Original Research

Mammographic density and breast cancer risk in breast screening assessment cases and women with a family history of breast cancer

Stephen W. Duffy [a,*], Oliver W.E. Morrish [b], Prue C. Allgood [a], Richard Black [b], Maureen G.C. Gillan [c], Paula Willsher [d], Julie Cooke [e], Karen A. Duncan [f], Michael J. Michell [g], Hilary M. Dobson [h], Roberta Maroni [a], Yit Y. Lim [i], Hema N. Purushothaman [j], Tamara Suaris [k], Susan M. Astley [l], Kenneth C. Young [m], Lorraine Tucker [d], Fiona J. Gilbert [d]

[a] Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Charterhouse Square, London EC1M 6BQ, UK
[b] Department of Medical Physics and Clinical Engineering, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge Biomedical Campus, Hills Road, Cambridge CB2 0QQ, UK
[c] Aberdeen Biomedical Imaging Centre, Lilian Sutton Building, Foresterhill, University of Aberdeen, Aberdeen AB25 2ZD, UK
[d] Department of Radiology, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge Biomedical Campus, Hills Road, Cambridge CB2 0QQ, UK
[e] Jarvis Breast Centre, 60 Soughton Road, Guildford GU1 1LJ, UK
[f] North-East Scotland Breast Screening Centre, Foresterhill Road, Foresterhill, Aberdeen AB25 2XF, UK
[g] Breast Radiology Department, King's College Hospital NHS Foundation Trust, Denmark Hill, London SE5 9RS, UK
[h] West of Scotland Breast Screening Service, Stock Exchange Court, 77 Mandela Place, Glasgow G2 1QT, UK
[i] The Nightingale Centre & Genesis Prevention Centre, University Hospital of South Manchester, Southmoor Road, Manchester M23 9LT, UK
[j] Imperial College Healthcare NHS Trust, Fulham Palace Road, London W6 8RF, UK
[k] Breast Screening Unit, St Bartholomew's Hospital, London EC1A 7BE, UK
[l] Centre for Imaging Sciences, Institute of Population Health, University of Manchester, Oxford Road, Manchester M13 9PT, UK
[m] National Co-ordinating Centre for Physics of Mammography, Royal Surrey County Hospital, Guildford GU2 7XX, UK

* Corresponding author.
E-mail addresses: s.w.duffy@qmul.ac.uk (S.W. Duffy), oliver.morrish@addenbrookes.nhs.uk (O.W.E. Morrish), prueallgood@hotmail.co.uk (P.C. Allgood), richard.black@addenbrookes.nhs.uk (R. Black), maureen.gillan@btinternet.com (M.G.C. Gillan), paula.willsher@addenbrookes.nhs.uk (P. Willsher), cookejulie@hotmail.com (J. Cooke), karen.duncan@ed.ac.uk (K.A. Duncan), michael.michell@nhs.net (M.J. Michell), h.dobson@ed.ac.uk (H.M. Dobson), r.maroni@qmul.ac.uk (R. Maroni), yit.lim@uhsm.nhs.uk (Y.Y. Lim), hema.purushothaman@imperial.nhs.uk (H.N. Purushothaman), tamara.suaris@bartshealth.nhs.uk (T. Suaris), sue.astley@manchester.ac.uk (S.M. Astley), ken.young@nhs.net (K.C. Young), lorraine.1.tucker@googlemail.com (L. Tucker), fjg28@cam.ac.uk (F.J. Gilbert).

Abstract *Background:* Mammographic density has been shown to be a strong independent predictor of breast cancer and a causative factor in reducing the sensitivity of mammography. There remain questions as to the use of mammographic density information in the context of screening and risk management, and of the association with cancer in populations known to be at increased risk of breast cancer.

Aim: To assess the association of breast density with presence of cancer by measuring mammographic density visually as a percentage, and with two automated volumetric methods, Quantra™ and VolparaDensity™.

Methods: The TOMosynthesis with digital MammographY (TOMMY) study of digital breast tomosynthesis in the Breast Screening Programme of the National Health Service (NHS) of the United Kingdom (UK) included 6020 breast screening assessment cases (of whom 1158 had breast cancer) and 1040 screened women with a family history of breast cancer (of whom two had breast cancer). We assessed the association of each measure with breast cancer risk in these populations at enhanced risk, using logistic regression adjusted for age and total breast volume as a surrogate for body mass index (BMI).

Results: All density measures showed a positive association with presence of cancer and all declined with age. The strongest effect was seen with Volpara absolute density, with a significant 3% (95% CI 1−5%) increase in risk per 10 cm^3 of dense tissue. The effect of Volpara volumetric density on risk was stronger for large and grade 3 tumours.

Conclusions: Automated absolute breast density is a predictor of breast cancer risk in populations at enhanced risk due to either positive mammographic findings or family history. In the screening context, density could be a trigger for more intensive imaging.

1. Introduction

High breast density has been shown to be a strong, independent risk factor for breast cancer [1−5]. It has been reported that women with a high breast density compared to women with a low breast density have a four- to sixfold increased risk of developing the disease [6−10]. High breast density has also been linked to cancers which are larger and have positive lymph nodes, although the reported results vary considerably [11−15] and high breast density has been found in women with cancers diagnosed outside of the screening programme [1,4,16−18]. One possible explanation for the latter is a masking bias, in that dense breast tissue could render breast cancers less sensitive to screen detection, leading to a higher incidence of breast cancer in those previously screened negative. A number of studies, however, indicate that this is only partly responsible for the observed increased cancer risk with high density [2,6,19]. Indeed, density has been shown to be a risk factor for screen-detected as well as symptomatic cancers [4,6].

There is no consensus on the most useful measure of breast composition in risk prediction, risk management and surveillance decisions. One meta-analysis found that absolute rather than proportional estimates of breast density are more strongly predictive of risk [2], whereas another found the opposite [20].

Younger, pre- or perimenopausal women are known to have a higher proportion of dense breast tissue, as breast density decreases with age [21,22]. The National Health Service Breast Screening Programme (NHSBSP) in the United Kingdom (UK) invites women aged 50−70 every 3 years for two-view digital mammography which is double read [23]. Extension of the age range to 47−73 is currently under investigation. Women at moderate risk with a significant family history of breast cancer may be screened annually from age 40 [24].

Issues outstanding in breast density include:

- identifying the breast density measure (percent density, absolute quantity of dense tissue) most strongly associated with breast cancer;
- the method of measurement (visual, automated volumetric measures, automated area measures) most strongly associated with cancer;
- age and tumour-specific associations with risk;
- the extent to which density contributes risk information in subjects already known to be at higher risk of breast cancer, such as women attending for screening who are recalled for assessment due to a suspicious mammographic finding (and which measure of density is most suitable in this population).

Also, it is worth noting that the identification of mammographic density as a risk factor took place in the predigital era, and most of the studies demonstrating the effect of density on breast cancer risk pertain to measures from film/screen mammography. There is a current need to demonstrate and validate measures of breast