Maturitas 79 (2014) 481–486

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

EMAS position statement: Individualized breast cancer screening versus population-based mammography screening programmes

Herman Depypere[a,*], Joelle Desreux[b], Faustino R. Pérez-López[c], Iuliana Ceausu[d,e], C. Tamer Erel[f], Irene Lambrinoudaki[g], Karin Schenck-Gustafsson[h], Yvonne T. van der Schouw[i], Tommaso Simoncini[j], Florence Tremollieres[k], Margaret Rees[l]

[a] Breast Clinic and Menopause Clinic, University Hospital, De Pintelaan 185, 9000 Gent, Belgium
[b] CHR de la CITADELLE – Boulevard du 12ème de Ligne, 1 à 4000 Liège, Belgium
[c] Department of Obstetrics and Gynecology, Zaragoza University Faculty of Medicine, Lozano Blesa University Hospital, Domingo Miral s/n, Zaragoza 50009, Spain
[d] Department of Obstetrics and Gynecology, 'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania
[e] Department of Obstetrics and Gynecology, 'Dr. I. Cantacuzino' Hospital, Bucharest, Romania
[f] Department of Obstetrics and Gynecology, Istanbul University, Cerrahpasa School of Medicine, Valikonagi Cad. No: 93/4, Nisantasi, 34365 Istanbul, Turkey
[g] Second Department of Obstetrics and Gynecology, National and Capodestrian University of Athens, Greece
[h] Department of Medicine, Cardiology Unit and Head Centre for Gender Medicine, Karolinska Institutet and Karolinska University Hospital, Thorax N3:06, SE 17176 Stockholm, Sweden
[i] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
[j] Department of Clinical and Experimental Medicine, University of Pisa, Via Roma, 67, 56100 Pisa, Italy
[k] Menopause and Metabolic Bone Disease Unit, Hôpital Paule de Viguier, F-31059 Toulouse cedex 09, France
[l] Women's Centre, John Radcliffe Hospital, Oxford OX3 9DU, UK

ARTICLE INFO

Article history:

Keywords:
Breast cancer
Mammography screening
Individualized

ABSTRACT

Introduction: Breast cancer is the most prevalent cancer in women, with slightly more than ten percent developing the disease in Western countries. Mammography screening is a well established method to detect breast cancer.
Aims: The aim of the position statement is to review critically the advantages and shortcomings of population based mammography screening.
Materials and methods: Literature review and consensus of expert opinion.
Results and conclusion: Mammography screening programmes vary worldwide. Thus there are differences in the age at which screening is started and stopped and in the screening interval. Furthermore differences in screening quality (such as equipment, technique, resolution, single or double reading, recall rates) result in a sensitivity varying from 70% to 94% between studies. Reporting results of screening is subject to different types of bias such as overdiagnosis. Thus because of the limitations of population-based mammography screening programmes an algorithm for individualized screening is proposed.

1. Introduction

Breast cancer originates from the malignant transformation of epithelial cells within the ducts and lobules of the breast. A malignant cell is the result of the accumulation of consecutive mutations. Up or down regulation of different mutated genes will ultimately result in the heterogeneity of breast cancers [1]. Some tumors will remain in situ and will never threaten the health of women. Other tumors will become invasive and ultimately metastasize and hence be fatal when not treated. The doubling time of tumor cells is estimated between 150 and 200 days [2]. With systematic screening one would expect to detect more tumors at a pre-invasive stage. With adequate local treatment these tumors are associated with a nearly one hundred percent survival rate. If, on the other hand, the tumors have already progressed to an invasive carcinoma, one would expect screen detected tumors to be smaller and hence have a lower chance of nodal involvement. Consequently that would reduce the extent of breast and axillary surgery. The latter could be limited to the well established, reliable sentinel procedure in women with an early breast cancer. If there is no

* Corresponding author. Tel.: +32 9 221 67 57; fax: +32 9 234 35 37.
E-mail address: Herman.depypere@ugent.be (H. Depypere).

http://dx.doi.org/10.1016/j.maturitas.2014.09.002
0378-5122/

nodal involvement, extensive axillary surgery and radiotherapy could be avoided. According to the Sankt Gallen guidelines [3] smaller, node negative tumors are less likely to require adjuvant chemotherapy. However, population based mammography screening increases radiotherapy and breast surgery rates, including mastectomy, partly due to overdiagnosis [4,5]. Moreover, mammography screening has not decreased the number of adjuvant chemotherapies and hormone therapies in the screened population [6].

2. Publicly organized population mammography screening

2.1. Screening: advantages, limitations and risks

Different mammography screening studies give conflicting results. Some studies indicate a survival benefit of systematic screening while others do not. Recent publications provide extensive comments on screening [7–11]. Since 1990, mortality from breast cancer in industrialized countries has been decreasing at the rate of approximately 2.2% per year [12]. This decline has been attributed both to advances in adjuvant therapy and to an increasing use of screening mammography. The St Gallen classification system categorizes invasive breast carcinomas into the following five distinct molecular subtypes; luminal A, luminal B (HER2−), luminal B (HER2+), HER2, and basal-like subtypes [3]. These subtypes together with the TNM stage will determine adjuvant systemic treatment. As treatments and healthcare systems continue to improve, the impact of screening on breast cancer mortality will further decrease. In most countries, the main decline of breast cancer mortality started before the implementation of population-based screening [13,14]. Moreover, the Cochrane meta analysis of 2011, involving 3 studies with adequate randomization following up women aged 50–69 years old over 13 years, has shown no significant effect of mammographic screening on breast cancer mortality (RR 0.90; 95% CI 0.79 to 1.02) [4]. A recent Cochrane review (2013) by Gøtzsche and Jørgensen [15], included seven randomized trials. Three of these trials with adequate randomization showed no statistical difference in breast cancer mortality. Adding the four trials with suboptimal randomization resulted in a breast cancer mortality reduction (RR: 0.81 (95% CI 0.74 to 0.87)).

The screening programmes in different countries vary in screening interval and the age at which population screening is started and stopped. Furthermore the quality and process of screening has changed over time and some studies were undertaken 30–50 years ago. Factors to consider include digital versus film imaging, involvement of experienced breast radiologists and nurses, double reading by different radiologists, the recall rate and the true positive and negative rates. The sensitivity between studies varies between 70% and 94% [16–23]. Some of the initial studies have a high interval breast cancer rate [21]. Furthermore one needs to accept that screening is subject to different forms of bias. Women undergoing screening may be more health conscious than those who do not, which may result in better survival rates. Even randomized trials may be subject to bias. Women invited for screening may decide against it, while uninvited women may organize a mammogram themselves(opportunistic screening). Many screen detected tumors will be slow-growing luminal A type tumors which have an intrinsically better prognosis. This may reflect in the better survival of screen detected tumors. This will result in a length bias. Another form of bias is the lead-time. A slow growing tumor, detected preclinically – before it is palpable or there is skin tethering – will be detected one or more years earlier in the screening arm. This time is not included when the survival time is reported in clinically detected tumors. Thus screen detected tumors will appear to have a longer survival. This is lead-time bias. Overdiagnosis has received considerable attention in recent years. Some tumors grow so slowly that they will not threaten the health of women during their lifetime [24–26]. The women will die from another cause and thus it is argued that these tumors should not have been treated. Treatments can be invasive and painful, have major side-effects, especially in those with significant co-morbidities. While this is easy from an epidemiological standpoint, it is a dilemma for the treating physician dealing with individual women. It is virtually impossible to make the diagnosis of breast cancer and to predict the future behavior of that tumor. An independent UK Panel on breast cancer screening, concluded that screening may result in a relative risk reduction of breast cancer mortality of 0.80 (95% CI 0.73–0.89), with an overdiagnosis of 19% (15–23) [27]. This means that for 10.000 UK-women aged 50 years, invited for screening over the next 20 years, 43 deaths will be prevented and 129 cases of breast cancer will be overdiagnosed (in situ + invasive). This review has been criticized [see for example 28] with concerns that this estimate is far too positive. Furthermore some of the healthy overdiagnosed women will die from their treatment. Welsch and coworkers report that for every breast cancer death prevented in the US in a 10 year annual screening setting starting at the age of 50, 490–670 women are likely to have a false positive mammogram with a repeat examination. A group of 70–100 women will undergo a biopsy and 3–14 will have an overdiagnosed breast cancer [29].

More than three out of four breast cancers occur after the age of fifty. In Flanders breast cancer incidence peaks in women aged 60–64 with four new cases per 1000 women per year [30]. With systematic screening, detection rate of 80 percent will result in three tumors detected by mammography and one missed. To detect three breast cancers 1000 mammographic exams have to be performed. In younger age groups the number of breast cancers per 1000 mammograms performed is even lower. Including women younger than 50 years of age may alter the results of organized screening. Based on the data of Surveillance, Epidemiology, and End Results program, Breast Cancer Surveillance Consortium, and the medical literature, it has been concluded that mammography every 1–2 years from age 40 to 80 is expensive if false-positives and the costs of over diagnosis are taken into account [31]. Population screening has now become so controversial that the Swiss Medical Board recommended abolition of screening programs and that 'Providing clear, unbiased information, promoting appropriate care, and preventing overdiagnosis and overtreatment would be a better choice.' http://www.nejm.org/doi/full/10.1056/NEJMp1401875.

Another concern on systematic screening is that ionizing radiation may actually induce breast cancers [32,33]. It has been estimated one tumor will arise due to mammography per 100 malignant detected tumors in women aged 50–69. In those aged between 40 and 50 years four tumors will arise per 100 detected breast cancers [32]. The total lifetime risk (until 85 years of age) of radiation-induced breast cancer has been evaluated by mathematical models as 10 per 100,000 women screened biannually from 50 to 69 years old. The number of deaths by radiation-induced breast cancer was 1 per 100,000-screened women in the same study [33].

2.2. Risk factors for breast cancer and screening

Risk factors for the development of breast cancer include: increasing age, gene mutations (BRCA1&2,CHEK2, ATM, FGFR2, MAP3KI), early menarche, late menopause, nulliparity/first pregnancy after 30, family history of breast cancer, history of breast surgery, high breast density, exposure of the chest to ionizing radiation, postmenopausal hormone therapy and postmenopausal obesity, alcohol use, absence of physical activity. A crucial step to optimize screening could be to implement all risk and protective factors in the screening strategy. To decrease the costs and the burden of false positives and over-diagnosis, lower risk women could

be screened less frequently (i.e. every 3 years as in UK) and screening could stop when co-morbidities are significant. Lower risk women include mainly no familial risk, Breast Imaging Reporting and Data System (BI-RADS) category 1 fatty breasts and menopause <35 years old. The other protective factors such as increased physical activity, history of breast feeding, low BMI are minor (RR > 0.5) and should not modify the screening strategy. As such proposals have ethical considerations, they are unlikely to be researched. Also, it could take 20 years to show an effect on breast cancer mortality. However mathematical models show altering the frequency of mammography according to risk is cost-effective [31,34].

2.3. Improving population screening

So with the extensive experience of current publicly organized screening, it can be concluded it is currently suboptimal. However, stopping all kind of screening of low- and average-risk women would be problematic as about 70% of breast cancers are diagnosed in those subgroups, and only undertaking screening in high-risk women would be insufficient. Consequently, there is an urgent need to improve the effectiveness of breast cancer screening.

Women should be informed about the advantages and disadvantages of systematic screening. In the invitation letter a clear and understandable information leaflet should be included. Prior to the examination health professionals should again explain what to expect and the risk of false positives and negatives. In the double reading setting, where initially no sonography is performed, the possibility of recall should also be explained. Individualized screening, could therefore be a better strategy.

3. Principles of individualized breast cancer screening

Screening effectiveness may be improved by individualizing the screening timing and modalities, as women have different levels of risk.

Optimal individual screening should follow these principles [35]:

- As most western societies have invested in public breast cancer screening programmes from age 50 for average risk women, individual screening should begin from the age at which the breast cancer risk is equal to that for an average risk women aged 50 years (≈2% in the next 10 years or remaining lifetime risk ≈8%).
- Individual screening should stop when the risk of co-mortality from other diseases exceeds the risk of breast cancer mortality.
- The frequency of screening rounds should be adapted to the individual level of risk.
- Imaging modality should be adapted to breast characteristics in order to reach the best sensitivity and specificity.
- The screening strategy should be regularly and individually reassessed.

Women should be informed with due care about the risks/benefits of screening and about their risk of breast cancer in comparison with other health issues (e.g. cardiovascular diseases). The doctor should accept an eventual thoughtful refusal. In all cases, participation to screening should be voluntary and individual. Information giving should be personally and not population focused.

4. Identifying women at higher risk

Attempts to reduce occurrence of interval cancers through more sensitive and/or intensive screening should focus on subgroups in which observed incidence of those cancers is increased: higher breast density, hormone use and family history [36].

A 2.45 fold increase in breast cancer incidence has been reported for women with extremely or moderately dense breasts compared with those with fatty breasts, and a 60% increase in the likelihood that a screened woman with dense breasts would develop interval versus screen-detected cancer [37]. High breast density may mask discrete mammographic abnormalities. Also high breast density is an even stronger predictor of interval cancers in older women (over 50 years) compared with younger women, as breast density decreases with age after the menopause [38].

Combined estrogen–progestogen menopausal hormone therapy (MHT) slows down the age-related decrease of breast density. Kerlikowske and coworkers found in the WHI study that low breast density was associated with low breast cancer risk and decreased risk of advanced-stage disease regardless of hormone therapy use [39]. On the contrary, in women with high breast density, combined MHT was associated with higher cancer risk and advanced stage at diagnosis, probably because of decreased mammography sensitivity and more aggressive tumoral phenotype [39]. The influence of hormone use on the incidence of breast cancer is complex. In the Women's Health Initiative (WHI) Study, continuous combined equine estrogens with medroxyprogesterone acetate (MPA) was associated with an increased risk of breast cancer when taken more than five years. Equine estrogens combined with MPA increase breast density and may obscure the detection of small tumors. This type of breast density disappears quickly when hormones are stopped, and is different from the dense formations used to define dense breasts [40]. However, estrogens combined with natural progesterone were not associated with an increased risk of breast cancer in the initial years of use in the French E3N study [41] and the Finnish study [42]. Equine oestrogens alone (WHI) were associated with a reduction in breast cancer [43]. There is no evidence at present to recommend increasing the frequency of screening in combined MHT users with no other risk factors.

In women with dense breasts, especially in those with familial risk or combined MHT users more sensitive imaging techniques are needed. Furthermore, because of the more aggressive tumoral phenotypes found in dense breasts, intervals between screening rounds should be shorter [44]. Incidence of interval cancers is increased in women at familial risk, as the absolute number of breast cancers is higher in this subgroup, and because of the more aggressive characteristics of the tumors [45]. Both extremely dense breasts and first-degree relatives with breast cancer are associated with at least a 2-fold increase in risk for breast cancer in women aged 40–49 years [46]. The FH01 trial has shown evidence of a reduction in advanced stage disease with yearly mammography in women aged 40–49 years with a medium familial risk of breast cancer [47]. In women with inherited gene mutations (BRCA1/2), it seems that annual MRI from age 25 and delayed alternating digital mammography from age 30 to 40 is probably the most effective screening strategy, despite false positives and radiation-induced cancers [48]. One could screen in these young women at high risk with MRI without mammography. MRI is not only more sensitive for detecting invasive cancers but also more sensitive in the detection of in situ cancers and avoids radiation.

Digital mammography was shown to be more sensitive than film mammography in women under the age of 50, in women with dense breasts, and in premenopausal or perimenopausal women [49]. However, specificity was lower and the extra tumors detected by digital mammography mainly had a more favorable prognosis, increasing thus the risk of false positives and overdiagnosis. Variations in mammographic density over the menstrual cycle are small for women examined by either film or digital mammography. Timing of mammography in the menstrual cycle is unlikely to have a significant influence in breast cancer detection screening mammography [50]. The American Cancer Society mentions that a mammography in the follicular phase may be less painful and may

be associated with better pictures. 'Try to schedule your mammogram at a time of the month when your breasts are not tender or swollen to help to reduce discomfort and assure a good picture' http://www.cancer.org/cancer/breastcancer/moreinformation/breastcancerearlydetection/breast-cancer-early-detection-acs-rec-mammograms. Although ACS does not mention anything on the timing of MRI, absence of congestion during the first half of the cycle, may facilitate the interpretation of the MRI examination.

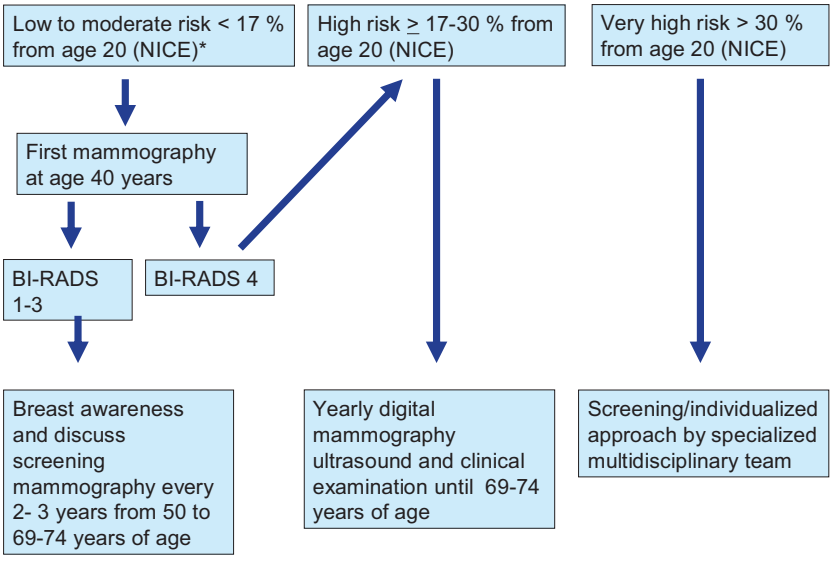
In a large retrospective cohort, ultrasonography has been shown to fully compensate the lack of sensitivity of mammography in dense breasts. Indeed, the rate of underlying cancers in dense breasts screened by mammography and ultrasonography was similar to mammography alone in non-dense breasts, despite the higher incidence of cancers in dense breasts [51]. However, adding ultrasonography systematically to mammography increases significantly the biopsy rate, averaging 5% of women screened, with only 7.4% of those women found to have cancer [52,53]. Moreover, this imaging technology is operator-dependent. We recommend that ultrasonography is added to mammography only in dense or very dense breasts, and is carried out by trained radiologists.

Despite its high sensitivity, addition of screening MRI rather than ultrasound to mammography in women at intermediate risk with dense breasts may not be appropriate, particularly when the current high false positive rates (especially in young women with dense breasts), the cost, and the reduced tolerability of MRI are considered [54].

5. Proposed algorithm

Further studies are needed for refining individual risk evaluation, improving sensitivity and specificity of imaging techniques and validating prognostic factors. However, prospective randomized controlled trials about individualized screening would need to follow-up large populations for at least 20 years and may never be conducted. Also rapid advances in imaging techniques, which would need validation, also needs to be borne in mind. We therefore propose that waiting for decades with the current evidence regarding population screening is not justified and that the time has come for individualized screening.

This algorithm is an example of individualized screening that can be used in clinical practice. This is based on familial risk and Breast Imaging Reporting and Data System (BI-RADS) category [55,56]. For the reasons explained before, it has not been validated by prospective clinical trials.



*NICE guidelines 2013 [55].

6. Conclusions

Individualizing screening appears to be a relevant strategy for improving effectiveness on breast cancer mortality without increasing costs and harms for the vast majority of women and society. There is a need to intensify screening in a minority of higher risk women by increasing the frequency of mammography and/or by addition of other imaging modalities to mammography. This intensification comes at the price of a higher numbers of false positives and biopsies. On the other hand, individualization reduces the screening burden in a majority of lower risk women. To decrease the costs and the burden of false positives and over-diagnosis, lower risk women should be screened less frequently (i.e. every 3 years as in the UK) and screening should stop when co-morbidities are significant. Lower risk women include mainly no familial risk, BIRADS 1 fatty breasts and menopause before the age of 35. The other protective factors such as normal postmenopausal BMI, no combined MHTuse and exercise are minor (RR > 0.5) and should not modify the screening strategy. Increasing screening in high risk women and decreasing screening in low risk women have not been and will probably never be studied in clinical trials because of ethical concerns. Moreover, it could take 20 years before showing an effect on breast cancer mortality can be demonstrated. However mathematical models show that intensifying in higher risk women and decrease frequency of mammograms in lower risk women is cost-effective [31].

Individualization of publicly organized population screening is a challenge and would be difficult to administer. It needs time-consuming discussion between women and health professionals about risks and benefit, recall and false positives. However a personalized strategy is likely to increase adherence to screening. Moreover, information about the possibility of false positive will reduce its psychological impact. Provision of balanced information does not appear to alter participation in screening but allows women to make an informed choice [57].

Contributors

HD and JD prepared the initial draft, which was circulated to EMAS board members for comment and approval; production was coordinated by MR and HD. HD and JD are joint first authors.

Competing interests

The authors have no conflicting interests to declare.

Funding

None was sought or secured for writing this statement.

Provenance and peer review

EMAS position statement.

References

[1] Dollé L, Depypere HT, Bracke ME. Anti-invasive/anti-metastasis strategies: new roads, new tolls and new hopes. Curr Cancer Drug Targets 2006;6(8):729–51.
[2] Santen R, Songa Y, Yuea W, Wanga J-P, Heitjanb D. Effects of menopausal hormonal therapy on occult breast tumors. J Steroid Biochem Mol Biol 2013;137:150–6.
[3] Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes – dealing with the diversity of breast cancer: highlights of the St. Gallen international expert consensus on the primary therapy of early breast cancer 2011. Ann Oncol 2011;22:1736–47.
[4] Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. CDS Rev 2011;(1):CD001877.
[5] Suhrke P, Mæhlen J, Schlichting E, et al. Effect of mammography screening on surgical treatment for breast cancer in Norway: comparative analysis of cancer registry data. Br Med J 2011;343:1–8.
[6] Burton RC, Bell RJ, Thiagarajah G, Stevenson C. Adjuvant therapy, not mammographic screening, accounts for most of the observed breast cancer specific mortality reductions in Australian women since the national screening program began in 1991. Breast Cancer Res Treat 2012;131(3):949–55.
[7] Autier P, Boniol M. Pitfalls in using case–control studies for the evaluation of the effectiveness of breast screening programmes. Eur J Cancer Prev 2013;22(September (5)):391–7.
[8] Berry DA. Failure of researchers, reviewers, editors, and the media to understand flaws in cancer screening studies: application to an article in cancer. Cancer 2014, http://dx.doi.org/10.1002/cncr.28795. PubMed PMID: 24925345 [Epub ahead of print].
[9] Kopans DB, Webb ML, Cady B. The 20-year effort to reduce access to mammography screening: historical facts dispute a commentary in Cancer. Cancer 2014, http://dx.doi.org/10.1002/cncr.28791. PubMed PMID: 24925233 [Epub ahead of print].
[10] van der Waal D, Verbeek AL, den Heeten GJ, Ripping TM, Tjan-Heijnen VC, Broeders MJ. Breast cancer diagnosis and death in the Netherlands: a changing burden. Eur J Public Health 2014, pii: cku088 PubMed PMID: 24972595 [Epub ahead of print].
[11] Weedon-Fekjær H, Romundstad PR, Vatten LJ. Modern mammography screening and breast cancer mortality: population study. Br Med J 2014;348:g3701, http://dx.doi.org/10.1136/bmj.g3701. PMCID: PMC4061379.
[12] American Cancer Society. Global cancer facts and figures; 2008 http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-027766.pdf
[13] Lietzen LW, Sørensen GV, Ording AG. Survival of women with breast cancer in central and northern Denmark, 1998–2009. Clin Epidemiol 2011;3(Suppl. 1):35–40.
[14] Autier P, Boniol M, Gavin A, Vatten LJ. Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database. Br Med J 2011;343:d4411.
[15] Gøtzsche PC, Jørgensen KJ. Screening for breast cancer with mammography. CDS Rev 2013;6:CD001877, http://dx.doi.org/10.1002/14651858.CD001877.pub5. PubMed PMID: 23737396.
[16] Alexander F, Roberts MM, Lutz W, Hepburn W. Randomisation by cluster and the problem of social class bias. J Epidemiol Community Health 1989;43(March (1)):29–36.
[17] Andersson I, Aspegren K, Janzon L, et al. Mammographic screening and mortality from breast cancer: the Malmö mammographic screening trial. Br Med J 1988;297(6654):943–8.
[18] Nyström L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet 2002;359:909–19.
[19] Tabar L, Vitak B, Chen TH, et al. Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. Radiology 2011;260:658–63.
[20] Shapiro S, Venet W, Strax P, Venet L, Roeser R. Selection, follow-up, and analysis in the Health Insurance Plan Study: a randomized trial with breast cancer screening. Natl Cancer Inst Monogr 1985;67(May):65–74.
[21] Miller AB, Wall C, Baines CJ, Sun P, To T, Narod SA. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. Br Med J 2014;348:g366, http://dx.doi.org/10.1136/bmj.g366.
[22] Frisell J, Lidbrink E, Hellström L, Rutqvist LE. Followup after 11 years – update of mortality results in the Stockholm mammographic screening trial. Breast Cancer Res Treat 1997;45(September (3)):263–70.
[23] Johns LE, Moss SM, Trial Management Group. Randomized controlled trial of mammographic screening from age 40 ('Age' trial): patterns of screening attendance. J Med Screen 2010;17(1):37–43, http://dx.doi.org/10.1258/jms.2010.009091.
[24] Autier P. Screening for breast cancer: worries about its effectiveness. Rev Prat 2013;63(December (10)):1369–77.
[25] Drukker CA, Schmidt MK, Rutgers EJ, et al. Mammographic screening detects low-risk tumor biology breast cancers. Breast Cancer Res Treat 2014;144(1):103–11.
[26] Zahl PH, Jørgensen KJ, Gøtzsche PC. Lead-time models should not be used to estimate overdiagnosis in cancer screening. J Gen Intern Med 2014 [Epub ahead of print].
[27] Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. Lancet 2012;380:1778–86.
[28] Gøtzsche PC, Jørgensen KJ. The benefits and harms of breast cancer screening. Lancet 2013;381:799.
[29] Welch HG, Passow HJ. Quantifying the benefits and harms of screening mammography. J Am Med Assoc 2014;174:448–54.
[30] Belgian Cancer Registry. http://www.kankerregister.org/ [accessed 28.08.14].
[31] Schousboe JT, Kerlikowske K, Loh A, Cummings SR. Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. Ann Intern Med 2011;155:10–20.
[32] Heys GJ, Mill AJ, Charles MW. Enhanced biological effectiveness of low energy X-rays and implications for the UK breast cancer screening programme. Br J Radiol 2006;79:195–200.
[33] Hauge IH, Pedersen K, Olerud HM, Hole EO, Hofvind S. The risk of radiation-induced breast cancers due to biennial mammographic screening in women aged 50–69 years is minimal. Acta Radiol 2013, pii: 0284185113514051. [Epub ahead of print].
[34] Onega T, Beaber EF, Sprague BL, et al. Breast cancer screening in an era of personalized regimens: a conceptual model and National Cancer Institute initiative for risk-based and preference-based approaches at a population level. Cancer 2014, http://dx.doi.org/10.1002/cncr.28771 [Epub ahead of print].
[35] Desreux J, Bleret V, Lifrange E. Should we individualize breast cancer screening? Maturitas 2012;73:202–5.
[36] Pace LE, Keating NL. A systematic assessment of benefits and risks to guide breast cancer screening decisions. J Am Med Assoc 2014;311(13):1327–35, http://dx.doi.org/10.1001/jama.2014.1398. PubMed PMID: 24691608.
[37] Olsen AH, Bihrmann K, Jensen MB, Vejborg I, Lynge E. Breast density and outcome of mammography screening: a cohort study. Br J Cancer 2009;100(7):1205–8.
[38] Checka CM, Chun JE, Schnabel FR, Lee J, Toth H. The relationship of mammographic density and age: implications for breast cancer screening. Am J Roentgenol 2012;198(March (3)):292–5.
[39] Kerlikowske K, Cook A, Buist DSM, et al. Breast cancer risk by breast density, age, menopause, and postmenopausal hormone therapy use. J Clin Oncol 2010;28(24):3830–7.
[40] Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med 2007;356:227–36, http://dx.doi.org/10.1056/NEJMoa062790.
[41] Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Int J Cancer 2005;114(3):448–54.
[42] Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estradiol-progestogen therapy. Obstet Gynecol 2009;113:65–73.
[43] Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. Lancet Oncol 2012;13(5):476–86.
[44] Yaghjyan L, Colditz GA, Collins LC, et al. Mammographic breast density and subsequent risk of breast cancer in postmenopausal women according to tumor characteristics. J Natl Cancer Inst 2011;103:1179–89.
[45] Eerola H, Heikkila P, Tamminen A, et al. Histopathological features of breast tumours in BRCA1, BRCA2 and mutation-negative breast cancer families. Breast Cancer Res 2005;7(1):R93–100.
[46] Nelson HD, Zakher B, Cantor A, et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. Ann Intern Med 2012;156(9):635–48.
[47] FH01 collaborative teams. Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: tumour characteristics and projected effect on mortality in the prospective, single-arm, FH01 study. Lancet Oncol 2010;11:1127–34.
[48] Lowry KP, Lee JM, Kong CY, et al. Annual screening strategies in BRCA1 and BRCA2 gene mutation carriers: a comparative effectiveness analysis. Cancer 2012;118(8):2021–30.
[49] Pisano ED, Gatsonis C, Hendrick E, et al. Diagnostic performance of digital versus film mammography for breast-cancer screening. N Engl J Med 2005;353:1773–83.
[50] Hovhannisyan G, Chow L, Schlosser A, Yaffe MJ, Boyd NF, Martin LJ. Differences in measured mammographic density in the menstrual cycle. Cancer Epidemiol Biomarkers Prev 2009;18(7):1993–9, http://dx.doi.org/10.1158/1055-9965.EPI-09-0074.
[51] Corsetti V, Houssami N, Ghirardi M, et al. Evidence of the effect of adjunct ultrasound screening in women with mammography-negative dense breasts: interval breast cancers at 1 year follow-up. Eur J Cancer 2011;47(7):1021–6.

[52] Berg WA, Zhang Z, Lehrer D, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. J Am Med Assoc 2012;307(13):1394–404.
[53] Nothacker M, Duda V, Hahn M, et al. Early detection of breast cancer: benefits and risks of supplemental breast ultrasound in asymptomatic women with mammographically dense breast tissue: a systematic review. BMC Cancer 2009;9:335.
[54] Morrow M, Waters J, Morris E, et al. MRI for breast cancer screening, diagnosis, and treatment. Lancet 2011;378(9805):1804–11.
[55] NICE guidelines [CG164]. Familial breast cancer: Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer; June 2013 [accessed 21.08.14].
[56] American College of Radiology BI-RADS® – Mammography 2013. http://www.acr.org/Quality-Safety/Resources/BIRADS/Mammography [accessed 27.08.14].
[57] Mathieu E, Barrat A, Davey HM, et al. Informed choice in mammography screening. Arch Intern Med 2007;167(19):2039–46.