Using education to inform breast density conversations

RAD Magazine, 47, 551, 14-15

Dr Athina Vourtsis
Director and founder, Diagnostic Mammography Center, Athens; European liaison, DenseBreast-info.org

Cheryl Cruwys
European education coordinator, DenseBreast-info.org
ccruwys@dense-info.org

Introduction

Breast cancer remains the most common malignancy among women worldwide with more than 523,000 newly diagnosed cancers in Europe each year (after excluding skin cancers).[1,2] According to the GLOBOCAN 2018 statistics, 137,707 deaths due to breast cancer have been recorded in Europe.[3]

Mammography has been in use for over half a century and it remains the gold standard imaging modality for the early detection of breast cancer. According to randomised trials, a reduction in breast cancer mortality rate by 20% has been attributed to mammography screening.[4-6] However, the performance of mammography is adversely affected by breast density and the reduction in mortality mediated by mammography is considerably lower in women with dense breasts compared to those with fatty breasts.[7] X-ray attenuation is very similar between the dense tissue and non-calcified cancers that both appear white on mammography and therefore dense breast tissue can hide cancer.[8,9] Breast density has been identified as the most prevalent risk factor for developing breast cancer.[10]

Implications of breast density

The more epithelial (glandular) and stromal (fibrous) tissue relative to fatty tissue in the breast, the greater the breast density. The latest American College of Radiologists (ACR) Breast Imaging – Reporting and Data System (BI-RADS) lexicon includes description of the visual estimation of fibroglandular density performed by radiologists as one of the four categories[11] (**figure 1**). Although having dense breasts is a normal condition that is seen in almost half of women aged 40-74 years, it is associated with a two to six-fold higher likelihood of developing breast cancer, with the risk increasing with increasing breast density.[12,13]

About half of breast cancers contain calcifications[14,15] and those are well seen in any breast density. However, in women with dense breasts, non-calcified cancers may be hidden by the dense tissue, a fact that significantly reduces the sensitivity of mammography.[16,17] This 'masking' (**figure 2**) increases the likelihood of interval cancers. Interval cancers are those cancers diagnosed after a negative/normal screening mammogram and before the next recommended screen, ie between recommended screening rounds (every three years in the UK). Interval cancers usually present as a palpable lump and tend to present with lymph node involvement and overall worse outcomes.[18,19] Boyd et al reported an 18-fold increased likelihood of interval cancer in women with extremely dense breasts compared to women with fatty breasts.[20] Similarly, Kerlikowske et al[10] demonstrated more advanced-stage interval cancers in women with extremely or heterogeneously dense breasts.

Understanding breast density implications is important to a woman's breast health. Most women are unaware of their own breast density and its associated risks. Women are often disappointed to learn that a "negative", "benign" or "normal" mammogram result does not necessarily exclude presence of a cancer, nor that mammograms miss approximately 40% of cancers present in extremely dense breasts.[21] Additionally, important knowledge gaps exist about breast density, breast cancer risk assessment and screening among technologists and radiologists.[22] In various screening programmes, including the UK, radiographers/technologists perform the mammogram, and sometimes have only limited knowledge about breast density. If a woman wishes to ask questions, there may not be access to a radiologist, and technologists might not be 'density-informed' enough to be able to respond.

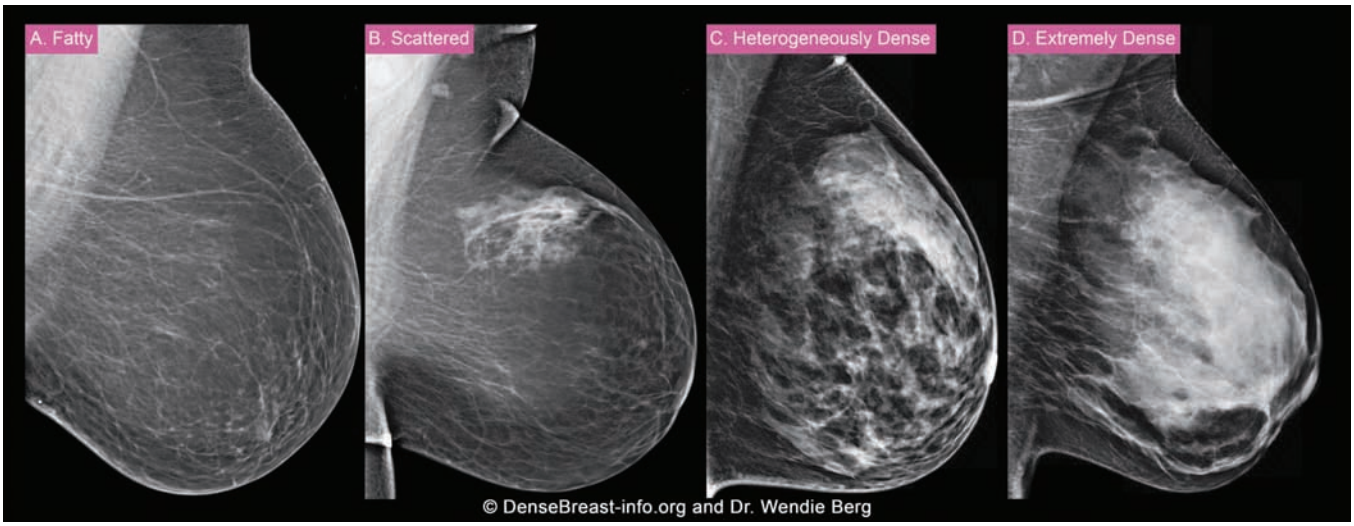

Figure 1
Examples of the four categories of breast composition. (A) The breast is entirely fatty. (B) Scattered areas of fibroglandular density. (C) The breast is heterogeneously dense, which may obscure small masses. (D) The breast is extremely dense, which lowers the sensitivity of mammography. Heterogeneously dense or extremely dense breasts are considered 'dense'. *©DenseBreast-info.org*

Supplemental screening beyond mammography in women with dense breasts

In a recent review,[19] Dr Athina Vourtsis and Dr Wendie Berg highlighted the implications of breast density and the positive impact of supplemental screening. Supplemental screening with other modalities beyond standard mammography, such as digital breast tomosynthesis (DBT), handheld ultrasound (HHUS), automated breast ultrasound (AUS), MRI, contrast-enhanced spectral mammography (CESM), and molecular breast imaging (MBI), have been shown to improve detection of invasive breast cancer at an early stage before it has spread to lymph nodes.

DBT is a mammographic modality that was Food and Drug Administration approved in 2011.[23] During DBT image acquisition, the x-ray tube rotates over the compressed breast in an arc, producing a set of low dose images from various angles, and a reconstruction algorithm combines these images into thin (usually 1mm) slices.[24,25] While DBT improves detection of non-calcified masses and cancerous distortions, there is little benefit (if any) in women with extremely dense breasts, and cancers can remain hidden even when breasts are less dense.[26]

HHUS is a supplemental breast cancer screening modality that uses ultrasound waves to form images of the breast. Recent technological advancements provide high quality, low cost examinations, without the requirement of intravenous contrast or exposure to ionising radiation. Various prospective studies have shown that addition of ultrasound to mammography in women with dense breasts increases breast cancer detection rates by 1.8-4.6 cancers per 1,000 women screened.[27-29] More importantly, cancers detected only with HHUS were >85% node negative, with a significant decrease in interval cancer rates in women with dense breasts.[19] AUS is a newer ultrasound system that addresses some of the limitations of HHUS, by providing reproducible examinations with performance comparable to HHUS, operator independence and large field of view images.[30-32] There is a continuous discussion on false positive results with HHUS and AUS; recall rates equal to 7.6%, 7.5% and 10.6% have been reported in physician-performed HHUS, technologist-performed HHUS and AUS, respectively. Recalls from AUS are usually evaluated with HHUS and interpretation of AUS entails assessment of numerous images.[33] Computer-aided detection and diagnosis software has been developed that has been FDA approved for AUS, with the aim to reduce interpretation time.[34]

Contrast-enhanced MRI does not use ionising radiation and cancer detection is not affected by breast tissue composition. However, MRI requires intravenous injection of gadolinium-based contrast as cancers are seen mostly because of contrast enhancement (due to increased and leaky blood supply compared to normal tissues). Gadolinium has been shown to accumulate in regions of the brain but without adverse effects. However, further research is ongoing in this issue. Breast MRI has been endorsed by various scientific societies globally in guidelines for screening women at high risk of breast cancer (lifetime risk of developing the disease 20-25% or higher).[35]

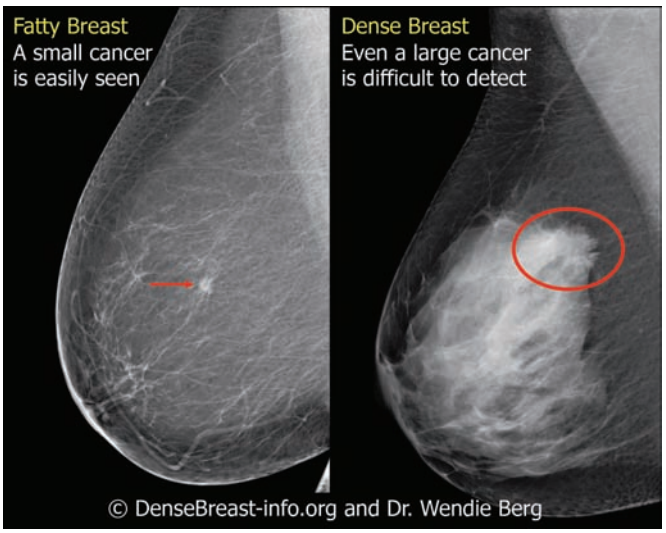

Figure 2
Mediolateral oblique mammograms demonstrating two different women with cancer. In a woman with fatty breasts (left) a small cancer is easily seen (red arrow). In a woman with dense breasts (right), even a large cancer is difficult to detect.
©DenseBreast-info.org

In the Netherlands, a randomised, multicentre controlled study, the Dutch Dense Tissue and Early Breast Neoplasm Screening (DENSE) trial, recruited women with extremely dense breasts and showed that biennial supplemental MRI versus mammography alone was associated with an increase in cancer detection rate of 16.5 per 1,000 screens, with a significant reduction in interval cancers during a two-year screening period and a false positive rate of 79.8 per 1,000 screenings.[36]

MBI requires intravenous administration of the radiotracer ^{99m}Tc-sestamibi. Currently, it has been considered a supplemental screening option for women at high risk and for women with dense breasts when MRI is not available or contraindicated. Enthusiasm for use of MBI is reduced due to whole body radiation exposure and the minimum 40-minute examination time as well as limited direct biopsy capability.[37,38]

CESM could be a potential alternative for screening high risk women and potentially women with dense breasts, when MRI cannot be performed for various reasons. CESM uses intravenous injection of iodinated contrast as is used in CT scans and the examination approximately doubles the radiation exposure of a standard mammogram.[39,40]

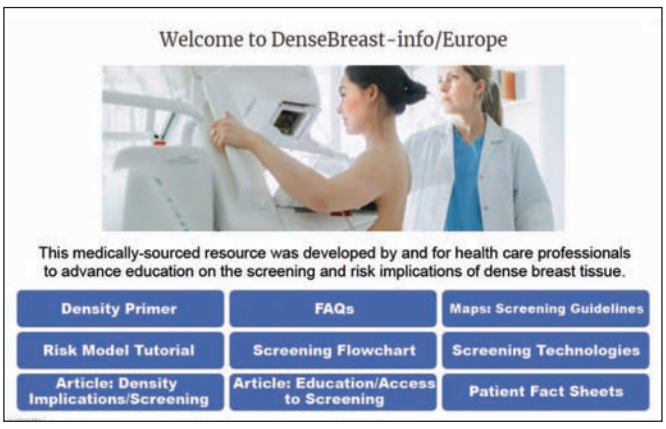

Figure 3
The website features multiple educational components.

Current screening approach in Europe and the USA

In Europe, there are diverse screening approaches across various countries. Currently, as per the UK national screening guidelines, asymptomatic women with dense breasts are screened solely with mammography. Information on breast density is not included in the standard mammography report nor in the results letter sent to women. Breast density is, however, among other factors included in the risk stratification Predicting the Risk of Cancer at Screening (PROCAS) studies.[41]

France and Austria, uniquely, have different screening approaches from other population-based programmes in Europe. Since 2011 in Austria, and for many years in France, breast ultrasound has been offered routinely in addition to mammography in women with dense breasts (category C/D, see **figure 1**). In a four-year audit published in

2018, the participation rate of Austrian women having supplemental ultrasound was 76.2% with cancer detection rate 3.7 per 1,000 screens.[42]

In the USA, 38 states and the District of Columbia have passed legislation that requires the woman to receive some information about breast density implications and some require inclusion of a woman's own breast density in the results letter after a screening mammogram. To address the increased need for medically sourced information in the context of USA 'density-inform' laws, DenseBreast-Info.org (DB-I) has been established to provide related information for both healthcare professionals and patients. The website (**figure 3**) is recognised as the most up-to-date, comprehensive online educational resource on the topic of breast density.

In 2018, DenseBreast-Info/Europe and the European Breast Density Educational Coalition was launched and attracted international media coverage. Europe-specific content has been developed to meet the needs of European healthcare providers through the collaborative input of European breast imaging experts.

DB-I's European liaison Dr Vourtsis leads the coalition and serves as one of the 19 breast imaging radiologist ambassadors from 15 countries. Cheryl Cruwys, a patient-advocate instrumental in breast density education in the UK, serves as the European education coordinator. The recently expanded website provides a dense breast primer, a map (**figure 4**) featuring a comparative analysis of country-specific European national breast screening guidelines, comprehensive FAQs with citations, explanation of screening technologies, a risk model tutorial, an easy-to-follow screening flowchart and, for patients, fact sheets available in multiple languages. On a regular basis, the DB-I team reaches out to a growing list of breast experts in Europe who provide information on density-related research, studies, articles and new website content/tools.

Continuous education of clinical providers and improvement of their communication skills are essential in enabling women to make informed decisions about breast density and the potential beneficial effects of supplemental screening. A CME programme has been developed (with credit designation through the European Accreditation Council for CME): Breast Density Matters, Why It Matters. Organisations linking to DenseBreast-info.org resources include The Royal College of Radiologists, the European Federation of Radiographer Societies, the Society and College of Radiographers (UK), the European Society of Radiology (Patient Advisory Group, Vienna), ecancer.org and leading research charity Prevent Breast Cancer.

Conclusions

Overall, supplemental breast cancer screening tools have the potential to improve breast cancer detection in women with dense breasts. Currently there is a lack of consistent screening guidelines and approach to incorporating breast density into screening considerations among European countries. In order to advance informed conversations, educational resources on the screening and risk implications of dense breast tissue are important. Educational resources can provide assistance to cover knowledge gaps about breast density, breast cancer risk assessment and screening among radiologists and healthcare providers. Continued development and refinement of targeted, medically sourced educational resources directed to radiologists may help patients receive accurate information. This should facilitate well-informed shared decision-making between patients and healthcare providers.

Dr Vourtsis comments: "In Greece, there is a lack of a national screening programme. Despite that, we feel that it is important to provide personalised breast assessment, which is tailored based on a woman's needs. In recent years there has been an improvement in the knowledge of breast cancer risk factors, and it is obvious that one size does not fit all. I discuss with my patients the issue of breast density and the potential benefits of supplemental screening, because I believe it is important that they are aware of their breast composition and related options. Furthermore, patients should have access to this information, to make informed conversations and shared decisions."

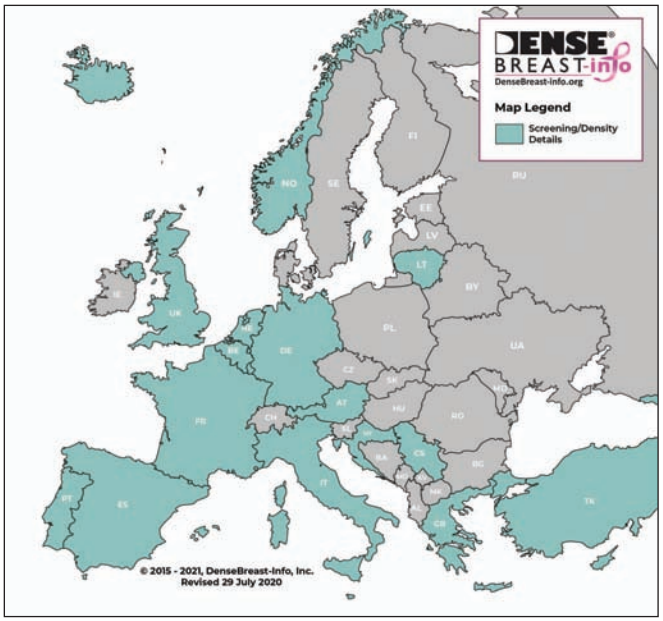

Figure 4
A map of screening guidelines by country.

References

1, *Siegel R L, Miller K D, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.*
2, *Ferlay J, Colombet M, Soerjomataram I et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer 2018;103:356-87.*
3, *International Agency for Research on Cancer. Breast – Globocan 2018. 2019. https://gco.iarc.fr/today/data/factsheets/cancers/20-Breast-fact-sheet.pdf*
4, *Berry D A, Cronin K A, Plevritis S K et al. Cancer Intervention and Surveillance Modeling Network. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353:1784-92.*
5, *Tabar L, Vitak B, Chen T H et al. Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. Radiology 2011;260:658-63.*
6, *Coldman A, Phillips N, Wilson C et al. Pan-Canadian study of mammography screening and mortality from breast cancer. J Natl Cancer Inst 2014;106.*
7, *van der Waal D, Ripping T M, Verbeek A L, Broeders M J. Breast cancer screening effect across breast density strata: a case-control study. Int J Cancer 2017;140:41-49.*
8, *Byrne C, Schairer C, Wolfe J et al. Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst 1995;87:1622-29.*
9, *Kerlikowske K, Ma L, Scott C G et al. Combining quantitative and qualitative breast density measures to assess breast cancer risk. Breast Cancer Res 2017;19:97.*
10, *Kerlikowske K, Zhu W, Tosteson A N et al. Breast Cancer Surveillance Consortium. Identifying women with dense breasts at high risk for interval cancer: a cohort study. Ann Intern Med 2015;162:673-81.*
11, *Sickles E A, D'Orsi C J, Bassett L W et al. ACR BI-RADS Mammography. In: D'Orsi CJ , Sickles E A, Mendelson E B, Morris E A, eds. ACR BI-RADS Atlas, Breast Imaging Reporting and Data System. Reston, VA: American College of Radiology 2013.*
12, *Sprague B L, Gangnon R E, Burt V et al. Prevalence of mammographically dense breasts in the United States. J Natl Cancer Inst 2014;106.*
13, *Bertrand K A, Tamimi R M, Scott C G et al. Mammographic density and risk of breast cancer by age and tumor characteristics. Breast Cancer Res 2013;15:R104.*
14, *Demetri-Lewis A, Slanetz P J, Eisenberg R L. Breast calcifications: the focal group. AJR Am J Roentgenol 2012;198:W325-43.*
15, *Tot T, Gere M, Hofmeyer S et al. The clinical value of detecting microcalcifications on a mammogram. Semin Cancer Biol 2019.*
16, *Mandelson M T, Oestreicher N, Porter P L et al. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. J Natl Cancer Inst 2000;92:1081-87.*
17, *Nelson H D, O'Meara E S, Kerlikowske K et al. Factors associated with*

rates of false-positive and false-negative results from digital mammography screening: an analysis of registry data. Ann Intern Med 2016;164:226-35.
18, *Posso M, Louro J, Sanchez M et al. BELE Study Group. Mammographic breast density: How it affects performance indicators in screening programmes? Eur J Radiol 2019;110:81-87.*
19, *Vourtsis A, Berg W A. Breast density implications and supplemental screening. Eur Radiol 2019;29:1762-77.*
20, *Boyd N F, Guo H, Martin L J et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med 2007;356:227-36.*
21, *Carney P A, Miglioretti D L, Yankaskas B C et al. Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. Ann Intern Med 2003;138:168-75.*
22, *Seitzman R L, Pushkin J, Berg W A. Radiologic technologist and radiologist knowledge gaps about breast density revealed by an online continuing education course. J Breast Imaging 2020;2:315-29.*
23, *US Food and Drug Administration. Premarket Approval (PMA) P080003. Selenia Dimensions Full Field Digital Mammography System. 2011. www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P080003*
24, *Ren B, Ruth C, Stein J et al. Design and performance of the prototype full field breast tomosynthesis system with selenium based flat panel detector. Proc SPIE 2005;5745:550-61.*
25, *Eberhard J W, Staudinger P, Smolenski J et al. High-speed large-angle mammography tomosynthesis system. Proc SPIE 2006;6142:61420C.*
26, *Peppard H R, Nicholson B E, Rochman C M et al. Digital breast tomosynthesis in the diagnostic setting: indications and clinical applications. Radiographics 2015;35:975-90.*
27, *Berg W A, Blume J D, Cormack J B et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA 2008;299:2151-63.*
28, *Corsetti V, Houssami N, Ferrari A et al. Breast screening with ultrasound in women with mammography-negative dense breasts: evidence on incremental cancer detection and false positives, and associated cost. Eur J Cancer 2008;44:539-44.*
29, *Ohuchi N, Suzuki A, Sobue T et al. Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial. Lancet 2016;387:341-48.*
30, *Vourtsis A, Kachulis A. The performance of 3D ABUS versus HHUS in the visualisation and BI-RADS characterisation of breast lesions in a large cohort of 1,886 women. Eur Radiol 2018;28:592-601.*
31, *Brem R F, Tabar L, Duffy S et al. Assessing improvement in detection of breast cancer with three-dimensional automated breast US in women with dense breast tissue: the SomoInsight Study. Radiology 2015;274:663-73.*
32, *Wilczek B, Wilczek H E, Rasouliyan L, Leifland K. Adding 3D automated breast ultrasound to mammography screening in women with heterogeneously and extremely dense breasts: report from a hospital-based, high-volume, single-center breast cancer screening program. Eur J Radiol 2016;85:1554-63.*
33, *Berg W A, Vourtsis A. Screening breast ultrasound using handheld or automated technique in women with dense breasts. J Breast Imaging 2019;1:283-96.*
34, *Yang S, Gao X, Liu L et al. Performance and reading time of automated breast US with or without computer-aided detection. Radiology 2019;292:540-49.*
35, *Sardanelli F, Cozzi A, Trimboli R M, Schiaffino S. Gadolinium retention and breast MRI screening: more harm than good? AJR Am J Roentgenol 2020;214:324-27.*
36, *Bakker M F, de Lange S V, Pijnappel R M et al. Supplemental MRI screening for women with extremely dense breast tissue. N Engl J Med 2019;381:2091-102.*
37, *Shermis R B, Wilson K D, Doyle M T et al. Supplemental breast cancer screening with molecular breast imaging for women with dense breast tissue. AJR Am J Roentgenol 2016;207:450-57.*
38, *Hruska C B. Molecular breast imaging for screening in dense breasts: state of the art and future directions. AJR Am J Roentgenol 2017;208: 275-83.*
39, *Cheung Y C, Lin Y C, Wan Y L et al. Diagnostic performance of dual-energy contrast-enhanced subtracted mammography in dense breasts compared to mammography alone: interobserver blind-reading analysis. Eur Radiol 2014;24:2394-403.*
40, *Berg W A, Rafferty E A, Friedewald S M et al. Screening algorithms in dense breasts: AJR Expert Panel Narrative Review. AJR Am J Roentgenol 2020.*
41, *Evans D G, Astley S, Stavrinos P et al. Improvement in risk prediction, early detection and prevention of breast cancer in the NHS Breast Screening Programme and family history clinics: a dual cohort study. Southampton (UK) 2016.*
42, *Geiger-Gritsch S, Daniaux M, Buchberger W et al. Performance of 4 years of population-based mammography screening for breast cancer combined with ultrasound in Tyrol/Austria. Wien Klin Wochenschr 2018;130:92-99.*