Chapter
08

General discussion

Female breast cancer has now replaced lung cancer as the most frequently diagnosed cancer worldwide, resulting in a substantial disease burden on society [1]. In the Netherlands where population-based screening programs have been introduced for decades, proper evaluation of current breast cancer screening programs and the exploration of the possibility of new screening strategies and modalities are essential to improve the screening effectiveness in the general population. However, for developing countries such as China, more studies are required on whether and how to implement a national screening program. This thesis aimed to provide evidence on the improvement of breast cancer screening practices in both the Netherlands and China from three perspectives: (1) Experience learned from current organised mammography screening programs; (2) Expanding the use of mammography in Asian countries, particularly for the Chinese population; (3) Exploring the feasibility of new technologies in women with dense breasts.

Summary of key findings

Although regular mammography screening has shown its potential in reducing mortality, the percentages of mortality reduction varied substantially from 0% to 50% among different studies [2]. The wide range of mortality reduction can be attributed to many factors, such as population characteristics, participation rate, mammographic sensitivity, different screening strategies (screening interval and eligible age), and different follow-up time [2]. To deliver better screening practices and to achieve a more favourable mortality reduction, enhancing the knowledge of mammographic sensitivity and improving participation rate are important. Therefore, in ***Part 1***, we first developed a novel method to improve the estimates of mammography sensitivity as a continuous function of tumour size by using aggregated data reported from the Dutch breast cancer screening program **(*Chapter 2*)**. Aggregated data which included 22,915 screen-detected and 10,670 interval breast cancers were used to develop the sensitivity model. The model showed that mammographic sensitivity increased from 0 to 85% for tumour sizes from 2 to 20 mm. Compared with other models which estimated a 100% sensitivity for tumours from 15-20 mm and over [3,4], the sensitivity of 85% for a tumour diameter of 20 mm estimated by our model seems more reliable. Such a size-specific model as presented in our study will provide more detailed information on mammographic sensitivity than only reporting an overall sensitivity or sensitivities categorized by breast density groups. In addition, our sensitivity model can be incorporated in cost-effectiveness models for breast cancer screening programs, which could provide relevant evidence on the optimization of screening strategies and thus assist screening program organisers in policy-making. ***Chapter 3*** assessed the determinants related to non-participation in organised, population-based screening programs using a meta-analysis. Only studies that obtained non-participation data from registration systems of screening programs were included as self-reported data are likely to overestimate levels of participation. The findings indicated that lower income, younger age, lower education, living at a larger distance from an assigned screening unit, being unmarried, being an immigrant, and having a male family physician are associated with a higher non-participation in organised, population-based breast cancer screening programs. Compared to other meta-analyses including self-reported data, or studies focused on an opportunistic screening setting,

similar determinants were found. However, in our study, the associations were less strong. Possible explanations include recall bias of self-reported data, and fundamental differences between organized opportunistic screening programs in terms of implementation strategies and population characteristics. In addition, substantial heterogeneity was found among the studies. Of note, when we stratified the analysis by sending a reminder or not, we found that in the strata where no reminder was sent, women living in urban areas were less likely to participate screening than women in rural areas, where if a reminder was sent, women who live in urban area were more likely to participate. The findings implied that for women who live in urban areas, sending a reminder is beneficial for the improvement of screening participation, however, it remains questionable whether such a positive effect is present in women who live in rural areas.

As Asian women tend to have more dense breasts and a younger onset age of breast cancer, and as the diagnostic accuracy of mammography is lower in dense breasts and in women at a younger age [5-7], in ***Part 2***, we explored whether mammography could be effective and cost-effective when used as a standard screening modality in the Chinese population. In ***Chapter 4***, a meta-analysis was performed to compare the diagnostic accuracy of mammography and ultrasound, where the latter was considered as a possible alternative for breast cancer screening in Asian women because of its superiority in dense breasts, accessibility, and low costs. The results showed that even in Asian countries where women tend to have smaller and more dense breasts, mammography still has a higher sensitivity and a comparable specificity compared to ultrasound, and therefore can be considered as a more favourable screening method. However, whether mammography screening should be recommended in Asian countries needs careful considerations, as evidence on long-term outcomes and the cost-effectiveness of mammography screening in Asian settings is required. Given the long follow-up period and large population required to evaluate the cost-effectiveness of breast cancer screening, we therefore used, in ***Chapter 5***, a validated simulation model (SiMRiSc) to evaluate the long-term benefits and cost-effectiveness of mammography screening in urban China. The SiMRiSc model was adapted to the Chinese population, by updating parameters based on available data for the Chinese population. The base scenario was biennial mammography screening for women aged 45–70 years in accordance with the 2019 Chinese breast cancer screening guideline [8], and seven alternative scenarios were then simulated by varying the screening intervals and participant ages. At a threshold of triple the GDP, the simulation elucidated that biennial mammography screening for women aged from 45-70 years was cost-effective in urban China, producing an average cost-effectiveness ratio of 17,309 USD/LYG when compared with no screening and an incremental cost-effectiveness ratio (ICER) of 25,261 USD/LYG when compared with the previous efficient scenario. The budget impact analysis showed that during ten years, screening would incur a substantial cost. Given China's large geographical and socioeconomic disparities, further research is needed to develop tailored screening strategies and therefore improve screening practices among Chinese women.

Due to the imperfect sensitivity and specificity of mammography, several advanced techniques have been proposed to improve screening effectiveness especially in women with dense breasts. The association between high breast density and mammography screening effectiveness are two-folds; higher breast density might elevate the risk of developing breast

cancer [9], meanwhile, on mammograms, tumours might be masked by dense tissues, which may lead to misdiagnosis [10]. Therefore, we explored the potential use of two advanced screening techniques (DBT and AP-MRI) in a population-based screening program in ***Part 3***. Specifically, ***Chapter 6*** assessed the cost-effectiveness of DBT in the general population and in women with dense breasts only. DBT is a relatively new technique with limited data reporting on its sensitivity in a population-based screening setting. To find the threshold sensitivity from which DBT could be cost-effective we performed this analysis by simulating a range of DBT sensitivities. Based on our analysis, DBT is more likely to be a cost-effective alternative to DM in women with dense breasts, and the threshold sensitivity was 90% and 80% at €96 and €80 per DBT screen. However, whether DBT could be a cost-effective alternative for women with non-dense breasts, highly depends on the costs of DBT per screen. In ***Chapter 7***, we investigated the cost-effectiveness of an abbreviated MRI protocol in women with dense breasts (heterogeneously/extremely dense) in a population-based biennial screening program. Again, the micro-simulation model SiMRiSc was applied, with parameters updated for women with dense breasts. In addition, in this analysis, instead of assuming that breast density remained constant, we modelled breast density dynamically to reflect the fact that breast density reduces with the increased age. The findings suggest that population-based biennial breast cancer screening with AP-MRI from age 50-65 for women with extremely dense breasts might be a cost-effective alternative to mammography with an ICER of € 16,038/LYG. However, it is not a cost-effective option for women with heterogeneously dense breasts. Although the results of our studies supported stratified screening strategies for women with dense or only extremely dense breasts, we need to emphasize that a differentiated screening strategy for this group needs future research on how to apply or incorporate in current screening programs (Figure 1).

Figure 1 Practical issues related to the implementation of a stratified screening programme [11]

Methodological considerations

With the development of internet and publication policies such as open-access, more and more data become accessible, which allows researchers to produce new knowledge by using published resources. These changes have boomed the use of meta-analyses and model studies especially in informing debates in the field which requires substantial investments in finance, human resources, and time like the implementation and evaluation of a population-based screening program. The results presented in this thesis are based on meta-analysis and model studies, using already available data. Although these study designs could provide reliable evidence on the topics of interest, some limitations need to be acknowledged.

Meta-analysis: the need of individual participant data

Although meta-analyses have been widely used and are considered the best source of evidence, heterogeneity, i.e., variations in study outcomes, may exist between studies [12]. The heterogeneity could be constrained by applying restricted inclusion criteria [13], however, sometimes a high heterogeneity is expected in certain types of meta-analyses such as a meta-analysis focusing on diagnostic accuracy (as shown in ***Chapter 4***). If there are plenty of studies included, subgroup analyses or stratified analyses are useful tools to explore the source of heterogeneity. In ***Chapter 3***, we performed several stratified analyses, and found that stratification factors such as income level, number of comorbidities could partly explain the heterogeneity across the studies, but the heterogeneity in almost all stratified groups remained above a substantial level ($I^2 > 50\%$). When possible, a meta-analysis based on individual data can be used to explore the source of heterogeneity in a more informative way. The use of individual patient data can improve the reliability of pooled estimations as it enables to define exposures and outcomes consistently and analyse them similarly. Although it is challenging to get access to individual-based data [13,14], systematic efforts have been devoted to eliminate barriers of data sharing. For example, the FAIR principle (Findable, Accessible, Interoperable and Reusable research data) has been advocated, which requires researchers to share their data and make data reusable to others [15,16]. With continuing efforts, meta-analyses using individual participant data would become easier to perform and therefore could provide more reliable results in the near future [16].

Modelling studies: Strengths and limitations

In this thesis, we used the SiMRiSc micro-simulation model to simulate the long-term effectiveness and cost-effectiveness of breast cancer screening in both the Netherlands and China after adapting the input parameters for the study purposes. Compared with the classic Markov cohort model, the micro-simulation model has several strengths. First, a micro-simulation model can provide detailed information on individual trajectories of disease progression and the impact of screening rather than just simulate the mean response of a homogeneous cohort [17,18]. In addition, the stochastic variations in disease progression on an individual's level can also be added in a micro-simulation model, which provides more reliable estimates on the outcomes [18].

Several improvements on the SiMRiSc model were made in this thesis. First, the input parameters related to mammographic sensitivity were renewed. In the previous version of the SiMRiSc model, mammographic sensitivity was only based on BI-RADS density categories. However, as tumour size is a crucial factor of mammographic sensitivity, in the new version (which was applied in ***Chapter 5 and 7***), mammographic sensitivity was modelled as a continuous function of tumour size and breast density. The validation using data from the National evaluation of breast cancer screening in the Netherlands (LETB) showed that the new version gave a better fit, especially for the tumour size distribution of the screen-detected cancers (Figure 2) [19,20]. In addition, with the cooperation of computer scientists, the code of the SiMRiSc model is open-access (available from https://fbb-git.gitlab.io/simrisc), which further improves model transparency.

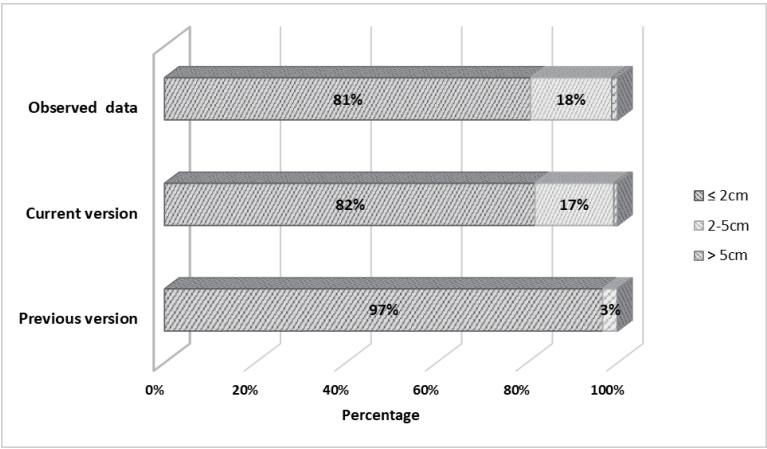

Figure 2 Tumour size distribution of screen-detected cancers [19,20]

Although the SiMRiSc model used in this thesis had been previously validated and the validation showed a good fitness with observed data, there are some limitations that can be improved in future studies. First of all, due to the scarce data on the natural history of ductal carcinoma in situ (DCIS), we did not simulate it although DCIS holds a share of approximately 20% of all mammography screen-detected tumours in the Netherlands [19]. The impact of excluding DCIS on the screening cost-effectiveness is two-fold. On the one hand, the early detection of DCIS might improve screening cost-effectiveness; on the other hand, some DCIS tumours, especially when categorized as low-grade, might lead to overdiagnosis and related harms (such as unnecessary diagnostic procedure, psychological stress and overtreatment) [21]. Currently ongoing low-risk DCIS trials such as the LORD trial and the LORIS have proposed an intensive monitoring strategy rather than a direct treatment of DCIS [22,23]. Such trials can provide a better understanding of the natural history of DCIS, which could be used as a reliable source for incorporation of DCIS in the SiMRiSc model. This will enable the SiMRiSc model to quantify the impact of DCIS on the cost-effectiveness of screening and overdiagnosis.

Second, the tumour progression in our model was reflected by tumour size (T stage) only, the node stage (N) and metastasis stage (M) were not included. Although our model showed

a good fit with the observed data, we anticipate that integrating NM stages in our model has the potential to improve the model performance and to produce more convincing and detailed outputs especially for overdiagnosis estimation. Specifically, the distributions of NM stage per T stage can be added to better reflect the TNM stage distribution in real-world. By doing so, stage-specific costs rather than tumour size-specific costs can be used because the latter ones are not always available from literature. Moreover, adding NM-stage to current T stage-specific breast cancer survival is expected to improve the quantification of overdiagnosis as node-negative tumours are more likely to be overdiagnosed [24,25].

Third, whether the simulation model could achieve reliable outputs highly depends on the input parameters used. To ensure a good quality of input parameters, we used data from the national registry (for incidence and mortality), meta-analysed data by performing a literature search (for test diagnostic accuracy and breast density distributions), or data from large population-based data sources. However, it is not always the case that 'optimal' input values can be found, and this challenge is especially true in ***Chapter 5***, where the cost-effectiveness of mammography screening in the Chinese population was evaluated. Specifically, due to the limited availability of data in the Chinese population, parameters related to tumour growth were obtained from other Asian populations or western populations. Even though we do not anticipate that these data will alter the major conclusion for the urban Chinese population, future studies related to tumour growth are warranted as it not only enriches the data source for modelling studies but also advances the understanding of tumour progression in the Chinese population.

Implications and future perspectives

Implementing breast cancer screening in China

Although mammography screening has shown its benefits regarding mortality reduction in developed counties, mammography units are typically unavailable in China because of limited medical resources. As a result, other screening approaches such as clinical breast exam (CBE) or ultrasound have been used as primary tools in Chinese screening trials. Although the long-term benefit (i.e., mortality reduction) for these two approaches has not been confirmed yet [26,27], certain harms have been well-documented such as more false-positives, more unnecessary biopsies, and increased psychological strain [28]. Therefore, to decrease the substantial disease burden of breast cancer in China, the Chinese government introduced in 2019 a mammography-based biennial screening strategy for women aged 45–70 years [8]. Although biennial mammography screening has shown to be cost-effective in Western women, its cost-effectiveness in the Chinese population remains unknown due to (but not limited to) population characteristics such as a lower incidence of breast cancer and a younger mean age of onset [1,5]. The cost-effectiveness analysis presented in this thesis focused on an urban population only as we anticipated that a mammography-based screening strategy will first be implemented in urban areas, where medial resources are less limited and mammography units are more available. In addition, the breast cancer incidence is much lower in rural areas than in urban areas (22 vs 33 per 100,000 women) [29], which suggests that for rural areas screening might not be a favourable method to improve survival.

In urban areas, we found that biennial mammography screening from age 45-70 years old is cost-effective given a threshold of 3GDP. However, we need to emphasize that this favourable cost-effectiveness result was achieved based on several assumptions. First, we assumed that sufficient mammography equipment is available and that all eligible women could get a mammogram. However, this seems to be unlikely. According to data published by WHO, in China there are only 0.5 mammographs for every 10,000 cancer patients (all types of cancer considered), while for countries like the Netherlands and USA, the numbers are at least ten times higher (5.3 and 84.9, respectively) [30]. A reasonable conclusion can be drawn that a tremendous investment in mammography equipment in China is required before mammography screening can be widely implemented. Thus, a budget impact analysis considering capital costs would be needed by policymakers. In addition, we assumed that all women who got a positive mammography test will receive timely diagnosis and treatment. However, as the cost of further diagnosis and treatment cannot be totally covered by insurance, the compliance rate of referral is rather low in China. Studies showed that the compliance rate of referral was even lower than 50% in large cities such as Guangzhou [31], and 50-55% of medical expenditure was paid by out-of-pocket money by breast cancer patients [32]. These findings suggest that great efforts should be devoted to improve the compliance rate by ensuring timely referral, raising the reimbursement rates and establishing more health education programs to the general population. In conclusion, apart from a well-organised screening program, a long-term effectiveness of mortality reduction of breast cancer in urban China can only be achieved with sufficient and accessible facilities and sufficient financial support for diagnosis and treatment, comprehensive healthcare networks, and appropriate health education programs for the general population [33].

In rural areas, it remains questionable whether a population-based screening program should be implemented. According to principles of screening proposed by Wilson and Jungner, screening should be applied only when enough facilities for diagnosis and treatment, and adequate financial support are in place [33]. However, it is unlikely the case due to limited medical resources such as facilities and human resources, and insufficient financial support in rural areas [34]. Although a screening trial based on clinical breast examination and ultrasound has been implemented, its effectiveness remained questionable as it can potentially do more harm than good given that the incidence of breast cancer is rather low in rural areas (22 per 100,000 women) and that too many false-positives can be introduced by ultrasound [29,35]. Therefore, instead of implementing a population-based screening program that requires a large amount of money, it might be more appropriate to improving accessible and affordable health care in case of symptoms. Currently barriers for breast cancer patients in rural areas include limited or no access to proper health care, lack of trained oncologists and specialised medication, and financial constraints [36-38]. Therefore, establishing accessible cancer care centres and providing financial support would be of great importance to ensure timely diagnosis and treatment for women living in rural areas. Additionally, improving disease awareness in the general population could also be a useful strategy of downstaging [38]. In summary, compared to screening a vast number of asymptomatic women in rural China, downstaging symptomatic cancers, and ensuring timely and adequate treatment are essential factors to reduce the burden of breast cancer disease and to possibly improve survival in a more cost-effective way.

Tailored screening for women with dense breasts

The limited performance of mammography in women with dense breasts has been well-documented. Although women with dense breasts suffer a higher risk to develop breast cancer, they do not obtain similar benefits from mammography screening as women with non-dense breasts, Therefore, tailored screening for women with dense breasts has been advocated for years. Before a tailored screening strategy for dense breasts can be implemented, there are several issues needed to address.

First, it is important to identify how breast density should be assessed for stratified screening. The current Breast Imaging Reporting and Data System (BI-RADS, fifth edition) suggests a more subjective four-category overall assessment (category A-D) rather than using the percentage of fibroglandular density [39]. Initially, the breast density was estimated visually. However, this method can be quite subjective and might therefore be less reliable and lead to inconsistent results among radiologists [40]. Recently, automated quantitative assessments tools became available which can provide reproducible and more reliable density percentages based on either area or volume. Ideally, the volume-based approach provides the most accurate estimates of fibroglandular density although it has limited use in the current screening setting as the volume-based assessment relies on specific software and complex algorithms [41]. Several fully-automated software tools have been developed to assess volumetric breast density, and some of these software tools such as Quantra and Volpara are commercially available [42]. Although these automated methods have a high reproducibility, some studies suggested that the agreement between the software and qualitative expert assessment still needs to be improved (the weighted kappa value ranged from 0.32-0.61) [43,44]. Recently, Lehman et al proposed a deep learning algorithm to assess mammographic breast density. The deep learning model showed good agreement with a manual BI-RADS density classification of radiologists in more than 10 000 consecutive mammograms (with a kappa value of 0.85) [45]. Therefore, it is promising to use artificial intelligence techniques for breast density classification and more studies on this topic are warranted.

Second, the age at which breast density should be assessed for screening stratification and the related screening frequency are also important issues that require further investigation. In ***Chapters 6 and 7***, the initial age for screening stratification was set at 50 years old, as it is the recommended starting age for women at average risk in the Dutch population-based breast cancer screening program. However, it is possible that more benefits and more favourable cost-effectiveness can be achieved if screening would be provided at an earlier age for women with dense or extremely dense breasts. A modelling study from the US suggested that breast density-stratified screening with baseline density assessment at age 40 years will be more cost-effective than stratified screening at age 50 years [46]. Although the results cannot be directly transferred to other screening settings, modelling studies that evaluating the starting screening age and screening frequency for women with dense breasts are required to provide more evidence on the optimization of breast cancer screening [46].

Third, which screening modality should be used as an alternative to mammography is an ongoing debate. In this thesis, we have evaluated the cost-effectiveness of DBT and MRI in the general population and women with dense breasts. Compared with mammography,

both DBT and MRI showed promising results in the screening of women with dense or extremely dense breasts in terms of cost-effectiveness. However, other methods such as contrast-enhanced mammography (CEM) are not studied in this thesis. CEM is an emerging technique that uses iodinated contrast materials for the visualization of breast neovascularity in a fashion similar to MRI [47]. The cost of CEM is slightly higher than that of DM, and is much lower than that of MRI [48]. Although the effectiveness of using CEM in population-based screening programs remains unknown, some studies suggests that the sensitivity of CEM and MRI is comparable in women at an elevated risk of breast cancer [49]. Therefore, CEM might be more cost-effective than MRI screening especially considering its lower cost [50]. In the future, studies that evaluate the effectiveness of CEM in a general population are warranted. Additionally, from a cost-effective perspective, comparisons among these three promising methods could provide more evidence on the preferred screening modality for women with dense breasts.

Conclusion

The work presented in this thesis provides evidence on the improvement of breast cancer screening practices in both the Netherlands and China. Specifically, for the Netherlands where a population-based screening program has been introduced for decades, a stratified screening strategy based on breast density can be a further improvement, and advanced screening modalities such as DBT and AP-MRI could be used as a cost-effective alternative to mammography in women with dense or extremely dense breasts. For urban China we found that mammography should be considered as a more favourable screening method than ultrasound, and biennial mammography screening from age 45-70 years old is economically attractive. Along with a well-organized screening program, providing sufficient facilities and financial support for diagnosis and treatment is also crucial to reduce mortality. For rural China, accessible and affordable health care and improved breast cancer awareness is of higher priority given the relatively low breast cancer incidence rate.

Reference

[1] International Agency for Research on Cancer. Global Cancer Observatory, http://gco.iarc.fr. Assessed on May 4th, 2021.

[2] Zielonke N, Gini A, Jansen EE, Anttila A, Segnan N, Ponti A, Veerus P, de Koning HJ, van Ravesteyn NT, Heijnsdijk EA, Heinävaara S. Evidence for reducing cancer-specific mortality due to screening for breast cancer in Europe: A systematic review. Eur J Cancer. 2020;127:191-206.

[3] Weedon-Fekjær H, Tretli S, Aalen OO. Estimating screening test sensitivity and tumour progression using tumour size and time since previous screening. Stat Methods Med Res. 2010;19:507-27.

[4] Abrahamsson L, Isheden G, Czene K, Humphreys K. Continuous tumour growth models, lead time estimation and length bias in breast cancer screening studies. Stat Methods Med Res. 2020;29:374-95.

[5] Leong SP, Shen ZZ, Liu TJ, Agarwal G, Tajima T, Paik NS, et al. Is breast cancer the same disease in Asian and Western countries? World J Surg. 2010; 34: 2308-24.

[6] Maskarinec G, Meng L, Ursin G. Ethnic differences in mammographic densities. Int J Epidemiol. 2001; 30: 959-65.

[7] Armstrong K, Moye E, Williams S, Berlin JA, Reynolds EE. Screening mammography in women 40 to 49 years of age: a systematic review for the American College of Physicians. Ann Intern Med. 2007; 146: 516-26.

[8] China Anti-Cancer Association. Breast cancer screening guideline for Chinese women. Cancer Biol Med. 2019; 16: 822–824.

[9] McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006;15(6):1159-69.

[10] Nelson HD, O'Meara ES, Kerlikowske K, Balch S, Miglioretti D. Factors associated with rates of false-positive and false-negative results from digital mammography screening: an analysis of registry data. Ann Intern Med. 2016;164:226–235.

[11] Dent T, Jbilou J, Rafi I, Segnan N, Törnberg S, Chowdhury S, Hall A, Lyratzopoulos G, Eeles R, Eccles D, Hallowell N. Stratified cancer screening: the practicalities of implementation. Public Health Genomics. 2013;16(3):94-9.

[12] Greco T, Zangrillo A, Biondi-ZoccaI G, Landoni G. Meta-analysis: pitfalls and hints. Heart Lung Vessel. 2013; 5(4): 219-225.

[13] Haidich AB. Meta-analysis in medical research. Hippokratia. 2010; 14(Suppl 1): 29–37.

[14] Lyman GH, Kuderer NM. The strengths and limitations of meta-analyses based on aggregate data. BMC Med Res Methodol. 2005;5:14.

[15] Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, Blomberg N, Boiten JW, da Silva Santos LB, Bourne PE, Bouwman J. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data. 2016;3:160018.

[16] Van Middelkoop M, Lohmander S, Bierma-Zeinstra SM. Sharing data–taming the beast: barriers to meta-analyses of individual patient data (IPD) and solutions. Br J Sports Med. 2020;54(14):822-824.

[17] Graves J, Garbett S, Zhou Z, Schildcrout JS, Peterson J. Comparison of Decision Modeling Approaches for Health Technology and Policy Evaluation. Med Decis Making. 2021;41(4):453-64.

[18] Krijkamp EM, Alarid-Escudero F, Enns EA, Jalal HJ, Hunink MM, Pechlivanoglou P. Microsimulation modeling for health decision sciences using R: a tutorial. Med Decis Making. 2018;38(3):400-22.

[19] LETB. National evaluation of breast cancer screening in the Netherlands 1990-2011/2012

[20] van Veldhuizen, Daniëlle. Optimization of mammographic sensitivity in breast cancer screening modeling. Internship Report, Biomedical Engineering. 2019. Available from: http://fse.studenttheses.ub.rug.nl/id/eprint/20223.

[21] van Seijen M, Lips EH, Thompson AM, Nik-Zainal S, Futreal A, Hwang ES, Verschuur E, Lane J, Jonkers J, Rea DW, Wesseling J; PRECISION team. Ductal carcinoma in situ: to treat or not to treat, that is the question. Br J Cancer. 2019;121:285-292.

[22] Francis A, Thomas J, Fallowfield L, Wallis M, Bartlett JM, Brookes C, Roberts T, Pirrie S, Gaunt C, Young J, Billingham L, Dodwell D, Hanby A, Pinder SE, Evans A, Reed M, Jenkins V, Matthews L, Wilcox M, Fairbrother P, Bowden S, Rea D. Addressing overtreatment of screen detected DCIS; the LORIS trial. Eur J Cancer. 2015; 51(16): 2296-303.

[23] Elshof LE, Tryfonidis K, Slaets L, van Leeuwen-Stok AE, Skinner VP, Dif N, Pijnappel RM, Bijker N, Rutgers EJ, Wesseling J. Feasibility of a prospective, randomised, open-label, international multicentre, phase III, non-inferiority trial to assess the safety of active surveillance for low risk ductal carcinoma in situ - The LORD study. Eur J Cancer. 2015;51(12):1497-510.

[24] Saadatmand S, Bretveld R, Siesling S, Tilanus-Linthorst MM. Influence of tumour stage at breast cancer detection on survival in modern times: population-based study in 173 797 patients. BMJ. 2015;351

[25] Brouckaert O, Schoneveld A, Truyers C, Kellen E, Van Ongeval C, Vergote I, Moerman P, Floris G, Wildiers H, Christiaens MR, Van Limbergen E. Breast cancer phenotype, nodal status and palpability may be useful in the detection of overdiagnosed screening-detected breast cancers. Ann Oncol. 2013;24(7):1847-52.

[26] Mittra I, Mishra GA, Singh S et al. A cluster randomized, controlled trial of breast and cervix cancer screening in Mumbai, India: methodology and interim results after three rounds of screening. Int J Cancer. 2010; 126: 976-984

[27] Dong H, Huang Y, Song F, Dai H, Liu P, Zhu Y, Wang P, Han J, Hao X, Chen K. Improved performance of adjunctive ultrasonography after mammography screening for breast cancer among Chinese females. Clin Breast Cancer. 2018;18(3):e353-e361.

[28] Nothacker M, Duda V, Hahn M, Warm M, Degenhardt F, Madjar H, Weinbrenner S, Albert US. 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(1):1-9.

[29] Zuo TT, Zheng RS, Zeng HM, et al. Female breast cancer incidence and mortality in China, 2013. Thorac Cancer. 2017;8(3):214-8.

[30] International cancer control partnership. https://www.iccp-portal.org. Assessed on June 25th, 2021.

[31] Yu HY, Li WP, Qi W, Xiu Z, Lian ZQ. Evaluation of breast screening in city women from 2006 to 2011. Chin J Cancer Prev Treat. 2013;20(12):894–897.

[32] Liao X, Shi JF, Liu JS, et al. Medical and non-medical expenditure for breast cancer diagnosis and treatment in China: a multi-center crosssectional study. Asia Pac J Clin Oncol. 2018;14:167-178.

[33] Andermann A, Blancquaert I, Beauchamp S, Déry V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bull World Health Organ. 2008; 86(4): 317-319.

[34] Guo B, Xie X, Wu Q, Zhang X, Cheng H, Tao S, Quan H. Inequality in the health services utilization in rural and urban China: a horizontal inequality analysis. Medicine (Baltimore). 2020; 99(2): e18625.

[35] Sun L, Sadique Z, dos-Santos-Silva I, Yang L, Legood R. Cost-effectiveness of breast cancer screening programme for women in rural China. Int J cancer. 2019;144(10):2596-604.

[36] Zhang H, Wang G, Zhang J, Lu Y, Jiang X. Patient delay and associated factors among Chinese women with breast cancer: A cross-sectional study. Medicine (Baltimore). 2019;98: e17454.

[37] Fan L, Strasser-Weippl K, Li JJ, St Louis J, Finkelstein DM, Yu KD, Chen WQ, Shao ZM, Goss PE. Breast cancer in China. Lancet Oncol. 2014;15:e279-89.

[38] Shah SC, Kayamba V, Peek Jr RM, Heimburger D. Cancer control in low-and middle-income countries: is it time to consider screening? J Glob Oncol. 2019;5:1-8.

[39] D'Orsi CJ, Mendelson EB, Ikeda DM et al. Breast Imaging Reporting and Data System: ACR BI-RADS. 5th ed. Reston, Va: American College of Radiology, 2013.

[40] Redondo A, Comas M, Macià F et al. Inter- and intra-radiologist variability in the BI-RADS assessment and breast density categories for screening mammograms. Br J Radiol. 2012;85(1019):1465–1470.

[41] Winkler NS, Raza S, Mackesy M, Birdwell RL. Breast density: clinical implications and assessment methods. Radiographics. 2015;35(2):316-24.

[42] Destounis S, Arieno A, Morgan R, Roberts C, Chan A. Qualitative versus quantitative mammographic breast density assessment: applications for the US and abroad. Diagnostics. 2017;7(2):30

[43] Youk JH, Gweon HM, Son EJ, Kim JA. Automated volumetric breast density measurements in the era of the BI-RADS fifth edition: a comparison with visual assessment. JR Am J Roentgenol. 2016;206(5):1056-62.

[44] Brandt K.R., Scott C.G., Ma L., Mahmoudzadeh A.P., Jensen M.R., Whaley D.H., Wu F.F., Malkov S., Hruska C.B., Norman A.D., et al. Comparison of clinical

and automated breast density measurements: Implications for risk prediction and supplemental screening. Radiology. 2016;279:710–719.

[45] Lehman CD, Yala A, Schuster T, Dontchos B, Bahl M, Swanson K, Barzilay R. Mammographic breast density assessment using deep learning: clinical implementation. Radiology. 2019;290(1):52-8.

[46] Shih YC, Dong W, Xu Y, Etzioni R, Shen Y. Incorporating baseline breast density when screening women at average risk for breast cancer: a cost-effectiveness analysis. Ann Intern Med. 2021;174(5):602-12.

[47] Patel BK, Lobbes MBI, Lewin J. Contrast Enhanced Spectral Mammography: A Review. Semin Ultrasound CT MR. 2018;39(1):70–79.

[48] Patel BK, Gray RJ, Pockaj BA. Potential cost savings of contrast-enhanced digital mammography. AJR Am J Roentgenol. 2017;208(6):W231-7.

[49] Jochelson MS, Pinker K, Dershaw DD, Hughes M, Gibbons GF, Rahbar K, Robson ME, Mangino DA, Goldman D, Moskowitz CS, Morris EA. Comparison of screening CEDM and MRI for women at increased risk for breast cancer: a pilot study. Eur J Radiol. 2017;97:37–43.

[50] Jochelson MS, Lobbes MB. Contrast-enhanced Mammography: State of the Art. Radiology. 2021;299(1):36-48.