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

Thesis-book

Dr. Ághné Dr. Tittmann Judit

Semmelweis University Doctoral School
Pharmaceutical Sciences and Health Technologies Division

Supervisor:
Zoltán Vokó, MD, D.Sc
Official reviewers:
Edit Paulik, MD, Ph.D, Habil.
András Terebessy, MD, Ph.D
Head of the Complex Examination Committee:
Romána Zelkó, PharmD, D.Sc
Members of the Complex Examination Committee:
András Inotai, PharmD, Ph.D, Habil.
Orsolya Varga, MD, D.Sc

Budapest
2025

1. Introduction

Breast cancer (BC) represents a major health concern at both the public and individual levels. It is the most common cancer among women worldwide (Ferlay et al., 2024). Hungary reflects this global trend: it is the leading type of cancer among women, responsible for nearly one in four cancer cases (Ferlay et al., 2024). This national burden is further underscored by the fact that both its age-standardized incidence and mortality rates exceed the averages of the European Union and other Central European countries (Dafni et al., 2019).

BC is not a single disease; rather, it constitutes a heterogeneous group of malignancies with distinct biological characteristics. However, all forms share a key attribute: mortality can be significantly reduced through early detection. Organised, population-based screening offers a robust route to earlier diagnosis.

In Hungary, BC screening has been in place since 2002. The program targets women aged 45 to 65 years at average risk using biennial mammography as the primary screening tool.

To maximize the benefits of the screening program, it must adapt to emerging scientific evidence, encompassing both our advancing understanding of the disease and the evolving knowledge of effective screening practices.

2. Objectives

The objective of my research was to examine potential improvements to the Hungarian BC screening program, guided by the following research questions:

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

3.1. Literature Review

A scoping literature review was conducted using PubMed, Google Scholar, and Google to map current BC screening practices, drawing on both international and Hungarian guidelines and policy documents. Grey

literature served as important sources in uncovering regional and national variations. A targeted literature review was also performed to explore the potential role of ABUS in screening. It focused on original clinical and observational studies evaluating its effectiveness as a complementary tool to mammography, as well as review articles on its use in population-based programs. The searches were conducted independently by two researchers and the final selections were reviewed and discussed collectively within the research team.

3.2. Methodological study

A screening protocol for the integration of ABUS into the existing mammography-based program was developed within the framework of the Interreg project. The protocol was created in several stages: its structure was first defined, followed by the specification of the content elements, that reflected both evidence-based standards and local clinical needs. This work was informed by the findings of the literature reviews and expertise of clinicians and hospital management, supported by in-person, online consultations and written expert feedback.

To ensure further monitoring and evaluation of the screening program, a comprehensive indicator system was established and a standardized Excel-based platform was designed for anonymized data collection using patient identifiers. This system enabled both retrospective and prospective data gathering. The pilot implementation of the protocol began in April 2022 at the regional mammography centre in Hódmezővásárhely. Ethical approval for the study was obtained 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

A retrospective observational study was conducted using database of the Clinical Centre, University of Pécs, covering female patients diagnosed with BC between 2010 and 2020 (ICD codes C50, D05). The dataset was developed in consultation with clinicians: age at diagnosis, year of diagnosis, TNM stage, and ER, PR, and HER2 status were extracted through a two-step process, combining structured coding and manual review of free-text records.

Patients were stratified into three age groups (<45, 45–65, >65 years) in line with the Hungarian screening protocol. TNM was analysed both at the individual stage level and in severity groups (early: 0–IIB; advanced: IIIA–IV). Molecular subtypes were defined by HR and HER2 status (HR+/HER2–, HR+/HER2+, HR–/HER2+, HR–/HER2–). Descriptive analyses assessed the distribution of demographic and clinical variables across the full cohort and by age group. Associations between year of diagnosis, TNM stage, BC severity and molecular subtype were evaluated with Chi-squared tests overall and within each age group. Aggregated analyses across the study period compared the distributions of TNM stages, BC severity, and subtypes between age cohorts. No imputation was conducted for missing data. Statistical significance was set at $p<0.05$. Analyses were performed in STATA 16.1 and as a quality control measure replicated in R 4.1.2. Ethical approval was granted by

the Hungarian Scientific and Research Ethics Committee (ETT TUKEB
IV/4068-1/2022/EKU).

4. Results

4.1. Literature Review

In the scoping review, Hungarian and international sources were analysed
separately. In Hungary, the current target age group for organized BC
screening remains 45–65 years, although professional discussions are
ongoing regarding a potential extension of this range. Breast density has
emerged as a key issue: it is internationally recognized both as an
independent risk factor for BC and as a major challenge for
mammographic detection due to its masking effect. While the Fourth
Consensus Conference for BC (Forrai et al., 2020) highlighted the critical
importance of standardized terminology for breast density, specific
recommendations for personalized screening in women with dense
breasts are still lacking.

At the international level, the reviewed studies indicate that digital
mammography remains the widely accepted method for average-risk
women, with broad consensus to screen those aged 50–70 years.
However there has been a trend in recent years towards extending
organized screening programs up to the age of 75 years, while others urge
caution pending further evaluation of benefits and harms, cost-

effectiveness, and points to a potential role for alternative screening strategies such as tailoring screening frequency to specific age groups.

For women with dense breasts, several organizations have issued specific recommendations, but consensus is still limited. More high-quality longitudinal data are needed to establish the benefit–harm balance of supplemental imaging strategies in this population.

The targeted review demonstrated that, compared with mammography alone, the addition of ABUS improves sensitivity and cancer detection rates, particularly for smaller tumours and early-stage cancers, without significantly reducing specificity. However, recall rates tend to be higher when ABUS is introduced, which may lead to more false-positive findings.

ABUS may therefore provide important added value for women with dense breast tissue, as it is not limited by breast density and offers a unique coronal view which allows that facilitates the visualization of minor structural changes.

The main limitations highlighted in the literature are higher recall and false-positive rates, though both can be reduced with dedicated training and with increasing reader practice.

4.2. Methodological study: Protocol and Evaluation Framework Development

The protocol was designed to integrate ABUS as a supplemental tool within the existing mammography-based screening program (Fig.1.). The target population includes women participating in the organized screening program and whose mammograms show no abnormalities but indicate dense breast tissue. Participation requires written informed consent.

The ABUS images are acquired by trained assistants, but evaluated independently by two radiologists.

If the findings are negative, women return to the regular two-year screening cycle, with mammography now supplemented by ABUS. Non-negative findings prompted recall for further diagnostic procedures, with cases subsequently discussed in a multidisciplinary team setting.

The protocol also addresses requirements related human resources, training, communication, and infrastructure. Particular emphasis was placed on communication with both patients and healthcare professionals to raise awareness of the risks associated with dense breast tissue and the potential incremental value of ABUS.
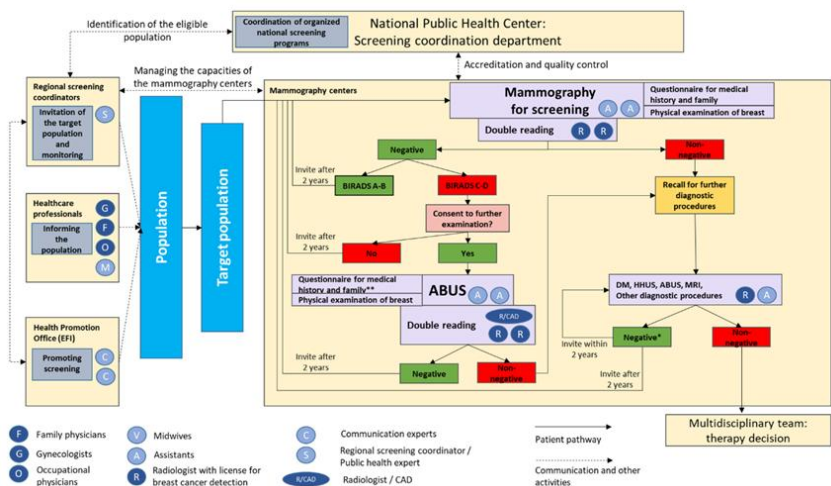
Figure 1. The flow chart of the ABUS screening
Source: (Tittmann et al., 2022)

In addition, an indicator system with 23 measures was designed to monitor screening activity, test performance, costs, and long-term clinical outcomes. The system was supported by a standardized Excel-based data platform to facilitate data collection and evaluation.

A pilot study conducted between April and June 2022 included 116 women; of these 34 met the criteria for ABUS. In one case, ABUS detected a lesion not visible on the mammography, which was subsequently confirmed as a malign tumour, stage T1bN1M0.

4.3. Retrospective Observational Study

The retrospective observational study analysed the data of 3282 women diagnosed with BC at the University of Pécs between 2010 and 2020.
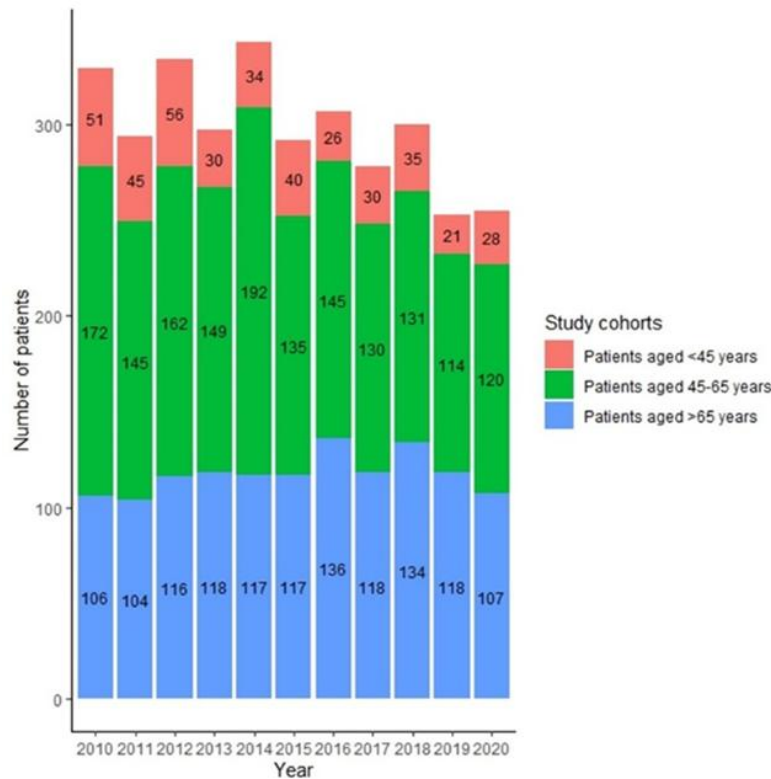

Figure. 2. Annual number of newly diagnosed breast cancer cases during the study period
Source: (Tittmann et al., 2024)

In terms of age distribution (Fig.2.), only 48.6% of newly diagnosed BC cases fell within the age group corresponding to the target population of Hungary's screening program, while as many as 39.3% occurred in

9

women over the age of 65 years. Over the ten-year period, no significant changes were observed in tumour stage at diagnosis, disease severity, or breast cancer subtypes, either in the overall cohort or within age-stratified subgroups.
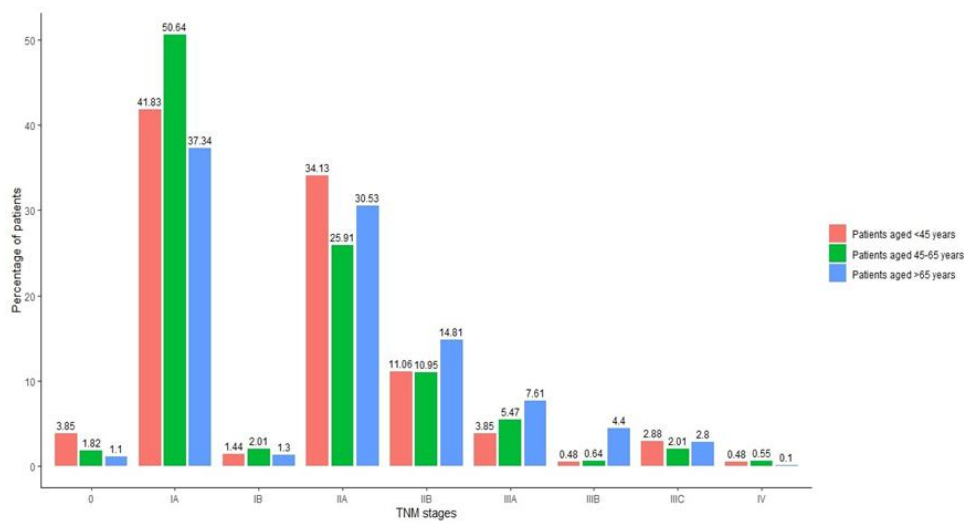

Figure 3. Distribution of TNM stages of breast cancer per age cohorts
Source: (Tittmann et al., 2024)

Stage IA was consistently the most frequent stage across all age groups (Fig.3.). 50.6% of women aged 45 to 65 years fell into this category, meaning that they were small tumours without lymph node involvement. In contrast, women older than 65 years had the highest proportion of advanced tumours throughout the study period. Advanced-stage cancers were significantly more common in this age group than in both younger cohorts.
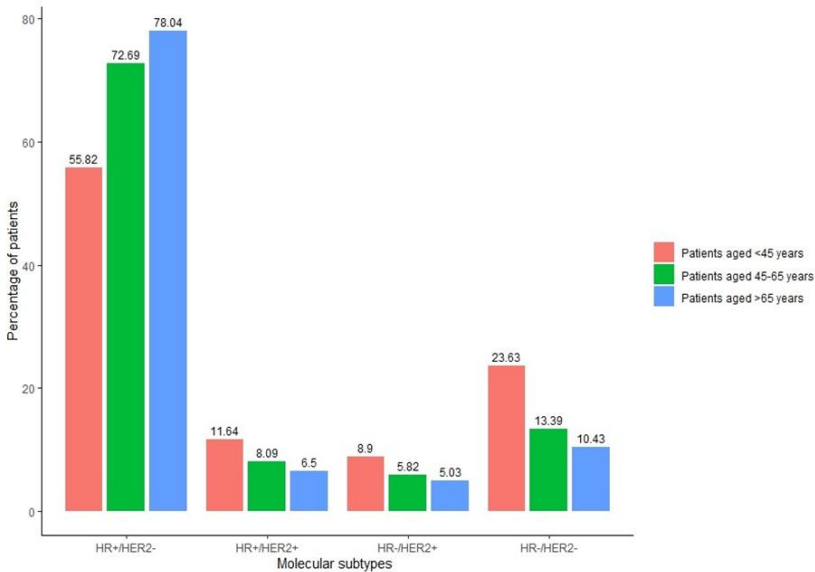
Figure 4. Distribution of breast cancer subtypes according to age cohorts
Source: (Tittmann et al., 2024)

With respect to molecular subtypes (Fig.4.), HR+/HER2– tumours represented the majority of cases across all age groups, increasing with age (55.8% in women <45 years; 72.7% in women 45–65 years; 78.0% in women >65 years). These tumours are characterized by a slow growth rate and are generally associated with a favourable prognosis, including lower recurrence and better survival prospects. By contrast, more aggressive subtypes, such as HR–/HER2– or HER2-positive tumours, were significantly more frequent among young women. This pattern suggests that age is not only linked to stage at diagnosis, but also to the biological characteristics of BC, underlining the importance of

11

considering molecular subtype differences when designing screening strategies across age groups.

This study has certain limitations that may have influenced the results.

First, concerning the literature review, it was not designed as a systematic review. While the database search was carried out primarily in PubMed, additional emphasis was placed on grey literature to improve comprehensiveness.

Second, with respect to protocol development, the primary aim was to establish a framework and define the initial processes of a protocol for integrating ABUS into mammography-based screening. Extended analyses of the effectiveness of the program were beyond the scope of this phase. Further studies are required to validate the findings and refine the methodology.

Third, the retrospective observational study was limited by missing data. The lack of information on TNM stage and molecular subtype in certain cases may have influenced the results. In addition, the database did not differentiate between cancers detected through screening mammography versus diagnostic mammography.

5. Conclusions

Our results indicate that the Hungarian BC screening guidelines are evolving in line with international standards. Nevertheless, screening uptake in Hungary remains suboptimal, below the EU average.

Increasing participation within the target population supported by a robust administrative and coordinating structure and well-designed communication strategies remains a key priority.

Breast density is increasingly recognized as an important factor, yet consensus is lacking on supplemental screening. ABUS is a promising complementary tool, but the balance of benefits and harms is not yet fully established. The developed protocol demonstrates that ABUS can be integrated into the existing screening framework in a structured way. Although limited international evidence suggests that ABUS may be a cost-effective method for BC screening in women with dense breasts, such findings are not directly transferable to different healthcare systems. National-level data are therefore essential to assess cost-effectiveness in the Hungarian setting and to support stakeholder adoption. The protocol developed in this study, designed with regard to the specific features of the Hungarian screening system, provides a solid foundation for generating such data and establishing a standardized database to inform evidence-based decision-making. A further important consideration for the future is the systematic integration of patient preferences and values into monitoring and evaluation, thereby strengthening patient-centred care.

Our findings further highlight that the proportion of newly diagnosed BC cases within the screening-eligible age group is relatively small, whereas older women are disproportionately represented. This suggests that expanding the age range could enhance program effectiveness.

Moreover, aggressive subtypes are more common among younger women, whose rapid progression and short asymptomatic phase make detection more challenging. These characteristics may call for adjustments in screening frequency across age groups. In addition, such tumours are also more likely to yield false-negative mammography results due to their resemblance to benign lesions. Alternative imaging modalities, such as US or MRI, together with the incorporation of molecular subtype into screening strategies, could support more personalised and effective approaches.

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.

References

Dafni, U., Tsourti, Z., & Alatsathianos, I. (2019). Breast Cancer Statistics in the European Union: Incidence and Survival across European Countries. Breast Care. 14(6), 344-353. https://doi.org/10.1159/000503219

Ferlay, J., Ervik, M., Lam, F., Laversanne, M., Colombet, M., Mery, L., Piñeros, M., Znaor, A., Soerjomataram, I., & Bray, F. (2024). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Retrieved March 2025, from https://gco.iarc.who.int/today

Forrai, G., Kovács, E., Ambrózay, É., Barta, M., Borbély, K., Lengyel, Z., Ormándi, K., Péntek, Z., Tasnádi, T., & Sebő, É. (2020). Radiology/Nuclear Medicine Group. Use of imaging methods in the current screening, diagnostics and treatment of breast cancer - Professional guidelines. 4th Breast Cancer Consensus Conference. *Magyar Onkologia*, *64*(4), 278-299.

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