Editorial
Overdiagnosis and breast cancer screening

Nick E Day

The Institute of Public Health, University of Cambridge, Cambridge, UK

Corresponding author: Nick E Day, nick.day@srl.cam.ac.uk

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See related review by Moss in this issue [http://breast-cancer-research.com/content/7/5/230]

Screening for breast cancer is now routinely performed in most countries where the disease is common. The benefits of screening have been established and are generally accepted. However, screening does have the potential for harm, the most important aspects of which are overdiagnosis and overtreatment. *Breast Cancer Research* has invited a series of papers to address the component dimensions of the field, and in particular to estimate the extent to which it occurs. The first article in the series, in which Sue Moss reviews overdiagnosis in randomised controlled trials of breast cancer screening, is published in this issue [1].

Screening for cancer is based on the supposition that earlier diagnosis will lead to improved prognosis. Experience of screening for several types of cancer (breast, cervix uteri or large bowel) has shown that on average this will be true, in the sense that groups targeted for screening for these cancers show reduced cancer-specific mortality. However, what is true on average may conceal major differences between individuals. For most cancer types there is a wide divergence of behaviour between individual cancers. Some, usually the most malignant, will be fast growing and less amenable to the benefits of earlier detection, particularly in the context of periodic testing in a mass screening programme; others, often the more benign, will be slow growing and probably successfully treatable whenever diagnosed. Among these slower-growing tumours will be a proportion that were never destined to surface as clinically apparent cancers in the lifetime of the individual. The effect of this heterogeneity has been seen particularly clearly in the early randomised trials of screening for lung cancer, in which despite an increase in the number of early (stage 1) cancers diagnosed on the screened arm of the trial, no reduction in lung cancer mortality rates was seen among those randomised to screening. That is, the cancers preferentially detected at screening were not those that prove fatal. Furthermore, many more early cancers were diagnosed through screening than appeared on the control arm even after extended follow-up. In these trials, screening yielded no benefit but generated considerable harm.

Lesions that are detected at screening but which would not have surfaced clinically in the lifetime of the individual constitute overdiagnosis, the major form of harm associated with screening programmes. The individuals concerned undergo unnecessary further investigations and treatment, with all the consequent side effects, and the health care system has to bear the unnecessary costs. Overdiagnosis arises because histopathology, the current basis for the diagnosis of malignancy, is not a precise predictor of outcome. If tests were available that could accurately predict behaviour – and the identification of such tests should be a high priority in screening research – then the problems associated with overdiagnosis would largely disappear. In the absence of such tests, however, overdiagnosis must form an important component of any cost–benefit assessment. The two factors that need ascertaining are, first, the extent of the problem – in a screening programme, how many lesions will be detected and treated that would never have progressed – and, second, the harm caused to an individual who receives such a diagnosis. Estimating the extent of overdiagnosis presents particular problems. Because, in the usual situation, detected lesions are treated, it will be impossible to tell for any specific individual whether a detected lesion represents overdiagnosis. Any approach to estimating the extent of overdiagnosis in a screening programme must be indirect and must be based on the performance of the programme as a whole.

The first attempt to investigate the extent of overdiagnosis was with cervical cytology screening, in which the large discrepancy between the number of lesions treated, almost all of which were pre-invasive, and the number of cancers that might have occurred in the absence of screening was referred to as the 'yawning gap'. Its identification was used initially in an attempt to discredit cervical screening but was

later recognised as simply a component, albeit important, of the overall cost–benefit balance. The degree of such overdiagnosis has been reviewed in the recent IARC *Handbook on Cervix Cancer Screening* [2]. With cervical cancer screening, overdiagnosis occurs at the pre-invasive stage, when the lesions are relatively easily treated. Prostate cancer screening provides a striking contrast: most preclinical lesions detected by testing for prostate-specific antigen are early invasive cancers, the treatment of which often has major and long-lasting side effects. It has been known for many years that many more men harbour histologically malignant tumours than will ever develop, or die from, clinical prostatic cancer, so that the question of overdiagnosis by screening becomes a major issue, of sufficient importance to inhibit the widespead adoption of such screening. An attempt to estimate the degree of overdiagnosis has been made within the European trial of prostate cancer screening, taking a modelling approach. The results suggest that about 50% of histologically diagnosed cancers arising in a screening programme might not have progressed to clinical cancers within the lifetime of the individual [3,4].

In breast cancer screening, the issue of overdiagnosis is presented descriptively in the IARC *Handbook on Breast Cancer Screening* [5]. This series of papers examines in greater depth a range of issues associated with screening-associated overdiagnosis, including a general discussion from both a biological and epidemiological perspective. Randomised trials of screening provide the clearest evidence from which to estimate the extent of overdiagnosis. A range of approaches are described, including the micro-simulation modelling developed in The Netherlands and used to great effect for prostate cancer screening. However, randomised trials often represent the effect of screening performed under optimum conditions: they indicate what can be achieved. In contrast, in public health terms, what is important is the result of screening when applied on a routine basis. Estimating the extent of overdiagnosis in these circumstances poses separate problems, and the issue is given specific attention. To complement these synoptic, population-based approaches, attention is also given to the process of overdiagnosis itself. Histologically, what seem to be the tumour characteristics that are associated with overdiagnosis? What is the role of ductal carcinoma *in situ* in breast cancer screening, what are the probabilities of progression to invasion over time? Rates of detection of ductal carcinoma *in situ* vary widely between screening programmes; what are the implications for the overall net benefit that the programme yields? Breast cancer screening is a multiphase process, the initial components of which are radiological. To what extent is overdiagnosis an issue for radiologists?

Breast screening is now established in many countries. The issues of current importance are not those referring to whether there is a net benefit, but how screening can be undertaken to optimise the net benefit. A crucial component of this is to understand the phenomenon of overdiagnosis, both quantitatively and qualitatively, so that the associated harm can be minimised. A secondary issue is the question of overtreatment of cancers that would progress but are diagnosed at a very early stage. It is hoped that publication of this series will contribute to clarification of these issues for the improvement of breast screening programmes.

Competing interests

The author(s) declare that they have no competing interests.

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