers detected outside the screening program. One mechanism that could accommodate for this finding contradicting other study results could be that discussed under Section 2 below.

Length biased sampling may explain part of the difference in CFR between screen detected cancers and others, especially for cases during the first (prevalent) screening round. It cannot, however, explain the persistent reduction in breast cancer mortality seen in the population invited to screening in the randomised clinical trials.

2. *Mammography has different sensitivity for different subtypes of tumours*

Mammography screening could select a less malignant group of cancers if mammographic signs leading to a cancer diagnosis in screening frequently corresponded with a less often fatal histopathological type of breast cancer. High quality mammography with high sensitivity, however, should be able to pick up the large majority of the invasive ductal cancers and it is those with a slightly better prognosis—e.g. mucinous and lobular cancers—that generally have vaguer mammographic signs. However, if the sensitivity in a screening program goes down, and only certain subgroups of ductal cancers may be detected—such as those giving rise to microcalcifications—thus cancers with a low metastatic potential may be diagnosed but more aggressive lesions missed. Under these circumstances, a low CFR among women with screen detected cancers and a high rate of interval cancers with a dismal prognosis would occur.

As with length-biased sampling, this mechanism can explain differences in CFR by screening status under certain circumstances (i.e. if a cancer is diagnosed in screening, in an interval between screening rounds, in the non-compliant group, etc.), but it cannot account for a reduction in breast cancer mortality.

3. *Mammography screening detects lesions that are cancers histopathologically but not biologically*

If clinically undetectable lesions are detected by mammography screening and biopsied, the histopathology of this type of lesion might never before have been described and their behaviour as cancers (for example, their ability to metastasise) and the clinical course of patients with such lesions might be unknown. If most of these lesions called cancers do not behave as cancers, then screening programs would have a high rate of overdiagnosis. The prognosis for screen-detected cases would be expected to be extremely good. However, none of these predictions appears to be true [1–9].

4. *Very small cancers are "localised" only in a clinical sense*

Cells from a breast cancer are disseminated already early into the lymph or the blood flow. In this sense, breast cancer is from early on a systemic disease. From a clinical point of view, however, the earliest time the disseminated cells give rise to distant tumour foci that can grow into clinical overt metastases during the patient's lifetime is of greater interest. If a substantial number of breast cancers in this clinical sense metastasise late in the preclinical detectable phase, a mammography screening may detect some primary tumours before disseminated cells have established viable foci for future distant metastases. An otherwise correctly designed and conducted screening program should thus reduce breast cancer mortality, and this is what has occurred [1–4]. Furthermore, some women should be clinically cured (i.e. never develop recurrences or die from breast cancer). A study of prognostic factors conducted during an ongoing screening program described a subgroup of about 30% of women with stage I cancers who had nearly a 100% relative survival [12]. These women were identified using a prognostic model based on S-phase fraction obtained from DNA flow cytometry, progesterone receptor status and tumour size. Thus, some women with early detected breast cancer might have clinically localised cancer.

Correspondence to L. Holmberg.
L. Holmberg and A. Ekbom are at the Cancer Epidemiology Unit, University Hospital, Uppsala, Sweden; and M. Zack is at the National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control, Atlanta, Georgia, U.S.A.
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5. *Very small cancers do inherently have less metastatic capacity*

Breast cancer may be highly genetically unstable and acquire more malignant properties even during the later stages of tumour promotion. If progression to a more malignant phenotype occurs during the preclinical detectable phase, screen detected cancers would metastasise less often than a comparison group of clinically detected tumours, not only because a smaller number of cells have had time to disseminate, but also because their cell population have less metastatic potential. If this scenario is true, we would expect an ever larger breast cancer mortality reduction than under argument 4 above. However, so far, the reduction of mortality seen in screening studies largely agrees with predictions from looking at the reduction obtained of stage II or more advanced cases early on in the screening programs [1–4]. Data that showed that screening detected and clinically occurring cancers had different setups of tumour markers or that screen detected patients had a lower risk of having axillary metastases given a certain tumour size would indirectly support the theory of a late tumour progression. Earlier studies [13–17] have not convincingly shown major differences in this respect. Data [15, 17] support that prevalent cases detected at the first screening round should be analysed separately, because their results could be heavily influenced by length biased sampling. However, the analyses so far have shown that there are tendencies for the screen detected cases to have more properties generally considered to be more benign [13, 17–19] and detailed analyses of the Swedish two-county study [20] clearly indicates that some tumours progress in tumour grade during the time they are preclinical but detectable with mammography. Further testing of hypotheses related to tumour progression late in the carcinogenesis is important for advancing knowledge both about screening and about treatment of early breast cancer.

6. *Healthy screenee effect*

Participants in a screening program may have characteristics that improve prognosis. They may have a better socioeconomic status with better chances for a healthier life overall and access to more qualified medical care. They may be more willing than non-participants to follow other health recommendations. Surveys summarised by Howard [21] suggest that these self-selection mechanisms occur. Because participants might also have been exposed to other carcinogens, promoters and effect modifiers than the non-participants, they may have different biological determinants for the natural history of their breast cancers.

Non-participants in the randomised screening trials contribute with a higher than expected proportion of the breast cancer deaths [5–7, 17, 22] compared with women with screen-detected cancers. The healthy screenee effect thus appears to operate in breast cancer screening programs. However, socioeconomic factors, patterns of risk factors for breast cancers and tumour characteristics for non-participants have not been studied in detail so far. As in the first three mechanisms considered, the healthy screenee effect cannot explain the reduction in breast cancer seen in randomised trials, since the breast cancer mortality for the whole targeted population whether they participated or not was used as an evaluation criterion. However, a high proportion of non-participants always endangers the overall success of a screening program, and the benefits of such a program could be very severely limited if the non-compliers had both a high rate of breast cancers and a higher breast cancer mortality than the average.

7. *To be diagnosed in a comprehensive screening program might assure high quality care*

A well-organised screening program may be closely coupled to good treatment and follow-up facilities. A woman with a screen-detected cancer should ideally meet surgeons and oncologists specially trained and interested in breast cancer treatment. If she was exposed to an optimal program with psychosocial support already from the start of screening, up-to-date surgical treatment and the best possible adjuvant regimens, this should improve her long-term survival compared with many of today's programs. This would imply that mortality would be less in such integrated programs than where screening was not used. Although this question has not been formally studied, it is at least very unlikely to have been of importance in, e.g. the Scandinavian studies, where accessibility to high quality care has been relatively uniform.

CONCLUSION

Although several of the mechanisms can help us explain differences between screen-detected and other breast cancers, only mechanisms 4 and 5 above can account for reduction in breast cancer mortality in a population where screening is applied. The notion that some breast cancer patients do not establish viable foci for distant metastases until late in the preclinical detectable phase (mechanism 4) is so far the best supported theory. The question whether tumour progression occurs late in the preclinical detectable phase or not is emerging as important, and research in how screening interacts with tumour biology needs further creative study, as do other testable hypotheses that come from the review above.

It is striking how many important questions about screening have been enlightened by the randomised clinical trials, breast cancer being an example of when screening can work and lung cancer an example of the opposite [23]. This underlines the need for randomised evaluations of other, new, screening procedures.

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