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3349.

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Exploring the potential for improving public health cancer screening through the example of breast screening

PhD thesis

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Budapest
2025

Table of Contents

List of Abbreviations 3
1. Introduction 5
1.1. Epidemiology of Breast Cancer 5
1.2. Classification of Breast Cancer 7
1.3. Population-Based Cancer Screening 9
1.4. Breast Cancer Screening 11
2. Objectives 16
3. Methods 17
3.1. Literature Review 18
3.2. Methodological study: Protocol and Evaluation Framework Development 19
3.2.1. Development of the Screening Protocol 20
3.2.2. Development of the Evaluation Framework 21
3.3. Retrospective Observational Study 23
3.3.1. Study Design and Population 23
3.3.2. Classification of Breast Cancer 24
3.3.3. Statistical Methods 24
3.4. Language Editing 25
4. Results 26
4.1. Literature Review 26
4.2. Methodological study: Protocol and Evaluation Framework Development 33
4.2.1. Screening Protocol 33
4.2.2. Evaluation Framework 38
4.3. Retrospective Observational Study 39
4.3.1. Patient Characteristics 39
4.3.2. Distribution of Breast Cancer Cases 40
5. Discussion 44
5.1. The Position of Hungary's Organized Breast Cancer Screening Program within the Framework of International Guidelines and Recommendations 44
5.2. The Potential Role and Feasibility of ABUS as an Imaging Method in the Current Hungarian Breast Cancer Screening Program 46
5.3. Potential Directions for Hungarian Breast Cancer Screening Improvement based on the Result of a Real-World Data Analysis Focusing on the Distribution of the Age and the Molecular Subtypes of Newly Diagnosed Patients 48
5.4. Limitations of the Research 50
6. Conclusions 52
7. Summary 54

8. References 55
9. Bibliography of the candidate's publications 82
10. Acknowledgements 83

List of Abbreviations

ABB-MRI	abbreviated magnetic resonance imaging
ABUS	automated breast ultrasound
ACR	American College of Radiology
AI	artificial intelligence
AJCC	American Joint Committee on Cancer
BC	breast cancer
BI-RADS	Breast Imaging Reporting and Data System
CAD	computer-aided detection
CDR	additional cancer detection rate
CESM	contrast-enhanced spectral mammography
COVID-19	coronavirus disease 2019
DBT	digital breast tomosynthesis
DM	digital mammography
ECIBC	European Commission Initiative on Breast Cancer
EESZT	Electronic Health Care Service System
EFI	Health Promotion Office
EGFR	epidermal growth factor receptor
ER	oestrogen receptor
EU	European Union
EUSOBI	European Society of Breast Imaging
HER2	human epidermal growth factor receptor 2
HR	hormone receptors
HHUS	handheld ultrasound
ICD	International Classification of Diseases
IHC	immunohistochemistry
ISH	in situ hybridization
IT	information technology
Ki67	proliferation marker protein Ki-67
MRI	magnetic resonance imaging
NNK	National Public Health Centre

PR	progesterone receptor
TAJ	health insurance identification number
UICC	Union for International Cancer Control
USA	United States of America
WHO	World Health Organization

1. Introduction

1.1. Epidemiology of Breast Cancer

Breast cancer (BC) is the most common cancer in females worldwide, with an estimated 2.3 million new cancer cases (1 in 4 new cancer cases) in 2022 (Ferlay et al., 2024). BC is characterized with a globally steadily increasing incidence rate between 1990 and 2017 (Ginsburg et al., 2017; Lima et al., 2021; Zhang et al., 2023). The global prediction indicates a further continued rise in BC incidence in the forthcoming decades (Arnold et al., 2022; Li et al., 2022; Lima et al., 2021). However, future projections reveal a decrease in incidence among individuals over 50 years in high-income countries, a slight increase in incidence is anticipated among women aged younger than 50 years (Li et al., 2022).

BC also ranks as the leading cause of cancer death in the female population (Ferlay et al., 2024). Nevertheless, distinct trends emerge across geographical regions. High-income countries exhibit a recent decline in mortality rates (Hu et al., 2019). The factors contributing to this positive trend may involve well-funded and appropriately implemented, comprehensive national cancer plans encompassing health promotion, early diagnosis and consistent access to treatments and palliative care (Arzanova & Mayrovitz, 2022; Trapani et al., 2022). Whereas low- and middle-income countries have been characterised by stagnating or increasing mortality tendencies (Trapani et al., 2022).

In Hungary, BC represents a major health concern on a public and individual level as well. BC is the most common cancer in the Hungarian female population (Ferlay et al., 2024). It is responsible for nearly a quarter of all cancer cases in women (Ferlay et al., 2024). The age-standardized incidence rate for BC in Hungary surpasses the European Union (EU) and other Central European countries' averages, recording 148.3 cases per 100,000 individuals compared to 144.9 and 90.0-128.5, respectively, in 2018 (Dafni et al., 2019). A nationwide study conducted in Hungary revealed a significant rise in BC incidence (30.02%) in the age group under 50 years, alongside a modest decline (5.97%) in newly diagnosed cases among older individuals (Kiss et al., 2023).

Regarding BC mortality, Hungary observed fluctuations between 2040 and 2250 cases from 2010 to 2019, according to the Central Statistical Office (Kenessey et al., 2022), with no significant change detected over the past decade (Kiss et al., 2023). The age-

standardised mortality rate for BC patients stands also higher than the EU average (European standard population), registering at 38.2 cases per 100,000 person-years compared to 34.8 in the EU (Dafni et al., 2019).

In March 2020, the Coronavirus Disease 2019 (COVID-19) was declared a global pandemic by the World Health Organization (WHO), posing great challenges to the world. The impact of the reduction in physician-patient encounters and the temporary suspension of screening programmes was also detectable for BC (Mayo et al., 2021). Several countries experienced a decrease in BC incidence in the first period of the pandemic compared to previous years (Eijkelboom et al., 2023; Eijkelboom et al., 2021a; Mentrasti et al., 2022; Ruiz-Medina et al., 2021; Voigtländer et al., 2023), with rates rising again as restrictions eased (Eijkelboom et al., 2023; Garrido-Cantero et al., 2023).

In Hungary, as part of the health policy response to the COVID-19 pandemic, population-based cancer screening programmes have been suspended for a 3-month period (16 March 2020 and 01 June 2020) and for a month between 9 April and 29 April 2021). As a consequence, a Hungarian study (Elek et al., 2022) indicated a 30% reduction in BC incidence in the second quarter of 2020. Although BC incidence subsequently started to increase in line with trends in the EU, it did not reach historical levels by the second quarter of 2021 (Elek et al., 2022). Consistent with another Hungarian study (Kiss et al., 2023), the decline in BC incidence was predominantly observed in the older population. Furthermore, the study noted an 11.58% drop in BC incidence from 2019 to 2020 across the entire target population, representing over 900 women who may have been received their BC diagnoses at more advanced stages due to interruptions in screening program (Kiss et al., 2023). The long-term consequences of delayed diagnosis and treatment remain uncertain. Modelling predictions suggest that a lag of 3 or 6 months lead to patients being diagnosed at later stages, potentially impacting their 5- and 10- year survival rates, and resulting in increased healthcare expenses (Degeling et al., 2021). This underlines the importance of the stage at diagnosis, which is crucial for the course of BC and its burden at both individual and societal level. Consequently, it is essential to examine in detail how BC is classified by stage and biological characteristics.

1.2. Classification of Breast Cancer

BC constitutes a broad group of disease with heterogeneous characteristics, with different prognosis, expected survival and treatment possibilities. The diagnosis of BC is based on a clinical examination combined with imaging techniques, confirmed by pathological evaluation. As a result of this process, the histological type of the breast tumour, its TNM classification, and immunohistochemical evaluation are available, which form the basis for multidisciplinary decision-making regarding tumour therapy. The histological classification of tumours is specified according to the WHO classification (IARC, 2019). The TNM Classification of Malignant Tumours is an internationally accepted classification system that divides tumours according to tumour size (T-tumour), lymph node involvement (N-regional lymph nodes) and the presence of distant metastasis (M-metastasis). According to the most recent recommendation (Zhu & Dogan, 2021), this classification is called, anatomic TNM staging, referring to the fact that it takes into account only the above-mentioned anatomical features of the tumours when categorising them.

However, following the update adopted by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), prognostic (affecting the outcome of the tumour) and predictive (affecting the treatment of the tumour) markers (i.e., oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and histologic grade) are incorporated into the BC prognostic stage groups (Amin et al., 2017), that facilitate more personalized treatments.

From an immunohistochemical perspective, BC is grouped in molecular subtypes based on certain molecular markers. ER and PR have a significant impact on tumour biology and treatment options. The presence of ER and PR in the tumour cells are tested with immunohistochemistry (IHC) (Allison et al., 2020), in the course of which the staining rate of the core biopsy or cytology sample is evaluated (Hammond et al., 2010). Cases with no staining or less than 1% staining are considered hormone receptor negative. Tumours with hormone receptor staining between 1% to 10% (including 10%) are classified in the low positive group. Tumours with staining greater than 10% are defined as hormone receptor positive (Allison et al., 2020).

HER2 receptor is a member of the epidermal growth factor receptor (EGFR) family. Its overexpression is associated with unfavourable prognosis (Cooke et al., 2001). Targeted

treatments for this type of BC are available that enable significant increases in patient survival (Smith et al., 2007). The HER2 receptor-related feature of the tumour is also investigated using IHC techniques. Tumours are classified into IHC 0, IHC +, IHC 2+ and IHC 3+ groups based on staining patterns. IHC 3+ tumours are considered HER2 positive without further testing, IHC 0 and + tumours are classified as HER2 receptor negative, while further in situ hybridization (ISH) assay is used to determine HER2 receptor status in IHC 2+ cases.

Factors affecting the prognosis of BC include Ki67 protein, whose expression level is characteristic of tumour cell proliferation (Davey et al., 2021). This is also tested using IHC method. Equal or less than 5% staining is clearly low, while a value above 30% indicates high proliferation. At values between these two, the tumour proliferation character is ambiguous (Burstein et al., 2021).

Taking these characteristics into account, the following main subgroups of BC have been defined (Orrantia-Borunda et al., 2022):

- Luminal A tumours (ER and PR +, HER2 - and low expression of Ki67) are characterized by a slow growth rate. They are associated with a favourable outcome, exhibiting a reduced likelihood of recurrence and an elevated rate of survival.
- Luminal B tumours (ER + and/or PR +, HER2 -/+ and high expression of Ki67) are of higher grade and worse prognosis than Luminal A.
- The HER2-positive tumours (ER and PR -, HER2 +, based on Ki-67 two subgroups Ki-67:15–30% or Ki-67>30%) grow faster and are more aggressive than cancers from the Luminal groups. However, HER2-targeted therapies have improved the prognosis of this type of BC.
- Triple-negative BC (ER and PR -, HER2 -, with several additional subgroups based on further immunohistochemical differences) is hallmarked by its aggressiveness, early relapse, and a greater tendency to present in advanced stages. It is also more frequently observed in women under 40 years of age.

While tumours across different molecular subtypes display distinct traits, all forms have a shared attribute, that outcomes and chances of survival improve with early detection. For those at risk, this can be ensured through regular, evidence-based screening programmes.

1.3. Population-Based Cancer Screening

Cancer screening aims to identify latent diseases in asymptomatic individuals. There are two main approaches for cancer screening. For opportunistic screening, patients can take the test on demand, lacking a structured invitation system and often lacking systematic evaluation. On the other hand, population-based cancer screening programmes are carefully coordinated typically at a national or a regional level and their performance and outcome are monitored.

For a screening program to achieve its expected public health benefit, it must meet certain criteria. The initial framework for evaluating the suitability of screening programs was established based on the Wilson & Jungner principles, developed in 1968 (Wilson et al., 1968). Since then, multiple expert organizations (WHO, 2020; WHO, 2022; Andermann et al., 2008; Council of the European Union, 2003; European Commission, 2022; Ponti et al., 2017; Lönnberg et al., 2017) have contributed to refining and augmenting these principles over the following decades. Although modifications and country-specific considerations have been introduced, the fundamental tenets governing population-based screening remain unchanged.

The disease targeted for screening should represent a substantial societal burden. Additionally, in the natural course of cancer, there is a long detectable presymptomatic or precancerous phase, wherein early detection offers the potential for mitigating disease incidence, severity or mortality (WHO, 2020).

The screening method should be simple, safe, accurate, affordable, accepted by both the population and the professional community (Sankaranarayanan, 2014). In the era of swift advancements in medical technology, research for the development of screening programs often explores this area. However, it is crucial to uphold the principles when introducing novel screening modalities.

Further important criterion for organised screening programs concerns the definition of the eligible population. It is characterized by an elevated risk of developing a specific cancer relative to the general population. The clarification is based on evidence that weighs the balance between benefits and harms. An effective screening program can yield substantial advantages such as diminished disease severity and morbidity, less invasive treatment, reduced incidence, and mortality (WHO, 2020). However, it is essential to acknowledge the potential harms associated with screening, including overdiagnosis,

overtreatment, false positives and negatives, as well as adverse physical and psychological effects of the screening test. A screening program is considered effective if the benefits of the screening outweigh its disadvantages (Lönnberg et al., 2017).

Within the framework of the population screening program, the eligible population is invited in person, at regular intervals. The invitation is centrally regulated, systematic, based on registers using a call and recall system (Council of the European Union, 2003). In order to realise the benefits of the screening programme, it is essential that the target group participates in the screening as much as possible. WHO calls for at least 70% participation rate to ensure public health benefit from screening programmes (WHO, 2008). Every participant should be provided with the access to the screening program with the same quality and support to ensure equality for the members of the target group (WHO, 2022).

Beyond carrying out of the screening test itself, a comprehensive screening programme encompasses the identification, outreach, notification, monitoring of the target population and diagnosing than treating positive cases, as well (Lynge et al., 2012). Ensuring adequate infrastructure, human and financial resources to every element of the process is imperative to optimize programme benefits (Sankaranarayanan, 2014). The success of this endeavour relies on the presence of a supportive health policy environment. This framework, with its diverse array of directive and regulatory functions, plays a pivotal role in decision-making regarding development and implementation. All decisions are based on evidenced protocols and guidelines; however, the unique characteristics of each country must be taken into account for adaptation (WHO, 2020). Health policy is also responsible for identifying and mitigating adverse trends, influencing healthcare financiers and providers, and perpetually monitoring and evaluating the performance of the health system (Lönnberg et al., 2017).

Quality assurance frameworks warrant that screening programmes are safe, effective, equitable, ultimately contributing to improved health outcomes for the target population and encourages continuous improvement (WHO, 2020). Based on standardized criteria, performance indicators are monitored and evaluated to assess whether they meet the desired level for screening services. This offers an opportunity to identify gaps, which through the introduction of additional investigation, quality improvement initiatives and

training programmes, ultimately leads to enhance the effectiveness of screening systems (WHO, 2022).

Currently, WHO recommends organized population-based screening programmes for only breast, cervical and colorectal cancer (Ponti et al., 2017). While significant progress has been observed in these areas in recent decades, achieving the WHO's recommended goals of high quality and a participation rate of at least 70% among the target population (WHO, 2022) necessitates ongoing efforts. Furthermore, continual adaptation to new research findings is essential to optimize the effectiveness and relevance of population-based screening programmes. However, any implementation of new approaches or changes must strictly adhere to established principles discussed above.

1.4. Breast Cancer Screening

In 2003, the Council of the EU issued a recommendation to the Member States to implement a population-based screening programme for BC, that provides mammography for asymptomatic women at average risk (Council of the European Union, 2003). However, it is essential to consider the benefits and harms of screening in order to determine the scope of indications.

The obvious advantage of BC screening is the reduction in mortality due to early detection of tumours and timely treatment (IARC, 2016). However, beyond the discomfort experienced during the procedure and the anxiety linked to the examination and its consequences, the adverse effects of false-positive and false-negative results, and overdiagnosis warrant attention. A false-positive result occurs when a test outcome is positive, yet the malignancy of the lesion cannot be confirmed through additional tests and procedures. This can lead to, unnecessary additional testing, unfavourable psychological implications (Brewer et al., 2007) and may adversely affect the future screening behaviour of the concerned women (Squillace et al., 2021).

According to a recent systematic literature review, the rate of false-negative results of mammography screening – when the test is interpreted as negative, however a cancer will be diagnosed within one year of the test – can reach up to 23% (Glechner et al., 2023).

Overdiagnosis refers to the phenomenon when the tumour discovered would not have caused clinical complications in the woman's lifetime if it had not been detected.

According to a meta-analysis conducted in 2023, 12.6% of cancers detected by screening in individuals aged 40 and older falls into this group (Flemban, 2023). Additional evidence suggests that the rate of overdiagnosis is even higher when screening is extended beyond the age of 70 years (Pinto-Carbó et al., 2024).

Selecting the most appropriate target population, the best imaging modality, and the optimal testing frequency can help minimize the negative impacts of BC screening programmes.

Target population is defined by taking into account BC risk factors. BC risk is frequently divided into three major categories: average, intermediate, and high risk. Women at average risk are typically defined as those with <15%, moderate-risk women as those with a 15% to 20% and high-risk women as those with a >20% estimated lifetime risk for developing BC (Niell et al., 2024). Numerous risk assessment tools are available that use family history (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm model (BOADICEA) also denoted as CanRisk); some also incorporate individual risk factors to calculate personal risk (International Breast Cancer Intervention Study model (IBIS) also known as Tyrer-Cuzick model; Breast Cancer Risk Assessment Tool (BCRAT) also referred to as the Gail model), others depend on genetic information (Polygenic Risk Scores) (Garcia-Closas & Chatterjee, 2019; Terry et al., 2019). Furthermore, artificial intelligence (AI) based risk predicting models (i.e., Mirai) are likely to play an increasingly important role in the future (Yala et al., 2022). Population-based BC screening programmes are designed for women with an average risk for BC. However, risk assessment tools can help to identify women who might benefit from intensified screening methods (Eriksson et al., 2017).

In the case of population-based BC screening programme, age and gender are the primary factors used to specify the group of women at risk. The risk of developing BC rises steeply until around the age of 50 years, then the rate of increase slows down between ages 50 to 75 years, and finally shows a decline after the age of 75 years (Anderson et al., 2006). Accordingly, the European Commission recommends BC screening strongly for women aged 50 to 69 years and conditionally suggests it for women aged 45 to 49 years and 70 to 74 years (Schünemann et al., 2020). Although mammographic screening is not recommended for women under the age of 45 years with average risk, it is crucial to identify young women at high risk. BC that occurs before the age of 45 years tends to be

aggressive and has a poor prognosis (Arikan et al., 2022). In these cases, timely detection and the initiation of appropriate therapy are of paramount importance. BC screening is also not recommended for women over 75 years of age in the framework of organize screening programme. The likelihood of mortality from other diseases is significantly higher than from BC and the potential benefits of screening may be outweighed by its disadvantages (Demb et al., 2020). However, on an individual basis, considering a woman's personal health status and life expectancy, the option for informed, shared decision-making regarding the continuation of screening might be retained (Mathieu et al., 2024).

Currently, roentgen- mammography is the standard imaging modality for BC screening. However, it is not without limitations. Breast density is a critical factor in BC screening. The dense nature of the breast is due to a high proportion of fibroglandular elements of the tissue. Breast tissue is classified into one of four groups according to the BI-RADS (Breast Imaging Reporting and Data System) categorization based on radiographic images (Tari et al., 2023; Tomlinson-Hansen et al., 2024). Group A represents the least dense, while groups C and D are labelled as dense breasts (Mann et al., 2022). Breast density is not only an independent risk factor for BC (Boyd et al., 2007) but also reduces the sensitivity of mammographic examinations due to the masking effect of dense tissue. The masking effect happens because dense breast tissue absorbs X-rays similarly to potential tumours, leading to less contrast between them, making it harder to detect abnormalities. While the sensitivity of mammographic examinations is 85.7% for BI-RADS A breast density, it decreases to 61.0% for the category BI-RADS D (Wanders et al., 2017). It is important to note that breast density typically decreases with age, beginning before menopause, continuing after menopause, and being most noticeable during the menopausal transition (Burton et al., 2017). This phenomenon affects approximately 40% of the female population aged 40 to 74 years overall (Melnikow et al., 2016). Recognizing the importance of this issue, developing new screening technologies to replace or supplement mammography is intensely researched.

Digital breast tomosynthesis (DBT), which enables the analysis of breast slices and their synthesis of three-dimensional X-ray images, can improve BC detection rates (additional 4 per 1,000 women cancer cases) (Mizzi et al., 2022), while reducing false positive recall

rates compared to X-ray mammography (Alabousi et al., 2021; Heywang-Köbrunner et al., 2022).

When supplemented with magnetic resonance imaging (MRI), mammography shows a notable improvement in the detection rate of BC, with an additional 20 cancer cases detected per 1,000 women with dense breast (Mizzi et al., 2022). Most investigations on MRI have focused on populations with high or extremely high breast density (Bakker et al., 2019; Melnikow et al., 2016), since its sensitivity does not appear to be affected by breast density (Vourtsis & Berg, 2019). Importantly, this benefit is not limited to these subgroups: when applied to an average population, MRI still improves detection, with 15.5 additional cases identified per 1,000 women (Kuhl et al., 2017).

Ultrasound is frequently used for breast examinations because it provides a detailed view of the tissue, does not use ionizing radiation or contrast material, and is generally well-accepted by patients (Zanotel et al., 2018). Mammography supplemented with handheld ultrasound (HHUS) improves the detection rate by an additional 3 cancer cases per 1,000 women, which is less effective compared to alternative methods such as DBT or MRI (Mizzi et al., 2022). Additionally, a significant drawback is that the examination strongly depends on the operator's skills and is not reproducible (Rella et al., 2018). Automated breast ultrasound (ABUS) aims to overcome these barriers. The acquisition of the breast is made automatically by the device and are stored in a dedicated workstation. The 2D images and the reconstructed 3D images of the breast enable a comprehensive analysis of the breast tissue (Allajbeu et al., 2021), increasing the cancer detection rate by an additional 6 cases per 1,000 women compared to mammography (Mizzi et al., 2022).

Determining the screening frequency is a subject of intense debate within the medical community due to the challenge of balancing benefits (e.g., early detection and rate of mortality reduction) versus harms (e.g., overdiagnosis, psychical burden, unnecessary biopsies) (Abu Abeelh & AbuAbeileh, 2023; Mandelblatt et al., 2016; Trentham-Dietz et al., 2016). Research based on modelling has assumed the priority of screening frequency and imaging procedures that consider individual risk factors, in contrast to traditional age-based breast screening (Arnold et al., 2019; Hill et al., 2023). Currently, studies are ongoing to evaluate the validity of this risk-based approach (i.e. PERSPECTIVE I&I (Brooks et al., 2021), WISDOM (Shieh et al., 2017), My Personal Breast Screening (MyPeBS) (Rouge-Bugat et al., 2022).

As we gain a deeper understanding of the heterogeneity of BC, the consideration of molecular subtypes becomes increasingly important in developing BC prevention strategies. Numerous studies (Farshid & Walters, 2018; Kobayashi et al., 2017; Wu et al., 2023) have shown that during screening, Luminal A tumours, which are characterized by a better prognosis and slower growth rate, are more commonly detected. Interval cancers, which are identified between two screening cycles, primarily originate from the aggressive, fast-growing subtypes such as triple negative and HER2+ cancers (Ambinder et al., 2023; Li et al., 2017). This might be partly because of the rapid growth provides a short time window during which these types of tumours can still be detected while asymptomatic. (Ding et al., 2022; Niraula et al., 2020). Furtehrmore, it has been shown that triple negative BCs are more likely to yield negative mammography results compared to other BC subtypes. This might be because these types of tumours often do not exhibit the typical features of malignancies (e.g., irregular shapes, speculated margins) making them difficult to detect, as they can often resemble benign lesions on mammography (Schopp et al.). However, ultrasound improves the sensitivity of mammography (92% to 100% (Chen & Lee-Felker, 2023) versus 52.9% (Perron et al., 2019), while MRI has nearly 100% sensitivity in detecting triple-negative BC (Chen & Lee-Felker, 2023). Thus, women with elevated risk to develop these types of BC, might benefit from incorporating other screening methods or undergoing more frequent screenings (Ambinder et al., 2023).

In addition to age and gender, breast density and individual risk profiles might also play a crucial role in determining appropriate BC screening strategies. While current recommendations are based on the best available evidence, there is ongoing uncertainty, and robust research is needed to better understand how these factors influence screening outcomes. As evidence becomes clearer, guidelines may need to be adjusted to ensure optimal screening approach tailored to individual risk profiles while adhering to Wilson's principles by emphasizing the importance of an effective, safe, acceptable screening program that ensures equity for all women.

2. Objectives

The issue of BC screening is complex, with many aspects. The aim of my thesis was to explore the development opportunities for BC screening practices, with a particular focus on the Hungarian national program, and to identify future research directions for further improvement in BC screening. Based on this, the following research questions were formulated:

1) Where does the current practice of the organized BC screening program in Hungary stand within the framework defined by international guidelines and recommendations?

2) What is the potential role of automated breast ultrasound (ABUS) as an imaging method within the current BC screening programs?

3) How can ABUS be implemented into the current Hungarian screening program?

4) How could the current Hungarian BC screening program be improved based on the result of a real-world data analysis focusing on the distribution of the age and the molecular subtypes of newly diagnosed BC patients?

3. Methods

The methods addressed to answer the research questions are summarized in Table 1.

Table 1. – Summary of Research Questions and Applied Methods

Research question	Methods
1) Where does the current practice of the organized BC screening program in Hungary stand within the framework defined by international guidelines and recommendations?	Scoping literature review
2) What is the potential role of automated breast ultrasound (ABUS) as an imaging method within the current BC screening programs?	Targeted literature review
3) How can ABUS be implemented into the current Hungarian screening program?	Methodological study
4) How could the current Hungarian BC screening program be improved based on the result of a real-world data analysis focusing on the distribution of the age and the molecular subtypes of newly diagnosed BC patients?	Retrospective observational study

(Source: Own creation)

3.1. Literature Review

Firstly, a scoping literature review was carried out to gain a broad overview of the current practices in BC screening programs. The literature review was conducted as part of the "Development and Testing of Efficient Screening and Prevention Programs in the ROHU450 project", in July and August 2021. Clinical guidelines and scientific publications were collected from the PubMed, Google Scholar, and Google databases. The use of Google and Google Scholar platforms enabled access to documents not typically found in traditional scientific databases but relevant for analysing international guidelines. Grey literature, such as government reports and guidelines from professional organizations, served as important sources in uncovering regional and national variations. We used variations on the following search terms: "breast cancer screening", "organized screening program", "breast cancer early detection", "guidelines", "recommendation". The exact search string is presented in the Appendix section. The search was independently conducted by another researcher, too. For the identified relevant literature, the reference lists were also reviewed to define additional sources. The search results were regularly compared, and the final selections were discussed within a broader research group. Hungarian and international documents were handled separately. In the case of national literature, guidelines were distinguished from recommendations and other official materials, as guidelines typically contain mandatory instructions, whereas documents in the second category are more advisory. International organizations generally provide non-binding recommendations, so these were not divided into separate groups. The following information was extracted: title and source of the documents, year of publication, methodology of the document, recommended imaging modality, screening ages and screening frequencies, recommendation on the use other imaging modalities, recommendation regarding breast density, other relevant recommendations. After mapping the regulations and the practices of the Hungarian screening system, we examined how well they align with the international context.

To write the dissertation, I expanded the literature review that had been conducted before August 2021 and published in 2022 (Tittmann et al., 2022), That review served as the basis for developing the ABUS protocol. It was complemented with studies published between August 2021 and January 2025, as significant developments occurred during this

period. To minimise the potential bias introduced by the post hoc nature of the review, the same database and search string were applied.

Based on the results of the scoping literature review, we formulated a second research question to explore ABUS's role in the current screening environment. Accordingly, we conducted a targeted literature review. We focused on identifying original clinical trials and observational studies that evaluated the effectiveness of ABUS as a complementary tool to mammography. Additionally, we searched for review articles discussing the use of ABUS in the population-based screening. Particular attention was given to specifying the target groups for implementation and to potential challenges or limitations. We used the following keywords: “breast cancer”, “screening”, “population-based”, “automated breast ultrasound”, “dense breast”, “cancer detection rates”, “sensitivity”, “specificity”. The exact search string is presented in the Appendix section. We limited our research to publications from the last five years (2016-2021 August). To enhance comprehensiveness, we applied the snowball method and, following professional consultation, retained key literature published earlier. We included publications in both Hungarian and English languages. From the relevant studies, we extracted the following information: the purpose, location, time, and type of the study, as well as the number and characteristics of patients involved, and the study outcomes. In case of review, we extracted the type of review, year of publication, time frame and the databases used in the literature reviews, objective and conclusion of the review. The search outcomes were consistently compared, and the final selections were reviewed and discussed with a larger research team.

3.2. Methodological study: Protocol and Evaluation Framework Development

To address the third research question, "How can ABUS be implemented into the current Hungarian screening program?", a screening protocol was developed and a methodology was established for integrating ABUS into the mammography-based screening program within the framework of the "Development and Testing of Efficient Screening and Prevention Programs in the ROHU450 project". This initiative was carried out in

collaboration with the Csongrád-Csanád County Health Care Centre Hódmezővásárhely–Makó.

The development of the protocol occurred in multiple steps. First, the structure of the protocol was designed, followed by the definition of its content elements. Finally, based on these, an indicator system and a platform for systematic data collection were developed to ensure the monitoring and the comprehensive evaluation of the screening process.

3.2.1. Development of the Screening Protocol

Primarily, the structure of the screening protocol was determined based on national and international guidelines (ECIBC, 2024; Forrai, 2016; Forrai, 2020), recommendations (ESR, 2016; Evans, 2018; IARC, 2016; Sardanelli, 2017a), and current protocols (Egészségügyi Minisztérium, 2001; Radiológiai Szakmai Kollégium, 2008; Sugárterápiás és Onkológiai Szakmai Kollégium, 2008) related to cancer screening, sourced from the literature reviews. Additionally, we considered the summary document on guideline development provided by the WHO (WHO, 2014).

Based on the documents, the main sections of the protocol were first formulated, covering the mandatory components of cancer screening protocols. Following this, subsections, which typically include elements specific to BC screening supplemented with ABUS, were identified. After the initial formulation, consultations were held with the management, the director of nursing, and clinicians of the Health Care Centre. The draft protocol underwent several rounds of refinement leading to the creation of the final structure.

The results of the literature reviews, along with the most recent national recommendations served as the basis for defining the content elements. At the time of writing the protocol, the latest Hungarian national protocol on BC screening and early diagnosis dated back to 2008 (Sugárterápiás és Onkológiai Szakmai Kollégium, 2008). Nevertheless, it served as a crucial foundation, as it outlined key principles for mammography-based screening. Additionally, Hungarian consensus papers on the methods for BC detection methods from 2016 and 2020 already acknowledge the ABUS technology. These findings were systematically integrated into the protocol. The protocol draft was developed and reviewed in several stages through an iterative process of personal online consultations

and written correspondence. Based on feedback from consultations, the content elements were continuously revised and improved to ensure the protocol's alignment with (1) general evidence-based protocol standards, (2) clinical practice and (3) operational needs.

3.2.2. Development of the Evaluation Framework

To enable the further monitoring and evaluation of the cancer screening program, the establishment of a comprehensive indicator system was an essential component of the protocol development process.

The EU-TOPIA H2020 project (Siljander et al., 2016), that aimed to conduct a thorough analysis and standardization of breast, colorectal, and cervical cancer screening programs across the EU, served as the foundation for this work. The indicators were thoroughly reviewed and then adjusted to correspond with the elements of the BC screening protocol supplemented with ABUS, as well as the findings from the literature review.

As an initial step in designing the indicator list, we identified the primary categories of indicators relevant to screening. Following this, we defined the specific indicators within each group, clarified their definitions, and outlined the methods for their calculation. As the next step, we considered the factors that determine the applicability of each indicator within the framework of the project: “Timeframe for data collection”, “Frequency of data aggregation”, “Relevant subgroups”, “Identification of data sources, “Feasibility of data collection within the project”, “Other critical information”. A critical aspect of the process involved regular consultations and ongoing discussions with clinicians and hospital management. These collaborative efforts ensured that the selected indicators were well-suited to the framework and operational constraints of the actual context of the hospital and the planned pilot program.

Subsequently, a standardized data collection platform was developed to facilitate the calculation of the previously defined indicators. By standardizing the data collection process, we aimed to improve data reliability and streamline further analysis.

This platform was carefully designed in Microsoft Excel format. Data entry is based on the patients' social security number (TAJ) and is facilitated by designated colleagues in Hódmezővásárhely within the project framework. Prior to data processing, the dataset is anonymized. This is achieved by generating a random patient identifier, which creates a

random number from the TAJ number, ensuring that the original TAJ number cannot be retrieved. The data collection protocol can be utilized for retrospective data gathering in cases of previously conducted screening events and within the framework of the project is intended for prospective data collection.

Data collection for the assessment of BC mammography screening supplemented with ABUS, commenced on April 15, 2022, as part of the pilot program at the regional mammography centre in Hódmezővásárhely. This pilot implementation was not preceded by a formal feasibility study or statistical power analysis, as its primary aim was to evaluate the real-world applicability of the protocol and to analyse all data which could be collected regardless of the power of the analysis.

The evaluation study protocol received approval from the Regional and Institutional Committee of Medical Science and Research Ethics at the University of Szeged (registration number: 771-462/2022).

3.3. Retrospective Observational Study

As part of my PhD research project, a retrospective observational study with a special focus on the age distribution and molecular subtypes of newly diagnosed BC patients was conducted to identify potential areas for further development in the Hungarian screening system by understanding its current characteristics.

3.3.1. Study Design and Population

The data platform of the Clinical Centre of the University of Pécs was utilized as the basis of the research. It connects and stores different types of real-word data (structured, semi-structured and unstructured) generated during routine care at the Clinical Centre. Related to BC, the database includes inpatient healthcare records since 1997 and outpatient data since 2007. Our research dataset aligned with our research questions was developed through multiple stages of consultations involving both the research team and a practicing oncologist. The data extraction process took place in two phases. We focused on collecting the following information: patients' age at diagnosis, year of the BC diagnosis, TNM stage, as well as the ER, PR, and HER2 statuses. First, the data was extracted based on a coding scheme that was refined and modified in several steps following continuous consultations. Then, two researchers manually reviewed the free-text data to extract more nuanced information. The uncertain or questionable cases were discussed within a broader research group, with the involvement of the oncologist. Approval for the use of this oncological database for both medical and health-economic research, as well as analytical purposes, has been granted by the Hungarian Scientific and Research Ethics Committee (ETT TUKEB IV/4068-1 /2022/EKU).

The study was extended to cover the period from January 1, 2010, to December 31, 2020. Female patients diagnosed with primary BC, based on the International Classification of Diseases (ICD) code C50 and D05, were included. Our analysis also considered in situ BC (corresponding to the ICD D05 code), encompassing ductal carcinoma in situ (DCIS), which is regarded as the precursor of invasive BC with therapeutic consequences. Cases of Paget's disease classified under the same ICD category were excluded from the

analysis. Patients who had been diagnosed with BC prior to the study period or those with secondary breast malignancies were also omitted from the study population.
The study cohort was stratified into age groups on the age of BC diagnosis based on the Hungarian BC screening protocol: (1) women under 45 years of age, (2) women between 45 and 65 years of age, and (3) women over 65 years of age.

3.3.2. Classification of Breast Cancer

For the analysis, we applied the anatomic TNM staging system based on the AJCC Cancer Staging Manual, 8th Edition (Amin et al., 2017), as outlined in detail in the Introduction section. For the further analysis, we established two categories: (1) early-stage BC, corresponding to stages 0–IIB, and (2) advanced-stage BC, encompassing stages IIIA–IV. The classification was determined based on literature data (Amin et al., 2017) and consultation with a practicing oncologist.
The method detailed previously in the Introduction section was followed for determining molecular subtypes. However, due to the lack of sufficient data on Ki-67 protein expression, its consideration was excluded. Consequently, the determination and naming of molecular subtypes were based solely on the presence or absence of hormone receptors (HR) (i.e., oestrogen, progesterone receptors) and HER2 protein. Tumours were labelled as HR positive if either ER or PR was positive, whereas they were categorized as negative when both ER and PR were negative.: (1) HR-positive/HER2-negative (HR+/HER2-), (2) HR-positive/HER2-positive (HR+/HER2+), (3) HR-negative/HER2-positive (HR-/HER2+), and (4) HR-negative/HER2-negative (HR-/HER2-) subtypes.

3.3.3. Statistical Methods

The analysis began with a descriptive statistical assessment of the whole study population's general characteristics, including the number of subjects, age at diagnosis, TNM stage, BC severity stage, and BC molecular subtype, stratified by year over the study period. Subsequently, the distribution of these variables was examined across age

groups (i.e., patients aged <45 years, 45-65 years, and >65 years) within the study period, and with annual stratification as well.

We then evaluated whether there was a statistically significant association between the year of diagnosis and the distribution of the TNM stage or the molecular subtype, considering the age-group stratification. Pearson's Chi-squared test was employed for these analyses, initially for the entire study population and subsequently for each age cohort individually.

Following this, data was aggregated across all study years to provide a comprehensive description of tumour distributions by TNM stages, BC severity, and BC molecular subtype for each age cohort. Chi-squared tests were also used to investigate whether there were statistically significant differences between the age groups regarding the distribution of TNM stages, BC severity, and molecular subtypes.

No imputation was conducted for missing data. In each analysis, all cases with available data for the respective variable were included, irrespective of missing information on other variables. A p-value of less than 0.05 was considered statistically significant. The statistical analyses were performed using STATA software (version 16.1), and as a quality control measure, the analyses were repeated using R software (version 4.1.2).

3.4. Language Editing

The sentence editing of this dissertation was assisted using ChatGPT4.0, a language model developed by OpenAI in San Francisco, CA, USA. However, the text of the dissertation does not include contents generated by ChatGPT4.0.

4. Results

4.1. Literature Review

The scoping literature review provided a more comprehensive understanding of the Hungarian BC screening system. A total of three Hungarian clinical guidelines related to BC were identified (Egészségügyi Minisztérium, 2001; Radiológiai Szakmai Kollégium, 2008; Sugárterápiás és Onkológiai Szakmai Kollégium, 2008). However, in January 2024, the guideline titled 'Diagnostic and Psycho-Oncological Care of Breast Cancer Patients' was published (Borbély et al., 2024), which also proposes notable changes regarding BC screening compared to previous guidelines. Therefore, while writing my dissertation, I also considered this document and supplemented the literature review accordingly. Four national recommendations address the modern screening, diagnostics, and the treatment of BC from the perspective of imaging examination methods. These were developed based on the Breast Cancer Consensus Conferences held in 1999, 2009, 2016, and 2020 (Forrai et al., 2016; Forrai et al., 2020; Kásler, 2000; Kásler, 2010). Additionally, we identified four quality assurance handbooks related to cancer screening (Döbrőssy, 2000, 2013; Elek et al., 2021; Országos Tisztifőorvosi Hivatal, 2008). Beyond the above, we found one more relevant textbook providing a broad overview of current practices in the technical process of BC screening (Forrai et al., 2017).

In Hungary, the nationwide organized BC screening program was launched in January 2002, based on the first mammography guideline issued in 2001 (Egészségügyi Minisztérium, 2001). This guideline outlined that asymptomatic women aged 45–65 years at average risk should be invited for biennial mammography screenings. This principle remains unchanged to this day. However, two subsequent updates to the guideline have refined BC screening recommendations.

The first update, issued in 2008 (Radiológiai Szakmai Kollégium, 2008), introduced specific guidance for high-risk populations. It recommended that women at high risk – such as those with a family history of breast or ovarian cancer, BRCA 1/2 mutation carriers, prior chest radiation, Ashkenazi Jewish descent, Li-Fraumeni or Cowden syndrome, or a personal history of BC – should begin screening at the age of 30 years. For these individuals, mammography was suggested as the primary screening tool, with

additional use of ultrasound and, if necessary, MRI. However, the 2008 guideline did not provide detailed instructions for implementing these supplemental methods.

The most recent update, published in 2024 (Borbély et al., 2024), aims to harmonize national practices with current international diagnostic algorithms and incorporates advances in screening technologies. The recommendations of the guidelines regarding the screening method are based on the conclusions of the 4th Breast Cancer Consensus Conference held in 2020. For high-risk groups, the 2024 guideline recommends annual screening with mammography or preferably using DBT, supplemented by ultrasound and, where available, MRI (Borbély et al., 2024). It proposes extending the screening program to women aged 40 to 44 years and 66 to 75 years; however, it considers further studies necessary to evaluate the professional and financial implications of these changes. However, the reduction of the screening frequency to 18 months for the 40–54 years age group, which was proposed at the 2020 Consensus Conference, did not appear in the recommendations. The significance of dense breasts is highlighted in the recommendations of the Fourth Consensus Conference (Forrai et al., 2020), which emphasizes the importance of informing women about breast density. Furthermore, it is suggested that a unified reporting system in breast examinations, the consistent use of the BI-RADS Atlas terminology is considered essential, that includes the categorization of breast density. The document also raises the possibility of the use of AI in determining breast density.

To overview the international environment with regard to BC screening and early detection, we thoroughly reviewed a total of 15 documents (ESR, 2016; IARC, 2016; Siu & USPSTF, 2016; WHO, 2014; WHO, 2020; Cardoso et al., 2019; DenseBreast-info, 2025; Dimitrova et al., 2016; Evans et al., 2018; Karsa et al., 2013; Oeffinger et al., 2015; Ponti et al., 2017; Sardanelli et al., 2017a; Sardanelli et al., 2017b; Smith et al., 2019), which were issued by international organizations. I supplemented the results, coming from the research within the framework of the project mentioned in the Methods section, with 7 additional recommendations (ECIBC, 2024; Forrai et al., 2022; Loibl et al., 2024; Mann et al., 2022; Marcon et al., 2024; Nicholson et al., 2024; Niell et al., 2024), which were published between August 2021 and January 2025.

Among the documents, 14 were related to the EU (ECIBC, 2024; ESR, 2016; Cardoso et al., 2019; DenseBreast-info, 2025; Dimitrova et al., 2016; Evans et al., 2018; Forrai et al.,

2022; Karsa et al., 2013; Loibl et al., 2024; Mann et al., 2022; Marcon et al., 2024; Ponti et al., 2017; Sardanelli et al., 2017a; Sardanelli et al., 2017b), 5 to the USA (Siu & USPSTF, 2016; Nicholson et al., 2024; Niell et al., 2024; Oeffinger et al., 2015; Smith et al., 2019), and 3 were issued by the WHO with global relevance (IARC, 2016; WHO, 2014; WHO, 2020). There were 7 guidelines (ECIBC, 2024; Cardoso et al., 2019; Dimitrova et al., 2016; Karsa et al., 2013; Loibl et al., 2024; Oeffinger et al., 2015; Smith et al., 2019), 7 recommendations (Siu & USPSTF, 2016; Evans et al., 2018; Mann et al., 2022; Marcon et al., 2024; Nicholson et al., 2024; Niell et al., 2024; Sardanelli et al., 2017b), 3 position papers (WHO, 2014; Forrai et al., 2022; Sardanelli et al., 2017a), one report (Ponti et al., 2017), three handbooks (ESR] 2016; IARC, 2016; WHO, 2020) and one educational platform (DenseBreast-info, 2025) that provided additional resources.

Traditionally, there has been a consensus that digital mammography (DM) is the most appropriate tool for BC screening in women at average risk. However, recent guidelines from the American College of Radiology (ACR) (Niell et al., 2024) and the U.S. Preventive Services Task Force (Nicholson et al., 2024) have considered DBT equivalent to DM for screening. Furthermore, the European Commission Initiative on Breast Cancer's (ECIBC) (ECIBC, 2024) has suggested using DBT over DM in routine screening programs.

For alternative screening methods, MRI is endorsed by several European and international organizations as an imaging technique to supplement mammography for women at high risk (ESR, 2016; Marcon et al., 2024; Niell et al., 2024). As of 2024, these guidelines have been extended to include women with extremely dense breast tissue, with MRI also recognized as a standalone technique for this specific group (Mann et al., 2022). While the use of ultrasound for screening is not widely supported, it is recommended as an alternative when MRI is contraindicated, although evidence is limited (Marcon et al., 2024).

Regarding age and screening frequency, there is considerable variation across recommendations. While there is general agreement on the effectiveness of mammography screening between the ages of 50 and 70 years, the intervals differ – typically every 2-3 years in Europe (Cardoso et al., 2019; Ponti et al., 2017; Sardanelli et al., 2017b) and annually or biennially in the USA (Nicholson et al., 2024; Niell et al., 2024).

For younger women, there is even more debate. The ECIBC's guidelines from 2024 recommend against organized BC screening for women aged 40-44 years at average risk, and suggest either triennial or biennial screening for those aged 45-49 years (ECIBC, 2024). In contrast, the ACR (Niell et al., 2024) recommends continual annual screening starting at the age of 40 years. The European Society of Breast Imaging (EUSOBI) advises annual screening for women aged 40-49, followed by biennial screening up to the age of 75 years (Sardanelli et al., 2017a).

As for the upper age limit, there has been a trend in recent years towards extending organized screening programs up to the age of 75 years, with women being notified of their eligibility for screening. Beyond 75 years, the continuation of screening is based on individual requests and shared decision-making with healthcare providers, considering comorbidities and life expectancy. However, clear evidence regarding the benefit of screening in this age group remains limited (Nicholson et al., 2024).

With regard to the application of ABUS, we conducted a targeted literature review, drawing on references from the presented guidelines and recommendations as well.

We reviewed 16 reviews (Allajbeu et al., 2021; Berg et al., 2021; Berg & Vourtsis, 2019; Boca Bene et al., 2021; Butler & Hooley, 2020; Freer, 2015; Karst et al., 2019; Kim et al., 2020; Lander & Tabár, 2011; Melnikow et al., 2016; Meng et al., 2015; Nazari & Mukherjee, 2018; Nicosia et al., 2020; Rella et al., 2018; Vourtsis & Berg, 2019; Zanotel et al., 2018) and 9 clinical studies (Arleo et al., 2014; Brem et al., 2015; Giger et al., 2016; Giuliano & Giuliano, 2013; Grady et al., 2017; Huppe et al., 2018; Kelly et al., 2010; Lee et al., 2019; Wilczek et al., 2016) to assess ABUS's role in the framework of an organized screening program, which I also supplemented with an additional 6 significant reviews (Galati et al., 2022; Gatta et al., 2023; Isautier et al., 2024; Spear et al., 2024; Spear & Mendelson, 2021; Zhang et al., 2024) and 2 clinical studies (Aribal et al., 2024; Klein Wolterink et al., 2024) published between August 2021 and January 2025. Among the 22 review articles, there are four systematic literature reviews (Gatta et al., 2023; Isautier et al., 2024; Meng et al., 2015; Zhang et al., 2024), three of which includes a meta-analysis (Gatta et al., 2023; Meng et al., 2015; Zhang et al., 2024), while the other publications are summaries based on targeted literature reviews. The sources span from 2011 to 2024, with the majority (16 out of 22) published after 2018. The periods investigated in these

publications range from as early as 1995 to as recently as April 2022. They cover a variety of databases for sourcing information, with frequent use of MEDLINE. Some reviews also reference CINAHL (Isautier et al., 2024), Embase (Isautier et al., 2024; Meng et al., 2015; Zhang et al., 2024) and grey literature (Isautier et al., 2024), however, in certain cases, no specific database was specified.

The assessed publications aim to explore various aspects of ABUS in the context of BC screening. The role of ABUS has consistently been examined as a complementary method for women with dense breasts, rather than as a replacement for mammography. This is highlighted in Gatta's meta-analysis (Gatta et al., 2023), which emphasizes that ABUS is not intended to substitute mammography. The rationale for its use lies in the fact that the sensitivity of mammography is significantly reduced by the masking effect of dense breast tissue. In contrast, ultrasound demonstrates high sensitivity for detecting breast cancer regardless of tissue density (Nazari & Mukherjee, 2018), making ABUS a valuable complementary tool. Six reviews (Allajbeu et al., 2021; Galati et al., 2022; Gatta et al., 2023; Nicosia et al., 2020; Spear & Mendelson, 2021; Zhang et al., 2024) highlight ABUS's diagnostic accuracy, especially noting the advantages of the 3D coronal view, which allows for a better evaluation of architectural distortions and large breast masses. Reproducibility and reduced operator dependency are also important advantages of ABUS, particularly when compared to handheld ultrasound (HHUS) (Butler & Hooley, 2020; Galati et al., 2022; Nicosia et al., 2020).

However, several limitations are consistently noted, including an increased rate of false positives (Freer, 2015; Gatta et al., 2023; Melnikow et al., 2016; Nazari & Mukherjee, 2018; Vourtsis & Berg, 2019; Zanotel et al., 2018), the lack of doppler and elastography capabilities (Berg et al., 2021; Nicosia et al., 2020; Spear & Mendelson, 2021), as well as the inability to examine axillary regions (Butler & Hooley, 2020; Nicosia et al., 2020; Zanotel et al., 2018). In addition, one review highlighted the high acquisition cost of ABUS (Spear & Mendelson, 2021).

Accurate interpretation is essential to mitigate the problem of false positives, which requires specific training regardless of the examiner's prior HHUS experience (Rella et al., 2018). As expertise develops, recall rates decrease along the learning curve, as reported in the reviews by Nicosia et al. (Nicosia et al., 2020) and Boca Bene et al. (Boca Bene et al.,2021). Nonetheless, Spear and Mendelson (Spear & Mendelson, 2021) caution

that reaching efficient interpretive performance may require a relatively long learning phase.

Computer-aided detection (CAD) systems can further enhance ABUS examinations by helping detect BC and improving the interpretation accuracy of less experienced observers (Berg & Vourtsis, 2019; Butler & Hooley, 2020), while also reducing reading times (Butler & Hooley, 2020; Kim et al., 2020). CAD facilitates distinguishing between benign and malignant lesions, providing valuable support in the diagnostic process (Nicosia et al., 2020).

Following the review findings, a total of 11 studies were included in the literature review, eight of which were conducted in the USA, one in Sweden (Wilczek et al., 2016), one in the Netherlands (Klein Wolterink et al., 2024) and one in Turkey (Aribal et al., 2024). Ten out of the 11 studies involved a single study arm. Exception was Giuliano et al. (Giuliano & Giuliano, 2013), where two groups were compared, such as a control group and an ABUS group. Nine studies analysed data from a single screening centre, while two studies (Brem et al., 2015; Kelly et al., 2010) involved collaboration between multiple centres. The largest multicentre study (Brem et al., 2015), conducted across 13 centres, evaluated the screening results of more than 15,000 women. In terms of the patient population, ten of the studies explicitly included only asymptomatic women with dense breast tissue, while one study (Grady et al., 2017) did not exclude women with symptoms. The age range of participants varied across studies, but most included women aged 18 years and older. Wilczek et al. focused specifically on women aged 40-74 years (Wilczek et al., 2016). Regarding the study design, six studies were prospective, while five studies were retrospective, analysing previously collected data.

These studies primarily focused on the use of ABUS in combination with DM for BC screening, particularly in women with dense breast tissue. More recent studies, published after 2019 (Aribal et al., 2024; Klein Wolterink et al., 2024; Lee et al., 2019) have adopted DBT as a screening method as well and examined it both as a standalone approach and in combination with ABUS. By evaluating the results of clinical studies, our main focus was on outcomes that are relevant from the screening perspective. The results showed that combining ABUS with DM or DBT increases sensitivity (DM: 40.0–76.0% vs. DM+ABUS: 74.1–100%, DBT: 84% vs. DBT+ABUS:94%). Multiple studies also found

that cancer detection rates were higher when ABUS was added to mammography or to DBT (additional cancer detection rate (CDR) of ABUS combined with mammography 1.9-7.6/1000 cases; CDR of ABUS combined with DBT was 0.9-2.77 /1000 cases). This combined approach improves the detection of smaller tumours (Kelly et al., 2010; Klein Wolterink et al., 2024) and early-stage cancers (Giuliano & Giuliano, 2013). According to Grady et al. (Grady et al., 2017), the use of ABUS alongside with mammography reduces the proportion of advanced-stage cancers by 5.7%. The addition of ABUS results in higher recall rates (DM: 1.4-15.0% vs. DM+ABUS: 2.3-28.5%; DBT: 3.3-6.0% vs DBT+ABUS: 10.7-14.9%), which may increase the number of false positive findings. Yet, in their 8-year study, Wolterink et al. (Klein Wolterink et al., 2024) found a significant decrease in the recall rate over the years for both ABUS (1.7% per year (P-value = 0.003) and ABUS+DBT (2.0% per year (P-value = 0.001)). However, the addition of ABUS does not appear to provide a consistent advantage in terms of specificity when compared with DM or DBT alone (DM: 78.1–99.0% vs. DM+ABUS: 72.0–99.7%; DBT: 94.7% vs. DBT+ABUS: 86.9%).

4.2. Methodological study: Protocol and Evaluation Framework Development

4.2.1. Screening Protocol

The protocol for mammography screening, supplemented with ABUS is structured as follows:

The scope of application and validity of the protocol

The screening protocol defines a guideline specifically for the use of ABUS as a supplemental imaging method for mammography within a pilot study conducted at the regional mammography centre of the Csongrád-Csanád County Health Care Centre Hódmezővásárhely–Makó, Hódmezővásárhely, Hungary. These non-binding recommendations are applicable at the institutional level and are designed to be used within the current Hungarian healthcare setting.

The target screening population of the protocol

The target group defined by the protocol includes asymptomatic women aged 45-65 years, with average risk for BC, who were invited through the national recall system and participated in the organized national screening programme. Eligible women had a negative screening result and their mammograms revealed dense breast tissue. Further requirement for the inclusion in the screening program supplemented with ABUS is that the patient provides written consent for the ABUS examination.

The characteristics of the applied technology

The screening technology used is ABUS, which combines several well-known benefits of ultrasound, such as being non-ionizing, relatively inexpensive, and well-tolerated by patients. In addition to these general strengths, ABUS provides further value by separating the processes of the automatic image acquisition and interpretation. This approach not only reduces the workload for physicians, as they are not required to perform the examination themselves, but also ensures that result evaluation remains independent of the place and time of image acquisition. For optimal image quality, proper patient

positioning is essential: the patient lies on their back, sometimes supported by a cushion, and a contact gel is applied to ensure good contact between the skin and the ultrasound transducer. The examination typically takes around 15 minutes.

The acquired data are transferred and stored on a dedicated workstation. The associated software facilitates rapid and systematic review of ultrasound images, including scanning and zooming in on areas of concern. The images can be analysed in slices, with 3D multiplanar reconstruction available and it also allows the comparative analysis of the breast tissue with previous scans. Moreover, CAD integration allows double reading to be performed with the support of the software, requiring only one radiologist for the final review.

The screening process

- **Organization of the screening program**

  The ABUS screening examination complements the national BC screening program and is offered to patients with dense breast tissue identified during mammography. If increased breast density is detected, the patient is informed via their preferred communication channel (e.g., phone, email) that an ABUS screening is recommended. If the patient accepts, an appointment is scheduled. If they decline, a follow-up mammogram is advised in two years, provided they remain symptom-free.

- **The process of an ABUS screening examination**

  The detailed process of the ABUS screening is illustrated in Figure 1. Upon arrival at the breast diagnostic centre, the patient is informed about the ABUS procedure and provides written consent. Thereafter, the patient's data is recorded, and the family and gynaecological history questionnaire is reviewed or updated if necessary. A qualified assistant performs a physical examination of the breast, noting any new findings. Finally, the patient is positioned correctly on the examination table, contact gel is applied to the breast. The necessary details are recorded in the ABUS system. The breast is scanned in three planes (anteroposterior, lateral, and medial) with the option for additional settings if needed. The assistant performs the imaging and adjusts automatic settings as necessary.

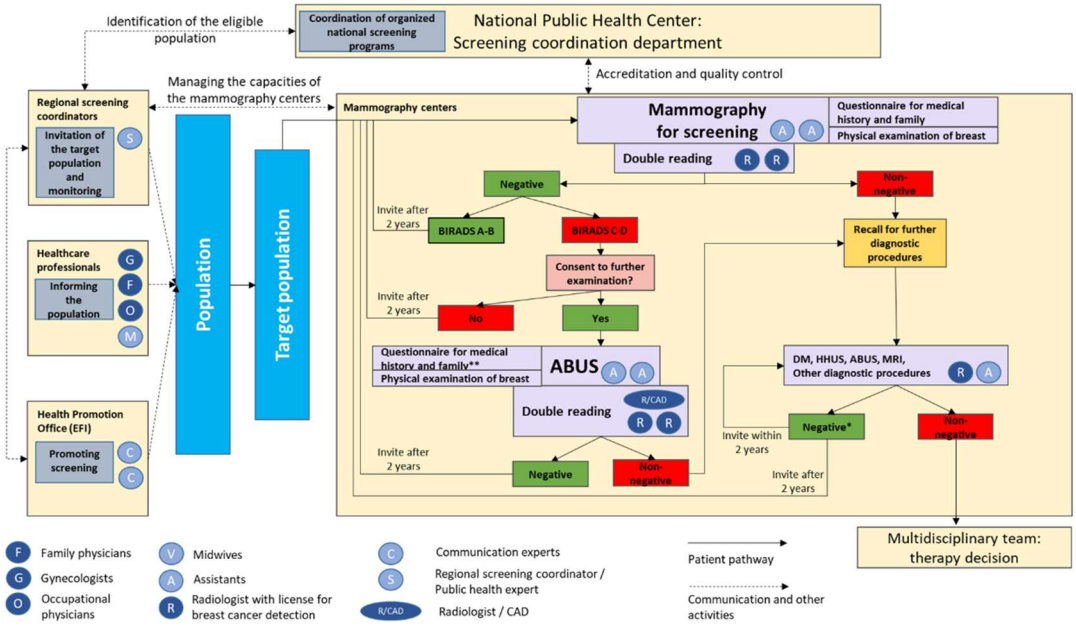

Figure 1. The flow chart of the ABUS screening

Source: (Tittmann et al., 2022)

- **Evaluation of examination results and further procedures**

  The ABUS examination results are reviewed with delayed, double interpretation, where two radiologists independently assess the images. If there is disagreement, a consensus is reached, or the diagnosis is based on the more serious prognosis. Alternatively, a radiologist and a CAD system may perform the evaluation.

  For negative findings, if no abnormalities are detected, a repeat mammography, supplemented with ABUS is recommended in two years if the patient remains symptom-free.

  If abnormalities are found, the patient is notified and advised to undergo further diagnostic tests. An appointment is scheduled to discuss results and necessary steps.

The human resources of the screening program

For the administrative, organizational tasks, one person is recommended. The administrator notifies the patient via the previously agreed communication method (e.g., phone, email) about the need for ABUS and schedules the ABUS examination. Their

responsibility is to record the results in the Electronic Health Care Service System (EESZT) and to recall the patient in positive cases, as indicated by the reporting specialist. Two specialists are required – at least one radiologist with comprehensive breast diagnostic certification and one additional radiologist – as ABUS results must be evaluated independently by both specialists to meet the double reading criteria. In case the CAD system is available, the evaluation of the results conducted by one specialist is sufficient to fulfil this requirement.

Two qualified assistants (radiology assistant, radiographer, or diagnostic imaging assistant) are advised. Before the ABUS examination, the assistant obtains the patient's informed consent, performs a physical breast examination and documents any abnormalities. Furthermore, the assistant is responsible for correctly positioning the patient, applying contact gel for optimal imaging, and maintaining the cleanliness of the ABUS machine.

The communication concerning the screening program

We defined several levels of communication. One key communication focus of the screening program is the target population. Since the ABUS screening builds on the national mammographic program, its communication is closely linked to mammography. The strategy emphasizes raising awareness of early BC detection through mammographic screening. The National Public Health Centre (NNK) leads this effort, supported by regional coordinators and healthcare professionals like general practitioners, gynaecologists, and nurses. Local health promotion offices (EFIs), civil organizations, and patient advocacy groups play a key role in reaching a wider audience and organizing targeted programs. A vital aspect of this communication is educating the public on the risks associated with dense breast tissue. In the context of the ABUS examination, patient counselling regarding the significance of dense breasts, the examination procedure, and its potential benefits and possible harms is provided by a qualified assistant.

In the ABUS screening process, team communication is critical, particularly during the double-reading evaluation. Regular meetings should be held to discuss discrepancies in evaluations, improving practical skills and speeding up the learning curve for effective tool use. This would help reduce false-positive results. Furthermore, effective and continuous communication between the reporting physician and the medical assistant is

essential for optimizing the screening process. Regular feedback and clear communication help ensure smooth operations and can shorten the time required to notify patients of their results. If the findings are negative, individuals are not contacted separately; instead, the information is uploaded to the EESZT online system.

Another important aspect of communication is to inform breast diagnostics specialists and other relevant professionals about ABUS research and its role. There is limited information available about the use of ABUS in organized public health screening programs. To address this, it is recommended to present ABUS protocols at consensus conferences and publish in professional journals. This will help raise awareness among specialists, professional organizations, and decision-makers about the possible benefits of this imaging modality. Civil organizations and patient advocacy groups may also play a significant role in this process by contributing to the dissemination of knowledge and promoting wider engagement.

Data protection

Healthcare providers participating in the ABUS screening program commit to ensuring that all data management related to screening activities complies with the regulations specified in applicable laws.

Conditions for the introduction of the protocol

- **Material conditions**

  For the ABUS examination, both the ultrasound equipment and its peripherals (such as a monitor), along with a dedicated room, are required. Healthcare providers must also comply with the professional minimum requirements as outlined in the 60/2003. (X. 20.) ESzCsM regulation. Disposable items for the procedure include a contact mesh and gel applied to the breast. Additionally, an information technology (IT) system with sufficient capacity is necessary for evaluating images and storing data.

- **Professional and training conditions**

  The training requirements for the ABUS examination involve both technical and professional education. Medical assistants receive technical training to ensure proper handling of the equipment and patient positioning. Basic training for using the device is typically provided by the manufacturer. The manufacturer also ensures knowledge

updates during any software or equipment upgrades. Radiologists with prior experience in mammography and other imaging diagnostics undergo professional training focused on interpreting ABUS results.

- **Financial conditions**

  Currently, the regular financing for the use of ABUS is not available within the Hungarian public healthcare funding system. To support the use of the device, funding is required for the purchase and maintenance of the equipment, human resources, consumable supplies, potential infrastructure development, and training costs.

4.2.2. Evaluation Framework

The indicator system enables the monitoring and evaluation of mammographic screening program supplemented with ABUS. The system categorizes indicators into four main groups, with the complete list provided in in the Appendix in Table 1. Within these groups, 13 indicators are derived from screening activities, 5 are related to screening tests, 2 refer to cost indicators, and 3 focus on long-term clinical outcomes.

The practical applicability of these indicators and the developed data platform was tested during the period from April to June 2022. Over this short timeframe, a total of 116 patients participated in the screening program, of whom 34 were included in this study. The participants had an average age of 53 years and a median age of 49 years. During the physical examinations conducted prior to imaging, palpable breast abnormalities were identified in 3 cases. Mammography results were negative for all 34 cases following dual assessment. Breast density was classified according to Tabár's system: in 21 cases, the breast tissue was fibrotic (5/5), and in 13 cases, it was adenotic (4/5). All 34 individuals recommended for ABUS examination based on mammographic findings consented to and underwent the additional screening.

Dual assessment of ABUS results by radiologists yielded consistent negative findings in 33 cases, while 1 case was unanimously identified as positive. The lesion detected via ABUS had not been identified during the prior physical examination or mammography. According to Tabár's classification, the mammogram categorized the patient's breast

tissue as grade 4. Diagnostic tests performed after screening confirmed the presence of a T1bN1M0 invasive lobular carcinoma.

4.3. Retrospective Observational Study

4.3.1. Patient Characteristics

This retrospective observational study analysed the data of 3,282 women newly diagnosed with BC at the Clinical Centre of the University of Pécs between 2010 and 2020. The general characteristics of the study sample are presented in the Appendix in Table 2. The average (standard deviation) annual number of patients diagnosed with BC was 298 (29), with the lowest count of 256 observed in 2019 and the highest count of 343 in 2014. The age distribution of the study population revealed that 12.1% of the participants were under 45 years old, 48.6% were between 45 years and 65 years—the target age group for Hungary's organized BC screening program—and 39.3% were over the age of 65 years. The annual age-specific distribution of cases is illustrated in Figure 2. The average (standard deviation) age of the study population was 61.2 (12.9) years.

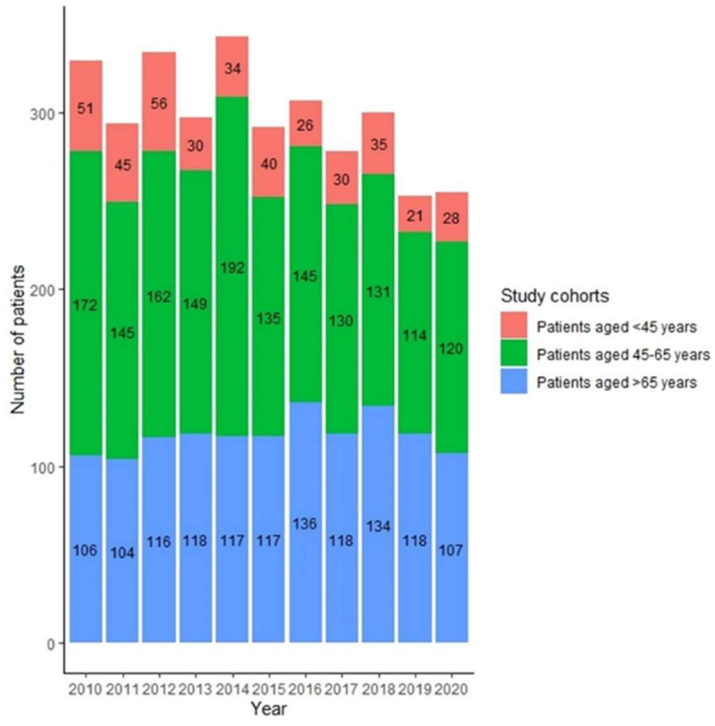

Figure. 2. Annual number of newly diagnosed breast cancer cases during the study period
Source: (Tittmann et al., 2024)

Data on the TNM stage was available for 70.5% of the newly diagnosed BC cases. Missing data were most prevalent in the youngest age group, with 47.7% of cases lacking TNM staging information. In the 45–65 age group, 31.1% of cases had missing data on TNM classification, while in the over-65 years age group, this proportion decreased to 22.6%. Datasets on HR and HER2 status at diagnosis were available for 83.1% of the study population. Missing HR and HER2 data were most frequent in patients under 45 years (26.3%) and least frequent in those over 65 years (15.3%).

4.3.2. Distribution of Breast Cancer Cases

Table 3 in the Appendix presents the annual number of newly diagnosed BC cases during the study period, categorized by age, anatomic TNM stages and severity. During the study period, no significant association was observed between the year of diagnosis and the distribution of TNM stages for the entire study population (P-value = 0.36). Similarly, when stratified by age groups, no significant changes were detected within any cohort (<45 years: P-value = 0.53; 45–65 years: P-value = 0.41; >65 years: P-value = 0.47). During the study period, no significant changes were observed in the distribution of BC severity for the entire study population (P-value = 0.35), or within the age cohorts individually (patients aged <45 years: P-value = 0.14, patients aged 45-65 years: P-value = 0.35, patients aged >65 years: P-value = 0.49).

Similarly, there were no significant changes in the distribution of BC subtypes for the entire study population (P-value = 0.55), or within any of the age groups (patients aged <45 years: P-value = 0.39, patients aged 45-65 years: P-value = 0.61, patients aged >65 years: P-value = 0.74). Table 4 in the Appendix presents the annual number of newly diagnosed BC cases during the study period, categorized by molecular subtype.

The distribution of tumours by TNM classification for each age cohort is presented in Figure 3. Stage IA was the most prevalent TNM stage across all three study cohorts. Among women in the screening target age group, 50.6% of the detected tumours were classified as stage IA. This indicates that in over half of the cases within this population, the tumour's largest diameter did not exceed 2 cm, and no lymph node metastases were present. In the cohort under 45 years of age, a high proportion of stage IIA tumours was also observed, accounting for 34.1% of all tumours in this group. From stage IIB onwards, tumours in the more advanced stages consistently showed the highest proportional occurrence within the oldest age cohort. The results indicate that older age groups (>65 years) have a distinct TNM stage distribution compared to younger age groups (Age Groups 1 (<45 years) and 3 (>65 years) P-value = 0.00250, Age Groups 2 (45–65 years) and 3 (>65 years) P-value:<0.001).

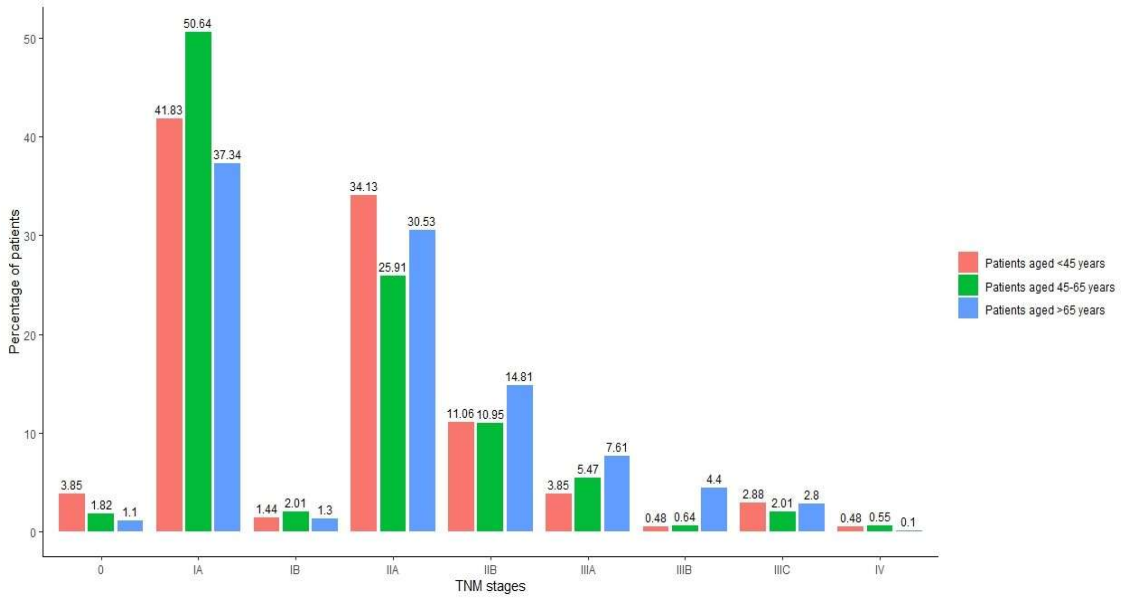

Figure 3. Distribution of TNM stages of breast cancer per age cohorts

TNM: Tumour, node, metastasis

Source: (Tittmann et al., 2024)

Analysis of BC severity showed that the vast majority of tumours fell within the early-stage category (stage 0-IIB), with a statistically significant difference in the distribution of BC severity across the age cohorts (P-value < 0.001). Specifically, the proportion of advanced-stage tumours (stage III-IV) was significantly higher in patients aged >65 years (14.91%) compared to both patients aged 45-65 years (P-value = <0.001) and those aged <45 years (P-value = 0.0058). No significant difference was observed between the <45 years and 45-65 years age groups (P-value = 0.64). The distribution of tumours by severity for each age cohort is presented in Figure 4.

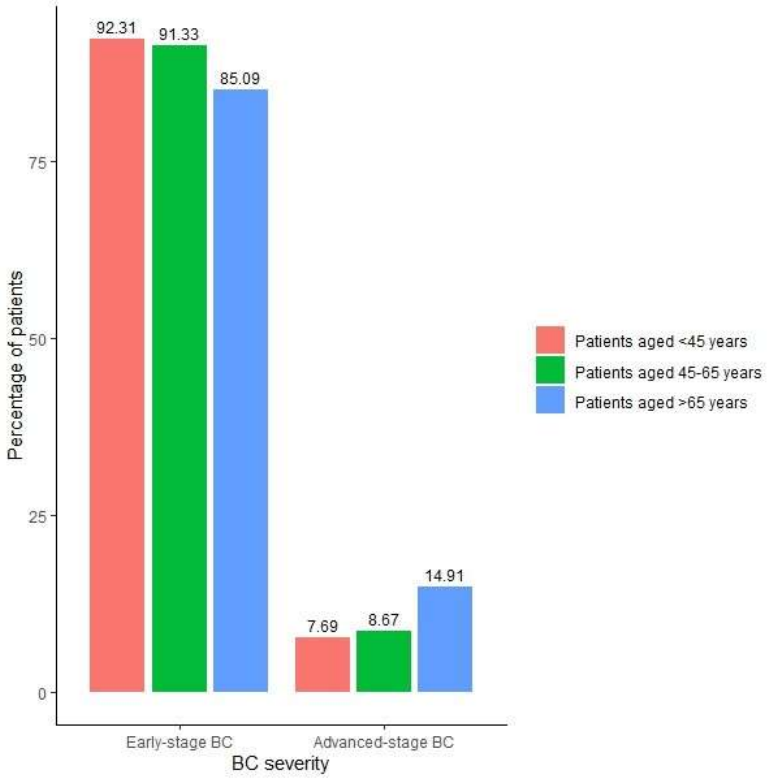

Figure 4. Distribution of breast cancer severity according to age cohorts

BC: breast cancer

Source: (Tittmann et al., 2024)

Regarding tumour subtypes, we found that in the total population, 73.0% of the newly diagnosed BC cases were HR+/HER2-, 13.3% were HR-/HER2-, 7.8% were HR+/HER2+, and 5.8% were HR-/HER2+. When examining differences in molecular subtype distribution between age groups, significant differences were observed between all age groups: <45 vs. 45–65 years (P-value <0.001), <45 vs. >65 years (P-value =

0.001), and 45–65 vs. >65 years (P-value = 0.025), suggesting that age may play a role in the biological characteristics of BC. The distribution of HR+/HER2- subtype, that is characterized with slow growth increases with age, while aggressive subtypes like HR-/HER2- are more common in younger patients (<45 years). The distribution of tumours by molecular subtype for each age cohort is presented in Figure 5.

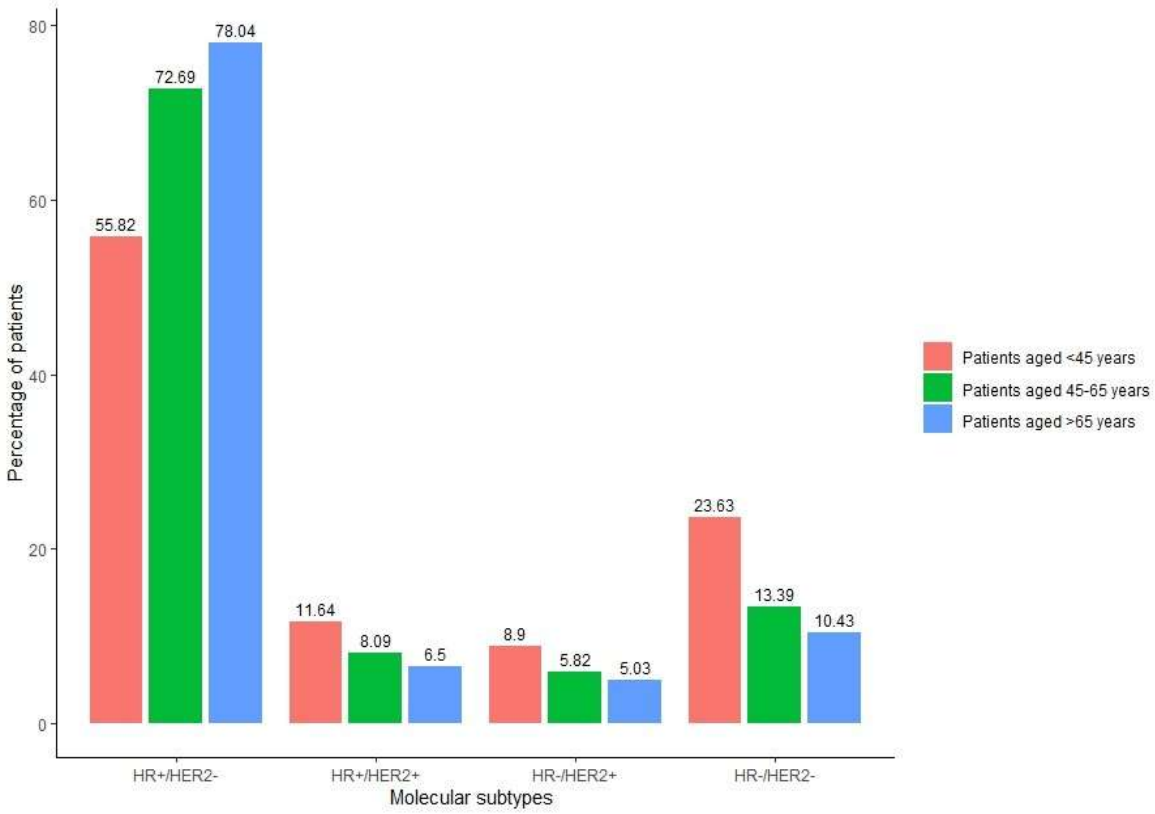

Figure 5. Distribution of breast cancer subtypes according to age cohorts
HER2: human epidermal growth factor receptor 2; HR: hormone receptor
Source: (Tittmann et al., 2024)

5. Discussion

5.1. The Position of Hungary's Organized Breast Cancer Screening Program within the Framework of International Guidelines and Recommendations

The Hungarian BC screening program has been available since 2002 and is based on an organized screening concept. Under this approach, eligible women receive a personalized letter via post informing them about the due date, location, and time of their screening. This model formally aligns with the EU's guidelines, which emphasize the importance of organized screening programs (Cardoso et al., 2019; Schünemann et al., 2020). In practice, however, the Hungarian screening uptake remains suboptimal. The screening participation rate in Hungary falls below the EU average. In 2021, the country ranked fourth worst among EU member states. Moreover, between 2011 and 2021, Hungary was among the few countries where the screening rate declined, ranking third worst in this regard (Eurostat, 2023). The underlying reasons are complex and multifaceted.

An essential component of an effective organized screening program is a well-functioning invitation system, as participation rates strongly depend on its reliability and coverage. In Hungary, this system has faced several challenges. According to data from the "Complex Public Health Screenings" EFOP 1.8.1 project, during the 2018–2019 screening cycle only 74.7% of the target population received invitation letters for the scheduled examination and the proportion of those invited for a second-round BC screening was only 29.4%. The contributing factors were assumed to include the reorganization of public administration, the restructuring of the screening organization framework, and staff reductions. Additionally, the lack of BC screening guidelines and protocols and an underdeveloped IT system in need of improvement were also identified as contributing factors (Pataki, 2020).

Participation willingness in BC screening is further influenced by several sociodemographic factors. Lower educational attainment (Mottram et al., 2021; Tavakoli et al., 2024) and residence in rural areas (Újhelyi et al., 2018) are both associated with lower participation. Educational level appears to be a major determinant: women with higher education levels were 50% more likely to attend screening than those with lower education levels (OECD, 2023). Beyond formal education, however, knowledge

regarding BC and screening practices also plays a critical role. A Hungarian study (Reményi Kissné et al., 2021) revealed significant knowledge gaps: among laywomen and screening attendees, respectively, only 35.2% and 86.6% knew the recommended age for the first mammography, and 33.9% and 12.9% were aware of the recommended screening frequency. Furthermore, awareness of risk factors (7.0% and 5.9%) and of signs and symptoms (16.7% and 28.9%) was also limited. These findings highlight the need for targeted education to strengthen awareness and understanding of BC and screening. In addition, tailored communication strategies are required, adapted to educational level and social background. According to the ECIBC recommendations (Schünemann et al., 2020), tailored approaches should already be integrated into the invitation process. This could ensure that disadvantaged groups receive information in an accessible and comprehensible way, which may ultimately improve participation rates in Hungary and thereby enhance the overall effectiveness of BC screening.

In Hungary, the target age group for BC screening consists of women aged 45-65 years. When comparing with European countries, differences in target group definitions can be observed (Cardoso et al., 2023): several countries, such as the Netherlands, Italy, and Portugal, extend screening beyond the age of 74-75 years, while others, including Turkey and Sweden, invite women from the age of 40 years. In Hungary, the lower age limit of 45 years aligns with or is lower than the recommendations in most European guidelines. However, the upper age limit of 65 years is more restrictive compared to the age of 69 years, which is applied in most of the countries. This limitation may reduce the potential impact of the Hungarian screening program on early detection and mortality reduction.

For screening frequency, the 4th Breast Cancer Consensus Conference advocates reducing the interval to 18 months for the age group of 40–54 years, compared to the currently uniform biennial screening interval (Forrai et al., 2020). This recommendation is based on the fact that tumours occurring at a younger age, are more likely to include aggressive, fast-growing subtypes (Arpino et al., 2015; Manjunath & Choudhary, 2021), for which early detection of the malignant lesions is particularly crucial. A similar practice is in place for the 45–49 years old age group in Italy, where annual screening is conducted (Bucchi et al., 2019). In Sweden, women aged 40–49 years have the opportunity to undergo screening every 18 months, compared to the biennial screening interval for older age groups (Lagerlund et al., 2021). However, in most EU countries,

mammographic screening is still performed every two or even three years (Zielonke et al., 2021). These differences indicate that more flexible, risk- and age-adapted screening intervals could be considered to improve the balance between benefits and harms of mammography.

5.2. The Potential Role and Feasibility of ABUS as an Imaging Method in the Current Hungarian Breast Cancer Screening Program

Professional communities are increasingly recognizing the significance of breast density in the development of screening strategies. Numerous international recommendations (Mann et al., 2022; Marcon et al., 2024; Nicholson et al., 2024; Niell et al., 2024) and, following their example, the Hungarian guideline (Forrai et al., 2020) also emphasize the importance of considering this factor. Accordingly, an increasing number of technological solutions are being explored to enhance the effectiveness of screening for women with dense breasts.

One promising solution is ABUS, which, as a supplementary imaging method, can increase the sensitivity of mammographic screening in this subpopulation. However, its applicability in organized screening programs is influenced by various other factors, considering compliance with Wilson & Jungner's principles as a fundamental requirement. Some of these factors are directly related to the technology itself (e.g., simplicity, safety, accuracy), while others are determined by the country's economic, infrastructural, and social characteristics - including healthcare systems, financing mechanisms, population-specific factors - as well as by patient values and preferences.

According to the position statements of international professional societies (Nicholson et al., 2024; Schünemann et al., 2020), there is not yet sufficient evidence to clearly define the role of ABUS within organized screening programs. To determine the balance between the benefits provided by this technology and the drawbacks associated with its use, well-designed and properly conducted clinical studies with adequate follow-up periods are required. Currently, a randomized, multi-centre study is underway in the UK (Allajbeu et al., 2024), comparing women with dense breasts who receive either the standard of care (no supplementary imaging) or supplementary imaging with abbreviated MRI (ABB-MRI), ABUS, or contrast-enhanced spectral mammography (CESM). The

study aims to evaluate and compare the sensitivity, specificity, and diagnostic effectiveness of each technology.

There is very limited research on the economic aspects of the use of ABUS. A recent study indicates that adding ABUS to mammography for women with dense breast tissue or elevated risk may represent a cost-effective screening strategy (Grady et al., 2025). Furthermore, a budget impact analysis conducted in Italy suggests that ABUS could have favourable budgetary effects within the screening program (Foglia et al., 2020) by allowing economic savings (ranging from –1.89% to –1.05%) compared to mammography screening alone.

However, it is important to note that when evaluating economic considerations, local factors must be taken into account, as international findings may not always be directly transferable to different healthcare systems. To address this, national-level studies are required to generate context-specific evidence. The ABUS protocol, we developed was designed with consideration of the Hungarian screening system and local factors, such as patient pathways within the Hungarian healthcare system and the institutional background of the screening organization. The associated data collection may provide the foundation for a standardized, comprehensive database focusing on BC screening for women with dense breasts.

A further key component of this process is ensuring that data collection is supported by a structured monitoring system with indicators covering clinical and economic aspects, in compliance with both international and national quality assurance standards. In addition to classical performance indicators, increasing emphasis is being placed on patients' preferences and values, and on the integration of these aspects into screening programs. Consequently, communication strategies should also aim to capture these values through the integration of patient-reported outcome and experience measures. When developing a screening protocol and its indicator system, such aspects should be systematically incorporated to ensure that patient perspectives are reflected, thereby strengthening patient-centred care and contributing to the overall effectiveness of the program.

5.3. Potential Directions for Hungarian Breast Cancer Screening Improvement based on the Result of a Real-World Data Analysis Focusing on the Distribution of the Age and the Molecular Subtypes of Newly Diagnosed Patients

Real-world data, derived from databases of indicator systems and cancer registries, provide invaluable insights into the performance of the screening program and trends of the disease. Additionally, real-world data obtained from the healthcare system and everyday cancer care serve also as an important source for analysing the effectiveness of screening programs. In our research, based on the database of the Oncology Centre at the University of Pécs, we analysed newly diagnosed BC cases at the centre to identify potential directions for improving the BC screening program.

We found that only 48.6% of the tumours were detected within the screening target age range (45-65 years). This falls behind the results observed in other countries in international comparisons. In the Netherlands, where the screening age range is 50–75 years, 62.7% of newly detected BC cases were found within the screening age group (van der Meer et al., 2021). Similarly, in France, where the target screening age range is 50–74 years, this proportion was 56.5% (Hassaine et al., 2022). Although women older than 65 years in Hungary no longer participate in organized BC screening programs, a considerable proportion of newly diagnosed BC cases still come from this age group (Sárváry et al., 2019). This factor may partly explain the underrepresentation of the age group targeted by screening among newly diagnosed BC cases. Supporting this assumption, the 4th Breast Cancer Consensus Conference included in its recommendations a call for reviewing the upper age limit of Hungary's screening program and evaluating its justification (Forrai et al., 2020).

Participation rates in screening programs have also a major impact on the number of detected tumours. During our study period, Hungary had the lowest participation rate in organized BC screening among the three countries, ranging from 20.0% to 30.8% (Laczó et al., 2022), compared to 76.8% to 79.4% in the Netherlands (Gong et al., 2023) and 49.9% to 52.1% in France (Statista Research Department, 2021). Increasing participation rates—through improvements in screening organization, education, and public awareness campaigns, as discussed earlier—could significantly enhance the detection of BC cases and improve the effectiveness of the screening program.

Our findings, consistent with international studies (Johansson et al., 2019; Mangone et al., 2022), confirm that BC detected among women eligible for screening are most often diagnosed at an early stage (Stage I), accounting for a substantial proportion of cases in this age group (50.6%). This proportion is higher than in women under the age of 45 years (41.8%) or over 65 years (37.3%). Moreover, when considering the overall stage distribution, BC in the screening age group is diagnosed at earlier stages than outside this group, indicating the effectiveness of screening in the target population.

In contrast, advanced-stage tumours were observed more frequently—both in absolute numbers and proportionally—among the oldest age group compared to younger individuals, indicating an age-related shift toward later stage at diagnosis. This trend may be influenced by the exclusion of older women from the organized screening program. Additionally, the potentially lower awareness of BC symptoms in this population (Linsell et al., 2008) could lead to delayed symptom identification and later diagnosis. Recognizing this pattern is crucial for developing and refining information protocols, as this subpopulation may require greater attention and a tailored approach distinct from that of the standard screening population.

In our study, we also analysed the distribution of newly detected BC cases based on molecular subtypes. Consistent with findings from other studies (Acheampong et al., 2020; Cortet et al., 2018), we observed a higher prevalence of HR-/HER2- and HER2+ tumours among women under 45 years of age. The molecular subtypes of BC differ in characteristics such as progression rate and radiologic appearance, notably influencing the likelihood of early detection. Fast-growing subtypes, including HR-/HER2- and HER2+, pose challenges for early diagnosis due to their short asymptomatic phase and rapid tumour progression. These features may call for adjustments in screening frequency by age groups.

Additionally, HR-/HER2- tumours can be challenging to identify since they may appear similar to benign lesions (Azzam et al., 2020) and are more likely to yield negative mammography findings compared with other BC subtypes (Lohitvisate et al., 2023). In contrast, alternative imaging techniques, such as US, BTS, and MRI, may be more effective in identifying this tumour type (Huang et al., 2020; Ian et al., 2021; Rashmi et al., 2018). Incorporating these considerations into screening strategies could support more personalized and effective approaches.

5.4. Limitations of the Research

A methodological limitation of our literature reviews is that the protocol was not registered in advance. While this step is not mandatory for the type of scoping and targeted reviews we conducted, it is generally recommended to enhance transparency and reproducibility. However, at the time when we performed our review it was not yet a common practice. For the reviews, we examined only a single database. However, due to the nature of the research question, reviewing the grey literature was of great importance, and we placed significant emphasis on this. We largely focused on finding Hungarian and international guidelines, many of which are not published as a scientific publication. Additionally, to enhance the comprehensiveness of our search, we applied the snowball method by reviewing the references of the identified publications to find further relevant studies. I also supplemented the previously conducted literature review with studies published between 2021 August and 2025 January, as several important methodological and technological developments emerged during this period It was carried out using the same database and search strings as in the initial search, in order to minimise potential bias. Given the continuous advancements in the field, a future systematic synthesis of newly emerging research could provide an up-to-date perspective, further strengthening the evidence base.

Furthermore, the protocol development and the associated evaluation framework were designed to establish the methodology for the screening program. As the primary goal was to define the framework and initial processes, further data collection and analysis were beyond the scope of this phase. This limitation underscores the need for subsequent studies to validate the findings and refine the methodology based on extended datasets and real-world application.

A limitation of the observational study was that the proportion of missing data on the anatomic TNM stage and molecular subtype at diagnosis varied across age groups, which could potentially influence our results. Nevertheless, we reported the extent of missing data across age groups to ensure transparency. The database did not distinguish between cases detected through screening or diagnostic mammography, which represents a limitation. This phenomenon may dilute the impact of examination on stage distribution, observed in the age group corresponding to the target population of the screening program. This constraint also highlights the importance of standardized methods and

platforms for data recording. When developing such systems, it is crucial to consider clinical, economic, patient-centered and research-related aspects to ensure accuracy, consistency, and usability.

Furthermore, our study results may have been influenced by the fact that the last year of the study period (2020) coincided with the COVID-19 pandemic. In Hungary, the BC screening program was suspended between March 16 and June 1, 2020, and again between April 9 and April 29, 2021. According to the research by Elek et al., BC incidence in Hungary decreased by 15.5% during the pandemic (Elek et al., 2022). The temporary suspension of screening programs may have affected our study outcomes; however, it is important to note that screening examinations were also periodically suspended in the comparator countries, France (Linck et al., 2022) and the Netherlands (Eijkelboom et al., 2021b).

6. Conclusions

BC poses a significant public health challenge in Hungary, however there has been steady progress in understanding the disease, as well as in improving its early detection and treatment strategies. Through population-based BC screening, there is an opportunity to detect tumours at an early stage, enabling the timely initiation of treatment, which significantly improves patients' prognosis and contributes to reducing mortality. Maximizing the benefits of national screening programs requires the regular review and updating of existing screening practices. It calls for the thoughtful integration of international research findings, updated clinical guidelines, and technological innovations, while carefully considering the local healthcare, economic, organizational, social, and regulatory context.

The reviewed international guidelines and recommendations indicate that the Hungarian BC screening guidelines are evolving in line with international standards from a professional perspective. However, following the example of international best practices, an important step for the national program would be to improve public awareness and increase participation rates, which requires strong support from a robust administrative and coordinating structure in close collaboration with civil society organizations and patient advocacy groups.

In light of recent scientific findings, increasing attention is being paid to optimizing BC screening practices for women with dense breast tissue. One promising approach is the introduction of new technologies tailored to this subpopulation. In Hungary, we investigated the conditions and possibilities for implementing ABUS. The ABUS protocol we developed demonstrated that this method can be integrated into the existing national BC screening program. The target group is easily identifiable, the examination itself imposes minimal burden on patients, and ABUS has been shown to significantly improve screening effectiveness. As such, it might represent an acceptable method both for patients and healthcare professionals.

To assess its implementation from the perspectives of patients and other stakeholders, further research based on national-level data is warranted. The indicator system embedded in our protocol is designed to ensure the systematic and standardized collection of data, forming the basis for transparent, evidence-based research.

The results of our retrospective observational study, when compared with the characteristics of the Hungarian screening system and with findings from both national and international research, revealed potential directions for further development of the Hungarian BC screening program. Improving participation rates in BC screening and extending the eligible age range to include older and younger women are goals aligned with both national and global efforts. Additionally, considering the molecular subtypes of BC – along with their distinct disease characteristics and age-specific prevalence – points toward the direction of personalized screening strategies, which remain an active area of intensive research.

In conclusion, the findings of my PhD research can provide practical insights that can support evidence-based decision-making in the ongoing development of the Hungarian BC screening program. By proposing a potentially feasible and patient-friendly supplementary imaging pathway for women with dense breast tissue, and by establishing a standardized protocol for data collection and evaluation, this work may contribute directly to improving the effectiveness of BC screening in Hungary. Furthermore, the study lays a solid foundation for future health policy planning, economic evaluation, and the integration of personalized screening approaches, thereby advancing both national and international efforts to reduce the burden of BC.

7. Summary

BC is the most frequently diagnosed cancer among women worldwide, with projections indicating a continued rise in incidence over the coming decades. In Hungary, both the incidence and mortality rates of BC are higher than the EU average.

Early detection is key to improving outcomes, highlighting the importance of organized, evidence-based screening programs. In Hungary, such a program has existed since 2002, targeting women aged 45–65 years with biennial mammography. To ensure that this program remains effective and responsive to changing epidemiological patterns and technological advances, it is essential to systematically evaluate and revise its components based not only on current scientific evidence and population-specific needs, but also with careful consideration of national and local contextual factors.

The dissertation applied a multi-method approach that included literature reviews, a methodological study, and a retrospective analysis of real-world BC data from Hungary to explore opportunities for optimization the Hungarian BC screening program.

The literature review indicated that while the core elements of the national screening protocol are aligned with international recommendations, the supporting organizational and coordinating structure of the system would benefit from further development to enhance the overall effectiveness of the program. Findings support the integration of ABUS into mammography-based screening for women with dense breasts, suggesting its feasibility and potential added value in enhancing early cancer detection. The retrospective study further highlighted the need for age- and subtype-specific screening strategies, as a significant proportion of advanced-stage and aggressive tumours occur in women outside the current target screening age range.

These findings may inform future revisions to Hungary's BC screening policy. The integration of these aspects into policy and practice has the potential to enhance screening outcomes, reduce disparities, and contribute to more equitable and effective BC control.

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9. Bibliography of the candidate's publications

1. Tittmann, J., Csanádi, M., Ágh, T., Széles, G., Vokó, Z., Ormándi, K., & Kallai, Á. (2022). Az automatizált emlőultrahang-daganatszűrés szakirodalmi áttekintése [Review of the scientific literature on the use of automated breast ultrasound for screening]. Orvosi hetilap, 163(35), 1374–1382. https://doi.org/10.1556/650.2022.32565

2. Tittmann, J., Csanádi, M., Ágh, T., Széles, G., Vokó, Z., & Kallai, Á. (2023). Development of a breast cancer screening protocol to use automated breast ultrasound in a local setting. Frontiers in public health, 10, 1071317. https://doi.org/10.3389/fpubh.2022.1071317

3. Tittmann, J., Ágh, T., Erdősi, D., Csanády, B., Kövér, E., Zemplényi, A., Kovács, S., & Vokó, Z. (2024). Breast cancer stage and molecular subtype distribution: real-world insights from a regional oncological center in Hungary. Discover oncology, 15(1), 240. https://doi.org/10.1007/s12672-024-01096-9

10. Acknowledgements

I would like to express my deepest gratitude to my supervisor, Professor Zoltán Vokó, for their unwavering support, expert guidance, and continuous encouragement throughout the course of my doctoral studies. Their insightful feedback, patience, and constructive criticism have greatly contributed to the development and completion of this dissertation.
I am also grateful to Marcell Csanádi, a colleague of Syreon Resaerch Institute, for his supportive assistance throughout our collaboration. I gained valuable insights from him, and their contribution was truly important to my work.
Acknowledgement is also due to Sándor Kovács, Antal Zemplényi, Dalma Erdősi and Bettina Csanády at the University of Pécs, whose support was of great help during the data analysis. Their expertise and assistance significantly contributed to the progress of this work.
I would like to sincerely thank my husband, Tamás Ágh, for his unfailing support, both professionally and personally, throughout this journey. His reassurance, understanding, and belief in me have been invaluable, especially during the most challenging moments. I am deeply grateful for his insightful advice, and the countless discussions that helped me develop and refine this work.

Appendix

Search strings for the literature review

Scoping Literature Review

PubMed:

("breast cancer screening"[Title/Abstract] OR "breast cancer early detection"[Title/Abstract]) AND

("organized screening program"[Title/Abstract] OR "guidelines"[Title/Abstract] OR "recommendation"[Title/Abstract])

with PubMed filter on „Articel type”: Consensus Development Conference, Goverment Publication, Guideline, Practice Guideline

Targeted Literature Review

PubMed:

("breast cancer"[Title/Abstract]) AND

("screening"[Title/Abstract] OR "population-based"[Title/Abstract]) AND

("automated breast ultrasound"[Title/Abstract] OR "ABUS"[Title/Abstract] OR "dense breast"[Title/Abstract]) AND

("cancer detection rates"[Title/Abstract] OR "sensitivity"[Title/Abstract] OR "specificity"[Title/Abstract])

Table 1 Indicator system for monitoring and evaluating the mammographic screening program supplemented with ABUS

	Screening activity-related indicators	Definitions and calculation methods
Indicator #1	Size of the target population	Number of individuals eligible for screening
Indicator #2	Invitation rate	Number of invited individuals / Size of the target population
Indicator #3	Screening coverage rate	Number of individuals who participated in screening / Size of the target population
Indicator #4	Participation rate	Number of individuals who participated in screening / Number of invited individuals
Indicator #5	Distribution of test results	Number of each test result (e.g., negative, positive, indeterminate) / Number of individuals who participated in screening
Indicator #6	Recall rate among screened individuals	Number of individuals referred for further examination after screening / Number of individuals who participated in screening
Indicator #7	Attendance rate among recalled individuals	Number of individuals who attended further examination after screening / Number of individuals referred for further examination
Indicator #8	Biopsy completion rate	Number of biopsies performed / Number of individuals who participated in screening
Indicator #9	Proportion of individuals recommended for therapy	Number of individuals referred for cancer treatment / Number of individuals who attended further examination after screening
Indicator #10	Proportion of individuals undergoing therapy	Number of individuals who started cancer therapy / Number of individuals referred for therapy
Indicator #11	Cancer detection rate	Number of malignant tumors detected through screening / Number of individuals who participated in screening
Indicator #12	Interval cancer rate	Number of malignant tumors detected during the screening interval after a negative screening result / Number of individuals who participated in screening

Indicator #13	Participation rate in subsequent/repeat screening	Number of individuals who participated in a repeated (subsequent) screening / Number of individuals eligible for the next screening

	Screening test-related indicators	Definitions and calculation methods
Indicator #14	Sensitivity of the screening test	Number of true malignant cancer cases detected during screening / Sum of true positive cases detected during screening and undetected malignant cancer cases
Indicator #15	Specificity of the screening test	Number of true negative cases in screening / Sum of true negative cases detected in screening and false positive cases (cases perceived as positive in screening but later diagnosed as negative)
Indicator #16	Positive predictive value	Number of true malignant cancer cases detected during screening / Sum of true positive cases detected during screening and cases perceived as positive in screening but later diagnosed as negative (false positives)
Indicator #17	Negative predictive value	Number of true negative cases in screening / Sum of true negative cases detected in screening and undetected malignant cancer cases (false negatives)
Indicator #18	False positive rate	Number of cases perceived as positive in screening but later diagnosed as negative (false positives) / Sum of cases perceived as positive in screening but later diagnosed as negative (false positives) and true negative cases detected in screening

	Cost-related indicators	Definitions and calculation methods
Indicator #19	Costs of invitation to screening	The cost of communication directed towards eligible individuals and other activities promoting screening (total cost or per capita cost).
Indicator #20	Cost of screening test and its evaluation	Costs associated with performing the screening activity and evaluating the test (total cost or per capita cost).

	Long-term clinical indicators	Definitions and calculation methods
Indicator #21	Cancer-specific survival	Number of individuals living with a specific malignant cancer at the end of a given observation period / Number of known malignant cancer cases.

Indicator #22	Cancer-specific mortality	Number of deaths due to malignant cancer in a given population / Size of the studied population.
Indicator #23	Incidence	Number of newly detected malignant cancer cases / Size of the studied population.

Source: (Tittmann et al., 2022)

Table 2. General characteristics of the study population

	Patients aged <45 years	Patients aged 45-65 years	Patients aged >65 years	Total
Study cohorts (N)	396	1595	1291	3282
Age at diagnosis (mean (SD))	38.63 (4.4)	56.6 (5.9)	73.7 (5.8)	61.2 (12.9)
TNM stage (N (%))				
0	8 (3.8)	20 (1.8)	11 (1.1)	39 (1.7)
IA	87 (41.8)	55 (50.6)	373 (37.3)	1015 (44.1)
IB	3 (1.4)	22 (2.0)	13 (1.3)	38 (1.65)
IIA	71 (34.1)	284 (25.9)	305 (30.5)	660 (28.7)
IIB	23 (11.1)	120 (10.9)	148 (14.8)	291 (12.6)
IIIA	8 (3.8)	60 (5.5)	76 (7.6)	144 (6.3)
IIIB	1 (0.5)	7 (0.6)	44 (4.4)	52 (2.3)
IIIC	6 (2.9)	22 (2.0)	28 (2.8)	56 (2.4)
IV	1 (0.5)	6 (0.5)	1 (0.1)	8 (0.3)
Missing data	188 (47.7)	499 (31.3)	292 (22.6)	979 (29.8)
Stage of BC (N (%))				
Early-stage	192 (92.3)	1001 (91.3)	850 (85.1)	2043 (88.7)
Advanced-stage	16 (7.7)	95 (8.7)	149 (14.9)	260 (11.3)
Missing data	188 (47.7)	499 (31.3)	292 (22.6)	979 (29.8)
Molecular subtype (N (%))				
HR+/HER2-	163 (55.8)	961 (72.7)	853 (78.0)	1977 (73.0)
HR+/HER2+	34 (11.6)	107 (8.1)	71 (6.5)	212 (7.8)
HR-/HER2+	26 (8.9)	77 (5.8)	55 (5.0)	158 (5.1)
HR-/HER2-	69 (23.6)	177 (13.4)	114 (10.4)	360 (13.3)
Missing data	104 (26.3)	273 (17.1)	198 (15.3)	575 (17.5)

Percentages of non-missing categories refer to the total number of patients with non-missing data.
BC: breast cancer; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; TNM: Tumour, node, metastasis
Source: (Tittmann et al., 2024)

Table 3. Annual number of newly diagnosed breast cancer cases during the study period per age, anatomic TNM stages and severity

Year Age cohorts	Anatomic TNM stages (N of subjects)									BC severity (N of subjects)	
	0	**IA**	**IB**	**II A**	**IIB**	**III A**	**III B**	**III C**	**IV**	**Early-stage**	**Advanced-stage**
2010											
Patients aged <45 y	2	12	0	9	1	1	0	0	0	24	1
Patients aged 45-65 y	4	54	4	32	16	4	0	2	0	110	6
Patients aged >65 y	1	26	0	23	11	6	3	3	0	61	12
Total	7	92	4	64	28	11	3	5	0	195	19
2011											
Patients aged <45 y	1	5	0	5	4	0	1	1	1	15	3
Patients aged 45-65 y	2	42	1	25	12	4	0	3	0	82	7
Patients aged >65 y	0	22	1	19	11	8	2	3	0	53	13

Total	3	69	2	49	27	12	3	7	1	150	23
2012											
Patients aged <45 y	2	13	0	10	3	1	0	0	0	28	1
Patients aged 45-65 y	0	55	0	28	8	11	2	3	1	91	17
Patients aged >65 y	2	26	0	27	14	9	4	5	0	69	18
Total	4	94	0	65	25	21	6	8	1	188	36
2013											
Patients aged <45 y	0	7	0	5	1	0	0	1	0	13	1
Patients aged 45-65 y	2	54	1	22	5	6	0	3	0	84	9
Patients aged >65 y	2	31	0	21	13	5	2	2	0	67	9
Total	4	92	1	48	19	11	2	6	0	164	19

2014											
Patients aged <45 y	0	12	0	6	0	0	0	0	0	18	0
Patients aged 45-65 y	5	74	4	26	8	9	0	2	0	117	11
Patients aged >65 y	2	29	0	40	5	3	4	0	0	76	7
Total	7	115	4	72	13	12	4	2	0	211	18
2015											
Patients aged <45 y	0	7	0	6	3	4	0	1	0	16	5
Patients aged 45-65 y	2	57	2	20	14	5	1	0	1	95	7
Patients aged >65 y	0	41	0	32	16	5	5	1	0	89	11
Total	2	105	2	58	33	14	6	2	1	200	23
2016											
Patients aged <45 y	1	3	0	6	2	0	0	1	0	12	1
Patients aged 45-65 y	2	50	2	30	14	3	0	3	3	98	9

Patients aged >65 y	1	38	2	37	22	6	5	4	0	100	15
Total	4	91	4	73	38	9	5	8	3	210	25
2017											
Patients aged <45 y	0	6	0	4	4	0	0	0	0	14	0
Patients aged 45-65 y	0	43	2	29	9	5	2	2	0	83	9
Patients aged >65 y	2	36	4	21	14	8	2	4	0	77	14
Total	2	85	6	54	27	13	4	6	0	174	23
2018											
Patients aged <45 y	0	8	1	9	1	1	0	1	0	19	2
Patients aged 45-65 y	1	46	2	29	8	5	2	1	1	86	9
Patients aged >65 y	0	48	1	32	17	10	6	1	0	98	17
Total	1	102	4	70	26	16	8	3	1	203	28

2019											
Patients aged <45 y	0	6	1	5	1	0	0	0	0	13	0
Patients aged 45-65 y	0	37	1	22	14	5	0	2	0	74	7
Patients aged >65 y	1	37	2	23	17	9	6	3	0	80	18
Total	1	80	4	50	32	14	6	5	0	167	25
2020											
Patients aged <45 y	2	8	1	6	3	1	0	1	0	20	2
Patients aged 45-65 y	2	43	3	21	12	3	0	1	0	81	4
Patients aged >65 y	0	39	3	30	8	7	5	2	1	80	15
Total	4	90	7	57	23	11	5	4	1	181	21

BC: breast cancer; TNM: Tumour, node, metastasis; y: year
Source: (Tittmann et al., 2024)

Table 4. Annual number of newly diagnosed breast cancer cases during the study period per age and molecular subtype

Year Age cohorts	**Molecular subtypes** (N of subjects)			
	HR+/HER2-	**HR+/HER2+**	**HR-/HER2+**	**HR-/HER2-**
2010				
Patients aged <45 y	22	1	4	4
Patients aged 45-65 y	97	8	7	21
Patients aged >65 y	67	2	3	8
Total	186	11	14	33
2011				
Patients aged <45 y	17	3	1	5
Patients aged 45-65 y	77	14	1	9
Patients aged >65 y	62	6	2	7
Total	156	23	4	21
2012				
Patients aged <45 y	18	3	3	10
Patients aged 45-65 y	94	9	4	16
Patients aged >65 y	60	5	7	13
Total	172	17	14	39
2013				
Patients aged <45 y	14	5	0	3
Patients aged 45-65 y	76	8	9	21
Patients aged >65 y	69	4	4	7
Total	159	17	13	31

2014				
Patients aged <45 y	9	2	2	10
Patients aged 45-65 y	102	12	10	18
Patients aged >65 y	73	7	7	8
Total	184	21	19	36
2015				
Patients aged <45 y	16	3	3	9
Patients aged 45-65 y	92	8	7	11
Patients aged >65 y	83	4	4	16
Total	191	15	14	36
2016				
Patients aged <45 y	10	4	0	7
Patients aged 45-65 y	88	13	7	20
Patients aged >65 y	97	8	7	16
Total	195	25	14	43
2017				
Patients aged <45 y	15	5	2	4
Patients aged 45-65 y	85	11	10	16
Patients aged >65 y	80	5	6	8
Total	180	21	18	28
2018				
Patients aged <45 y	19	1	5	8
Patients aged 45-65 y	81	9	8	21
Patients aged >65 y	94	10	4	14
Total	194	20	17	43

2019				
Patients aged <45 y	10	4	3	3
Patients aged 45-65 y	81	9	7	12
Patients aged >65 y	92	8	4	9
Total	183	21	14	24
2020				
Patients aged <45 y	13	3	3	6
Patients aged 45-65 y	88	6	7	12
Patients aged >65 y	76	12	7	8
Total	177	21	17	26

HER2: human epidermal growth factor receptor 2; HR: hormone receptor; y: year
Source (Tittmann et al., 2024)