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Reduction in mortality from breast cancer

Screening and increased use of adjuvants are responsible—adjuvants more so

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The survival of women who will be diagnosed with breast cancer in the United Kingdom and Europe in 2005 is significantly better than that for their counterparts diagnosed in the 1970s and '80s, although five year survival remains lower in Europe than in the United States (79% *v* 89%).[1] What is known about the reasons for these differences, and what could increase survival still more?

Any improvement in survival is unlikely to be attributable to a change in the biological behaviour of breast cancer. It must reflect improvement, therefore, in diagnosing and managing breast cancer, leading to fewer distant relapses and deaths. This could be a consequence of early detection through screening or improved systemic treatment with adjuvants after surgery to eliminate micrometastases and prevent recurrence. However, screening amounts to secondary prevention rather than primary prevention. Delay in diagnosing symptomatic breast cancer is associated with inferior survival,[2] but as no absolute correlation exists between the chronology and biological behaviour of breast cancer, the term early can be misleading. Even patients with small tumours which are node negative may have a poor outlook despite apparently favourable prognostic factors at diagnosis.

The two papers in this issue look at the impact of screening and adjuvant chemotherapy on survival after breast cancer, with follow up of 10 years and 30 years respectively.[3 4] Both approaches have been studied and integrated into service at the same time; we cannot evaluate one without the other.

Olsen and colleagues report a 25% reduction (relative risk 0.7, 95% confidence interval 0.63 to 0.89) in mortality due to breast cancer in the population invited for screening in Copenhagen.[3] The study covered the 10 years after the introduction of mammographic screening in 1991 and compared the population during screening with historical, national, and national historical controls. Significant results were found after six years of follow up. The improvement in mortality was not related to change in systemic treatment. Diagnostic and treatment strategies across the whole of Denmark had been coordinated and standardised by the Danish Breast Cancer Cooperative Group since 1977 and the study data were controlled for time trends and regional differences such as the introduction of screening in other regions of the country.

The size of the benefit attributed to screening in this study is broadly in keeping with reported trials from other northern European screening programmes where screening had been in place for 10 years or more.[5] While showing a reduction in mortality in the screened population, the UK programme acknowledges that most of the benefit could be due to both earlier presentation of symptomatic breast cancer and the uptake of systemic treatment with adjuvant.[5] Although better breast cancer survival between 1990 and 1992 in the United States than in Europe can be attributed to differences in stage,[1] screening has no influence on survival once stage has been taken into account. Furthermore, for both the screened and non-screened populations, adjuvant systemic therapy (both cytotoxic and hormonal) is likely to have an important role in improved survival.

The 30 year follow up of adjuvant chemotherapy with cyclophosphamide, methotrexate, 5-fluorouracil also reported in this issue confirms that relatively short term adjuvant after optimal locoregional treatment for breast cancer is associated with improved survival.[4] The overall 21% reduction in relative risk of death from all causes at 30 years in the Bonadonna study[4] is in keeping with the overview analysis by the Early Breast Cancer Trialists Collaborative Group.[6] The paper's findings are also consistent with improved population survival in Canada following the introduction of systemic treatment according to consensus guidelines for women with node negative breast cancer.[7]

The mainly postmenopausal population in the Bonadonna study benefited from systemic treatment in steroid hormone receptor positive and negative cancers, which is again consistent with the worldwide overview. The introduction of more effective adjuvant endocrine treatment with aromatase inhibitors may reduce the additional benefit that cytotoxic chemotherapy can bring over and above steroid hormone treatment for women with receptor positive cancer.[8–10] This presupposes, however, at least in part, a common mechanism for action. Most women who take part in screening programmes are postmenopausal, and for these women, introducing increasingly effective systemic endocrine therapy for small cancers detected on screening may improve survival further. Similarly, while the paper by Bonadonna proves the benefit of chemotherapy for women with operable breast cancer, the regimen used in that study has been superseded largely by more effective regimens including anthracyclines and more recently taxanes.[6]

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Where next? Identifying more breast cancers at earlier stages with "good prognosis" can make decisions about appropriate adjuvant treatment more complex, bringing a real risk of relative overtreatment of some women. This could be particularly important in lymph node negative and steroid hormone receptor positive breast cancer. Better understanding of the gene expression signatures of breast cancers may lead to new classifications that may have both prognostic and predictive information.[11] A trial is already investigating this approach in premenopausal women, comparing selection by microarray signature against conventional criteria.[12]

Finally, while the work discussed here highlights the improvements in survival from breast cancer attributable to systemic therapy and diagnosis of small, node negative tumours, neither approach affects incidence. The diagnosis of breast cancer, even with a supposedly good prognosis, can be devastating, and we should not lose sight of primary prevention as a real goal.

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Investigating infant deaths

The protocol suggested by the Kennedy report is good, but will it work?

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There is now another "Kennedy report" for paediatricians to consider.[1] This time the chair was Baroness Helena Kennedy QC, the working group was set up by the royal colleges of Paediatrics and Child Health and of Pathology, and the subject was the investigation of sudden unexpected deaths in infants (SUDI). The report recommends a systematic and evidence based protocol for the history, examination, investigation, autopsy, death scene investigation, and subsequent multiprofessional meeting in relation to each death.[1] It also recommends that this should be compulsory, although it doesn't say how that might be enforced. But will it have the desired effect?

The background is several recent high profile cases in the United Kingdom of mothers accused of killing their infants: the quashing of the convictions of Sally Clarke and Angela Cannings; the acquittal of Trupti Patel; and cases such as that of Maxine Robinson, who originally protested her innocence of the deaths of the two children she was convicted of murdering but who this year admitted their murders, together with the murder of her first child.[2] The death of this infant, who died aged 9 months, was originally labelled as a cot death. These cases highlight the widespread problem of the inadequate investigation of infant deaths. Improvements should work both ways: a greater chance of avoiding criminal proceedings for innocent parents (the majority) but also a higher chance of identifying homicide. Whether the criminal justice system is an appropriate place to deal with infant murder is debatable, but the need for a more coherent and evidence based approach to investigating infant deaths is hard to dispute.

Much of the UK evidence base for an improved and comprehensive approach has come from the large scale case-control study of sudden unexpected deaths in infancy conducted by the Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI) in the early 1990s.[3] Helena Kennedy's recommendations bear a close resemblance to those in the CESDI-SUDI report and are explicitly based on the practices that are routine in Bristol and the south west region.

So will the protocol recommended by Baroness Kennedy make a difference? Here we are on uncertain ground. The mere existence of a protocol is not a guarantee that it will be followed, however much it might be "compulsory"; the history of protocolology is one of worthy aspirations that largely fail to change practice in the real, messy world.[4 5] This issue includes data from Sussex that indicate that the messy world has once again triumphed (p 227) [6]. Even in the management of sudden unexpected deaths in infants, trying to change practice needs a whole lot more than a protocol, however much the protocol has been agreed among the different agencies and disciplines.

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