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COMMENTARY

Screening detects a myriad of breast disease – refining practice will increase effectiveness and reduce harm

¹IAIN D LYBURN, FRCR and ²SARAH E PINDER, FRCPath

¹Cheltenham Imaging Centre, Cobalt Medical Charity, Cheltenham, United Kingdom

²School of Cancer & Pharmaceutical Sciences, King's College, London, United Kingdom

Address correspondence to: Prof Iain D Lyburn

E-mail: ian.lyburn@nhs.net

ABSTRACT

For many individuals, the term ‘cancer’ equates to a disease that if untreated will progress, spread from the area initially affected and ultimately cause death. ‘Breast cancer’, however, is a diverse of range of pathological entities, incorporating indolent to fast-growing and aggressive lesions, with varying histological patterns, clinical presentations, treatment responses and outcomes. Screening for malignancy is based on the assumption that cancer has a gradual, orderly progression and that detecting lesions earlier in their natural history, and intervening, will reduce mortality. The natural history of epithelial atypia, ductal carcinoma *in situ* and even invasive breast cancer is poorly understood, but widely variable. We believe that population breast screening methodology needs to change to focus on diagnosis of lesions of greatest clinical relevance.

COMMENTARY

There is a growing understanding of the heterogeneity of breast cancer and its associated behaviour. Some lesions may never progress to ‘cancer’ and may potentially be managed with watchful waiting. Randomised clinical trials are underway investigating this approach; for instance, active surveillance trials for low risk ductal carcinoma *in situ* (DCIS).¹ With evolving systemic therapies and improved molecular tools, there is the potential to reduce treatment burden in lower-risk tumours.² Truly personalised medicine involves tailoring, not only clinical management with more intensive treatment for some cancers *vs* less intensive or no intervention for others, but potentially also dovetailing investigations for detection and for surveillance. Breast screening should aim to detect clinically relevant cancers, not lesions that would cause no harm during lifetime.

Cancer progression is variable. The wide range of factors that influence invasion and metastasis, including general physiological and nutritional status, co-morbidities, stromal and tumour characteristics, remain imperfectly understood. If a tumour develops slowly but is likely to progress if unchecked, early detection is likely to be beneficial. For tumours that develop rapidly or disseminate early, screen detection may not improve patient outcome. Screening detects a higher proportion of indolent disease,

due to the inherent tendency to preferentially identify slower growing cancers because more rapidly growing cancers are more likely to present symptomatically between screens (interval cancers). Thus, some subtypes of invasive breast cancer (*e.g.* Grade 1 tubular cancers) are more often screen-detected than symptomatic in presentation.

Two-dimensional full field digital mammography (FFDM) is currently the imaging basis of breast screening. Integrated FFDM and digital breast tomosynthesis (DBT) improves breast-cancer detection.³ Screening in centres in some countries now incorporates integrated FFDM and DBT. Mammography is an imperfect science. In women with dense fibroglandular tissue, the sensitivity and specificity are lower than in those with more radiolucent breasts. The efficiency, and possibly the effectiveness, of mammographic screening is also lower in users of hormone replacement therapy, in females with previous breast surgery, and those of lower body weight.⁴ Partly for these reasons, but multifactorially, the reported estimates on the effect of mammography screening on breast cancer mortality reduction vary widely. Nevertheless, a review of randomised controlled mammography trials reported an estimated mortality reduction of 20% in females aged between 50 and 70 years old.⁵

There is, however, increasing debate on the importance of the negative impact of breast screening, including over diagnosis – the identification of tumours that would otherwise not become symptomatic within the female's lifetime – and subsequent over treatment of such lesions. Another negative impact of screening is that of recall for further assessment in those without malignancy ('false-positive recalls'); approximately, 4% of females screened in the UK are invited to attend for further investigation, with a wide range of recalls between centres.⁶ There is evidence that increases in recall rates above-defined levels are almost exclusively associated with false-positive recalls with only a very small increase in detection of low/intermediate grade DCIS (*i.e.* not cancers likely to be life-threatening).⁷ Under current diagnostic algorithms, recall leads to tissue sampling in approximately 50% of females. This yields specimens which are definitively benign or malignant in most cases but, in 5–9% of core biopsies,⁶ not clearly either, *i.e.* a lesion of uncertain potential (B3).

The B3 category represents a heterogeneous group of lesions that have an increased risk of adjacent malignancy, but this ranges from a few percent to up to 40%, depending on the abnormality and the method of biopsy.⁸ B3 lesions with epithelial atypia include atypical intraductal epithelial proliferation (AIDEP), lobular neoplasia (the combined term applied in core biopsy for atypical lobular hyperplasia (ALH) and lobular carcinoma *in situ*) or flat epithelial atypia (FEA). The histopathological diagnostic criteria for some of these include assessment of extent of the process, and thus require a volume of tissue which is often not possible on a 14G sample ('standard core'). There is an upgrade rate – chance of adjacent DCIS or invasive cancer – of about 40% for AIDEP in a 14G sample⁸ which is less (about 20%) in vacuum biopsy (obtaining a larger sample). About 30% of cases of lobular neoplasia on 14G core biopsy will have adjacent DCIS or invasive cancer.⁹ The upgrade rate for FEA is lower (11%)¹⁰. In addition to the risk of there being contemporaneous adjacent cancer, the risk of subsequent cancer in females with atypical ductal hyperplasia or ALH is increased by three- to fourfold,¹¹ *i.e.* the risk of progression is low. B3 lesions are more common in screening than symptomatic practice but, despite guidance recommending vacuum-assisted excision for many,¹² 41% of females with a screen-detected B3 lesion in the UK in 2018 to 2019 underwent surgical excision.¹³ There are no biological markers available which can be used to predict either the risk of adjacent or subsequent cancer and there is no global agreement on management or follow-up of such patients. The long-term benefits to the patient, and at population level, of identifying these lesions at screening is unclear.

DCIS is not one disease, as shown by different presentations, appearances (imaging and histological), biomarkers and genetics. Information on the natural history of DCIS is limited because current standard of care is surgical excision. Reported series of untreated DCIS are of modest numbers and most direct evidence is from series where histological reviews of disease were originally diagnosed as benign and therefore not completely excised (most often low grade).¹⁴ Overall, between 14 and 53% of DCIS progresses to invasive cancer over a period of 10 or more years,¹⁵ but not all DCIS is equal; low-grade DCIS has a slower rate of

progression over a very long time (up to 40+ years). Significantly, whilst low-grade DCIS is associated with low-grade invasive cancer, high-grade DCIS tends to progress to Grade 2 and Grade 3 disease. At the population level, there is a negative correlation between DCIS detection rates and interval cancer (notably including Grade 3 cancer) rates, albeit in observational studies,¹⁶ indicating that the screen detection of, at least some, DCIS is worthwhile.

Invasive breast cancer encompasses an even broader range of patterns than atypia and DCIS. Although about three-quarters are of no special type (ductal), there are many histological types (and subtypes of types) of invasive breast cancer. Some 'special types' of breast carcinoma, including tubular, tubulolobular, invasive cribriform and Grade 1 mucinous carcinomas, have a good prognosis with >80% 10-year-survival, whilst others have a poorer outcome.¹⁷ Histological grade adds significant prognostic information to tumour type. However, no individual patient, imaging or pathological feature is very informative regarding the natural history of the lesion's origins. None are used alone for clinical management purposes; none are sufficiently good at identifying an excellent (or poor) group for recurrence or patient survival. Nevertheless, it is clear that the intrinsic biology of the cancer has a significant effect on long-term patient outcome – a small tumour may have a high metastatic potential and a large tumour may have low potential for dissemination. A greater understanding of more detailed biological factors will improve strategies for prevention and screening.

The identification of Grade 1 cancers less than 20 mm in size and Grade 2 and 3 cancers less than 10 mm in size at screening is likely to be beneficial, with a lower likelihood of developing metastatic disease from such lesions.¹⁸ The significant negative association between screen-detected DCIS and the rate of invasive interval cancers suggests that detection and treatment of (at least some) DCIS is worthwhile in prevention of future invasive disease.¹⁶ We believe that screening methodologies should concentrate on the identification of small high grade lesions (both DCIS and invasive), which are those most likely to influence patient outcome, rather than small low-grade tumours, which are those most likely to represent over diagnosis and subsequent over treatment.

Although associated with histological grade and type, genomics and other biomarkers provide additional information. Gene expression profiling categorises breast cancers into molecular subtypes: luminal A, luminal B, human epidermal growth factor receptor2 (HER2)–enriched, and basal-like, which have different patterns of disease, response to therapy and survival outcomes. The initial presentation of disease and subsequent metastatic spread are also influenced by molecular subtype.¹⁹ For example, patients with luminal A and B cancers are more likely to develop metastases in the skeleton than are those with basal-like subtype tumours, who more frequently develop lung and brain metastases.²⁰ Breast carcinomas of differing molecular subtypes also show variation in response to therapies; such knowledge guides initial treatment planning and imaging follow-up. However, formal molecular genomic subtype analysis in UK day-to-day practice is currently not practical or cost-efficient and surrogate

immunohistochemical markers are utilised. Oestrogen receptor (ER), progesterone receptor (PR), and HER2 status are used to define surrogate molecular subtypes, but concordance with formal genetic analysis ranges from 41 to 100%.²¹ Biomarkers may, however, be variably expressed within a cancer, e.g. heterogeneous expression of Her2 and Her2 amplification is recognised, highlighting the presence of intratumoral heterogeneity.²² However, driver genetic variations (e.g. in TP53, PIK3CA, PTEN, MYC and BRCA2) occur early in some cancers, and late in others, reflecting the complexity of tumour progression.²³ Although our understanding of the diagnostic and clinical implications of such intratumoral heterogeneity is imperfect, the presence of subclones within individual tumour may impact optimum approaches to imaging, tissue sampling and to patient treatment.

Given the heterogeneity of breast pathologies histologically and genomically and their variable behaviours and outcomes, more tailored approaches to detecting, classifying and managing screen detected entities are required. Artificial intelligence (AI) systems have been demonstrated to have the potential to be capable of surpassing human experts in breast cancer prediction on FFDM; using UK and USA data sets respectively, reductions of 5.7 and 1.2% in false positives, and 9.4 and 2.7% in false negatives have been demonstrated.²⁴ The AI system maintained non-inferior performance and reduced the workload of the second reader by 88%. Further AI system development and testing on data sets is likely to lead to clinical trials to improve the accuracy and efficiency of breast cancer screening. For instance, currently the morphological type of a mammographically indeterminate lesion does not appear to be correlated with cancer risk, but AI/machine learning could potentially extract imaging features to aid more refined categorisation.

The incidence of invasive breast cancer has risen since the early 1980s, especially those which are of less aggressive phenotype²⁵ with about 30% of screen detected invasive breast cancers being low risk by molecular profiling. We believe the future lies in risk-based screening, and identification of those for whom less screening is the best strategy as well as those who may potentially benefit from more frequent screening (e.g. based on their genetic risk).²⁶ The use of modalities other than mammography may aid detection of malignancy in dense breast tissue, identify biologically significant lesions and lead to developing more tailored screening regimens. Imaging with low-dose mammography,

contrast-enhanced mammography, automated whole breast ultrasound, molecular imaging and/or MRI (including abbreviated protocols), could all contribute to breast screening programmes. The first 2 year screening round of the Dense Tissue and Early Breast Neoplasm Screening (DENSE) trial, evaluating the use of supplemental MRI screening in females with extremely dense breast tissue and normal results on mammography, led to the diagnosis of significantly fewer interval cancers than mammography alone.²⁷ Using an abbreviated MRI protocol for breast cancer screening, the high diagnostic accuracy of full MRI protocols can be maintained, while the time and cost associated with traditional MRI examinations are minimised; in females with dense breasts undergoing screening, abbreviated breast MRI compared with DBT, has a significantly higher rate of invasive breast cancer detection.²⁸ Currently, in the UK and other countries, there are enhanced programmes for those at highest risk for lethal and rapidly growing cancers, for instance, carriers of BRCA1 and BRCA2 mutations but the efficacy of population-based screening will be also be improved by reducing the frequency of screens for those at lower risk.

In order to maximise the benefit of screening and tailoring regimens, high quality data capture is essential. Cancer registries should be enabled to allow integration of information including detailed tumour characteristics, treatment and outcome, to better understand tumour biology and prognostic significance. Many countries, including the UK, collate these at national level – analysis of ‘bigger data’ is likely to yield more fruitful results. Evolving models of stratified screening could be developed with lessons learnt and extrapolated to screening for other conditions.

In conclusion, to increase the effectiveness of breast screening, we should focus attention on methods for identification of lesions of greatest clinical consequence and adapt a more sophisticated, tailored approach to recall and to the range of pathological lesions, with subsequent reduced or enhanced intervention, potentially using various imaging modalities, as appropriate. At present, a large number of biopsies are carried out in a ‘catch all’ strategy for breast cancer, resulting in the diagnosis of a range of benign lesions, with or without epithelial atypia, and low-risk DCIS and low grade invasive disease, in addition to more clinically relevant cancers. The benefits of detection of this myriad of breast disease requires further research to increase our understanding of the relationship between screening methods and clinical outcome.

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