„CAROL DAVILA” UNIVERSITY OF MEDICINE
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FIELD OF MEDICINE

BARRIERS TO IMPLEMENTATION AND LACK OF ADHERENCE TO MAMMOGRAPHIC SCREENING OF BREAST CANCER

SUMMARY OF THE DOCTORAL THESIS

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TABLE OF CONTENTS

SUMMARY OF THE DOCTORAL THESIS

The doctoral thesis is structured into two parts. The general part consists of two chapters. The first chapter presents general information about breast cancer, such as its global and national impact, risk factors, screening, diagnosis, and treatment. Additionally, it discusses its economic impact through a comparison of the costs associated with breast cancer treatment and the costs involved in organized screening. The second chapter of the general part outlines the current situation in Romania regarding breast cancer screening. The personal contributions section includes the results of two studies conducted during the doctoral research.

I. GENERAL PART

Chapter 1. Breast cancer

1.1. The Global and National Impact of Breast Cancer

Breast Cancer Incidence

Breast cancer is a global health issue that affects women of all ages and backgrounds, with rising incidence and high mortality rates, having a significant impact on individuals and society.

According to the International Agency for Research on Cancer (IARC), cancer-related deaths worldwide have increased by 66% from 1960 to the present [1].

It is estimated that one in eight women in the United States will develop invasive breast cancer during their lifetime [1]. This type of cancer is the most frequently diagnosed in women, accounting for approximately 25% of all cancers, with 2.26 million cases recorded in 2020 [1].

It is the leading cause of cancer-related death in women [2].

Unlike other European countries, breast cancer mortality in Romania has consistently increased since 1996, when the rate was 21.97 per 100,000 [3]. Data from 2020 shows a 5-year prevalence of 45,263 cases in Romania, compared to 7,790,717 globally, and 2,138,117 in Europe [4].

1.2. Breast Cancer Risk Factors

Breast cancer is a complex and multifactorial condition, where multiple biological mechanisms contribute to the development and progression of the disease. Carcinogenesis, the process through which normal cells become malignant, involves significant pathological changes in various tissues and organs, resulting in a variety of cancer types. Key mechanisms facilitating this transformation include the evasion of apoptosis, unrestricted cellular proliferation, enhanced angiogenesis, resistance to anti-growth signals, and the ability of cells to metastasize. These processes are influenced by both genetic predispositions and environmental factors, highlighting the complex and interdependent nature of carcinogenesis in breast cancer [5].

1.3. Genetic Substrate in Breast Cancer Development

Breast cancer is a multifactorial condition driven by the complex interaction between genetic, environmental, and lifestyle factors. In recent decades, genetic testing has become an indispensable tool for identifying inherited mutations that significantly contribute to the risk of developing breast cancer. This technology not only aids in assessing individual susceptibility but also plays a crucial role in prevention, early detection, and personalized disease management [6].

The Impact of BRCA1 and BRCA2 Mutations

Research indicates that approximately 5-10% of all breast cancer cases are hereditary, caused by inherited genetic mutations. The most notable genes involved in these cases are BRCA1 and BRCA2, which, when mutated, significantly increase the risk of both breast and ovarian cancer [7].

Other Genes Involved in Breast Cancer Risk

In addition to BRCA1 and BRCA2, there are other genes that contribute to breast cancer risk, including TP53, ATM, and PTEN [7].

1.4. Breast Anatomy

The breasts are a secondary sexual characteristic in women, whose development and functionality are profoundly influenced by hormones. In men, the breasts remain rudimentary and do not develop significantly. In childhood, there are no notable differences between sexes, but at puberty, girls begin to develop breasts, a process that continues throughout the reproductive life, with eventual regression at menopause.

The mammary gland consists of the parenchyma, which contains a complex system of branching ducts, and stroma, composed of connective and adipose tissue. It contains between 10 and 20 lobes, each subdivided into lobules, with each lobe drained by a lactiferous duct that opens at the nipple. The stroma surrounding the parenchyma is crossed by numerous blood vessels, lymphatics, nerves, and capillaries.

A detailed understanding of breast anatomy is crucial in the clinical context as it plays a key role in the early diagnosis of breast cancer, surgical planning, and administering appropriate treatments. Knowledge of the ductal structure and lymph node distribution allows for precise tumor localization and accurate assessment of disease spread.

Breast anatomy also influences the choice and effectiveness of imaging techniques such as mammography, ultrasound, and MRI, which are fundamental for detecting breast lesions [3]. In oncological surgery, a deep understanding of this anatomy allows for conservative or radical interventions to be performed with maximum efficiency and minimal impact on breast aesthetics and functionality.

1.5. Pathophysiological Evolution of Breast Cancer

There are two main theories regarding the initiation and progression of breast cancer: the malignant stem cell theory and the stochastic theory. The first suggests that all tumor subtypes originate from the same stem cells, with acquired genetic and epigenetic mutations leading to various tumor phenotypes. In contrast, the stochastic theory posits that each tumor subtype originates from a single type of cell (stem, progenitor, or differentiated), with a gradual accumulation of mutations transforming these cells into tumor cells. While both theories are supported by studies, neither fully explains the origin of breast cancer in humans [8], [9].

Primary Tumor Extension in the Breast

The primary tumor extends within the breast through direct infiltration of the mammary parenchyma, along the mammary ducts, and through intramammary lymphatics. Parenchymal infiltration is the most common form of local invasion, leading to the appearance of a palpable tumor with increased consistency and an irregular shape, characterized by stellate extensions. In advanced stages, the invasion may reach the overlying skin and deeper planes, such as the fascia, pectoral muscle, and chest wall. When cancer extends to the chest wall, including the ribs and pleura, it is classified as stage T4, a severe condition requiring complex treatments such as radiotherapy and chemotherapy [3], [10], [11].

Lymph Node Invasion in Breast Cancer

At the time of diagnosis, approximately 30-40% of patients with breast cancer present with axillary lymph node invasion, influenced by the stage and size of the tumor, as well as other risk factors such as hormone receptor status and the presence of lymphovascular invasion [12]. The axilla, which drains approximately 95% of the breast's lymph, is the main region where lymph node metastases are observed, with a higher probability as the size of the primary tumor increases [3].

In rare cases where breast cancer regresses on its own, these attract significant interest, particularly in the case of ductal carcinoma in situ (DCIS). Studies have shown that certain DCIS lesions can remain stable or even regress without ever progressing to the invasive stage. This spontaneous regression is considered an extremely rare and not fully understood phenomenon, but some theories suggest that host immune responses and the microvascular environment play a role in this process. It is important to emphasize that while these cases provide an interesting perspective on the biology of breast cancer, they do not alter the need for active treatment for most cases of DCIS, given the risk of progression to invasive forms. This observation opens discussions about the possibility of overdiagnosis and overtreatment in some cases of DCIS, highlighting the ongoing need for research to differentiate between lesions that require intervention and those that could remain harmless [13]–[15].

1.6. Breast Cancer Classification and Staging

The classification of breast cancer is essential for managing the disease, allowing differentiation into distinct groups based on histopathological type, tumor grade, stage, and molecular expression of proteins and genes. In recent years, classification has evolved to include molecular profiling, such as hormone receptors (ER, PR) and HER2, which has enabled the development of more personalized treatment strategies [16].

Histopathological Classification of Breast Cancer

Histopathological classification provides essential information about the tumor's structure and cellular origin, being crucial for choosing the appropriate treatment. According to the 2012 WHO classification, breast cancers are categorized into carcinomas and sarcomas. Carcinomas, which represent the majority of breast cancers, develop from the epithelial cells of the breast and can be subdivided into in situ and invasive carcinoma. Invasive carcinomas, such as invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC), are the most common types, with IDC being the most frequent (approximately 80%) [17], [18]. Unlike carcinomas, which usually arise from milk ducts, sarcomas originate from connective tissues, such as blood vessels and myofibroblasts, and account for less than 1% of all breast cancer cases [1].

Staging of Breast Cancer

Breast cancer staging, usually evaluated using the TNM system (Tumor = tumor size, Node = lymph node involvement, Metastasis = metastasis), is essential for assessing the extent of cancer spread. Accurate staging is critical not only for prognosis but also for guiding treatment decisions, as the stage at diagnosis is a strong predictor of patient outcomes [19].

Molecular Classification of Breast Cancer

Understanding breast cancer at the molecular level has revolutionized its classification, leading to more personalized treatment approaches. This classification is based on the expression of specific genes and proteins in breast cancer cells (estrogen receptors - ER, progesterone

receptors - PR, and human epidermal growth factor receptor 2 - HER2), which categorizes breast cancer into five molecular subtypes.

1.7. Breast Cancer Screening

Screening is a method of secondary prevention aimed at detecting breast cancer cases before symptoms appear. The main goal is the early identification of the disease, which can improve the chances of effective treatment and survival [20]. According to the World Health Organization, improving breast cancer outcomes and survival through early detection remains the cornerstone of breast cancer control.

One of the most important advances in breast cancer treatment is the early detection of non-palpable masses. Mammography is the only imaging modality proven to reduce mortality caused by breast cancer. In the 1960s, the first randomized controlled studies comparing periodic mammography screening versus clinical examination showed a reduction in mortality by about one-third in the experimental group [21].

Benefits of Mammography

Studies have shown that screening mammography can reduce mortality by up to 30% among women aged 50 to 69 years [22]. Smaller tumors and early-stage disease detected through mammography have improved prognosis and offered more treatment options.

Limitations of Mammography

Mammography may have limitations, including overdiagnosis, false-positive results, and false negatives.

Overdiagnosis is the detection of cancer during screening that otherwise would not have been clinically evident during a woman's lifetime. Well-designed studies provide a general estimate of breast cancer overdiagnosis of 10% or less. These estimates apply to all women over 40 years of age but are increased by older women who have concurrent comorbidities and shorter life expectancies [23].

Breast Cancer Screening in High-Risk Populations

Mammography is the only imaging modality proven to reduce mortality caused by breast cancer. For high-risk women, magnetic resonance imaging (MRI) can be used alongside mammography as a screening test [24].
High-risk women include those with a known BRCA1 or BRCA2 mutation and their first-degree relatives, women with a lifetime risk of 20-25% or higher for breast cancer, and women with a history of chest radiation between the ages of 10 and 30 [25]. Between 9,000 and 18,000 new breast cancer diagnoses annually in the United States are associated with a genetic predisposition, with more than 60% due to a BRCA1 or BRCA2 mutation [24].

1.8. Breast Cancer Diagnosis

Breast cancer diagnosis is suggested by clinical examination, supported by paraclinical and laboratory tests, and confirmed by histopathological examination.

Anamnesis

To assess the risk of breast cancer, the anamnesis must identify the presence of specific risk factors, such as: patient-related factors (age, family history of breast cancer, personal physiological history such as early menarche, late menopause, first childbirth at an advanced age, spontaneous or therapeutic abortion in the first trimester of pregnancy, nulliparity, and personal disease history) and exogenous risk factors (prolonged use of high-dose estrogen, prolonged exposure to ionizing, electromagnetic, or solar radiation at a young age, and a diet high in fats and sugars). It is important to note that approximately half of women diagnosed with breast cancer do not present with known risk factors [3].

Clinical Examination

The physical examination should include a thorough visual inspection with the patient undressed to the waist. The inspection is performed both in a vertical and horizontal position, with arms either extended by the sides or resting on the hips, or behind the neck or above the head.

Imaging Diagnostic Methods

Although mammography is one of the oldest medical imaging techniques, it remains one of the most valuable and widely used methods for diagnosing breast conditions [26]. It is based on the differences in X-ray absorption between tumor tissues, whether benign or malignant, and normal tissues, such as glandular and fatty tissues, allowing for images with excellent natural contrast, facilitating the identification of abnormalities [3].
Breast ultrasound, after mammography, is the most useful imaging investigation for diagnosing breast conditions, based on the differential absorption of ultrasound depending on the characteristics of the tissues. Frequencies used, between 7 and 12 MHz, ensure optimal resolution and good tissue penetration. Among the advantages of ultrasound are its non-invasive, painless nature, ability to differentiate solid structures from liquid ones, and real-time imaging that can guide procedures such as aspiration, making it suitable for young women where high breast density may limit mammography's accuracy. One major benefit of breast ultrasound is the ability to adjust the patient's position and examination angle in real-time, optimizing the detection of abnormalities. Furthermore, ultrasound allows simultaneous physical examination, which facilitates correlation with previous mammographic and ultrasound results. Images are selected based on suspicious areas, and normal tissue images are not routinely documented [3], [27].

Elastography – Elastography measures the elasticity or stiffness of tissues using either elastography waves or vibration technique to create an image based on this stiffness variability [28]. It is based on the principle that harder tissues, often associated with malignant lesions, will resist deformation more compared to softer tissues [29].

Computed Tomography of the Mammary Gland - The indication for computed tomography in breast cancer is determining the extent of chest wall involvement in large tumors. The resolution of tomographic images is inferior to that obtained through mammography and does not provide additional precision in routine examination [3].

Magnetic Resonance Imaging (MRI) - Breast MRI has become an indispensable tool in diagnosing and managing breast cancer, being used in specific cases. The main indications for using breast MRI include: evaluating patients with breast augmentations, such as silicone or saline implants and silicone injections, which may limit mammography's visibility;

determining the extent of the disease, including identifying invasion into major pectoral muscles, serratus anterior, and intercostal muscles; clarifying inconclusive results from clinical examination, mammography, or ultrasound; screening the contralateral breast in patients with newly diagnosed breast carcinoma and asymptomatic patients at very high risk for breast cancer, in combination with routine mammography; evaluating the response to neoadjuvant chemotherapy through imaging before, during, and after treatment; and identifying residual disease in patients with positive margins after lumpectomy [3], [30].

Ductoscopy, Xerography, and Breast Scintigraphy are less commonly used methods in breast cancer diagnosis [3].

Definitive Diagnosis in Breast Cancer - Histopathological diagnosis of breast cancer is essential for confirming the presence and characteristics of the tumor, being the only method to establish a definitive diagnosis. Methods for collecting biopsy material are varied and include: imprint or scraping (for ulcerated breast tumors, with the role of obtaining cells from the surface of the lesion for cytological analysis), fine needle aspiration (FNAC – involves aspirating cells from the tumor for cytological examination; used when immediate surgery is not recommended), cytological examination of nipple discharge, and biopsy puncture (allows obtaining larger tissue fragments for histopathological diagnosis) [31]–[33].

1.9. Breast Cancer Treatment

Breast cancer treatments include surgery, chemotherapy, radiotherapy, endocrine therapy, targeted therapy, and immunotherapy, requiring close collaboration between various medical subspecialties. In cases of non-metastatic breast cancer, surgery is considered the standard treatment, and preoperative chemotherapy can reduce tumor size, facilitating breast conservation and reducing the need for axillary lymph node dissection [34]. For metastatic breast cancer, systemic therapy remains the primary option, while surgery is reserved for selected cases requiring palliative care [35]. Additionally, advances in endocrine therapy, targeted therapies, and immunotherapy offer valuable options for both metastatic and non-metastatic cancer patients. Moreover, innovative therapies such as gene therapy, vaccines, and adoptive cell therapies are under investigation, with promising results [36].

Cost of Treatment vs. Breast Cancer Screening

The costs of breast cancer treatment can vary greatly depending on the stage of the cancer, the type of treatment required, the duration of treatment, and the healthcare system of the country. The cost of breast cancer treatment can represent a significant financial burden for patients and their families. Treatment expenses may include hospitalization, medications, medical consultations, supportive care, and rehabilitation. Patients without health insurance or adequate financial resources may face severe challenges in accessing essential treatments, leading to delayed or inadequate care and potentially worse outcomes.

1.10. Breast Cancer Prognosis Based on the Stage at Diagnosis. Importance of Early Detection and Assessing Breast Cancer Risk.

A crucial aspect of the breast cancer journey is the prognosis, which provides insights into the probable course of the disease and anticipated outcomes for the patient. Understanding the prognosis of breast cancer empowers patients and healthcare professionals to make informed decisions about treatment and supportive care.

Importance of Early Detection

Early detection of breast cancer is essential for improving prognosis and increasing survival rates. Regular breast self-examinations, clinical breast exams, and mammograms play a crucial role in identifying breast cancer at an early stage when it is most treatable. Early detection allows for less aggressive and more successful treatment options, leading to an improved quality of life and higher chances of survival. For women diagnosed at an early or localized stage, the cumulative probability of surviving cancer at least five years after diagnosis is on average 96% in the EU. However, survival for women diagnosed at an advanced stage remains low (38%) [37].

Chapter 2. Breast Cancer Screening in Romania

Breast cancer represents a major public health issue in Romania, being the most frequently diagnosed cancer and the leading cause of cancer-related death among women in Romania [38]. Romania shows a rising incidence of breast cancer, accompanied by an increase in mortality, which differs from countries that have organized breast cancer screening programs, where incidence is rising but mortality has been decreasing in the last five years. This difference is attributed to the early detection of the disease in less advanced stages, unlike Romania, where a large percentage of cases are diagnosed at advanced stages [3].

Although there is consistent evidence that organized population-based breast cancer screening is an effective method for detecting this type of cancer in its early stages and thus increasing survival rates, such screening has not yet been introduced in Romania. Instead, there has been opportunistic screening (mammographic examination - more accessible to women in urban areas) and a regional feasibility study involving a population of 5,000 women aged 50-69. Starting in 2014, the introduction of organized population-based screening procedures, including for breast cancer, was explicitly mentioned in the National Health Strategy, followed by actions to access non-reimbursable funding for the development of methodologies, an integrated screening IT platform, and the implementation of a multi-regional pilot for organized population-based breast cancer screening. The final goal of these efforts is to establish a National Breast Cancer Screening Program [39].

In 2020, while the European average screening participation rate was 60%, Romania had the lowest rate among all participating countries, with only 9% of eligible women undergoing screening. Countries with participation rates above the EU average included Sweden (95%), Denmark (83%), Finland (80%), and Portugal (80%) [37]. However, it is important to note that Romania currently lacks a well-organized data collection system, as there is no national screening program or data integration centers.

II. PERSONAL CONTRIBUTIONS

Chapter 3: Hypotheses and General Objectives

Hypotheses:

1. Participation in mammography screening programs is influenced by socio-demographic factors such as age, education level, and place of residence.
2. Accurate information and the accessibility of medical services contribute to increasing the participation rate in mammographic screening.
3. The main reasons why women do not attend screening include fear of diagnosis, lack of adequate information, and difficulty accessing medical services.
4. Many women believe that it is necessary to undergo investigations only in the presence of symptoms.

Study Objectives:

1. Our study aims to reflect how women in Romania perceive and access breast cancer screening.
2. Evaluation of the participation rate of women in opportunistic mammography screening between 2019-2021 at the "Alessandrescu-Rusescu" National Institute for Mother and Child Health.
3. Identification of factors influencing women's decision to participate in screening, including both motivating and inhibiting factors.
4. Evaluation of the impact of quality of life on the decision to participate in screening, using WHOQOL-Bref scores.
5. Investigating associations between other demographic characteristics and preventive behavior for detecting breast cancer.
6. Investigating predictors of women's self-preventive behavior based on their annual visits to the gynecologist.
7. Proposing measures to improve participation rates in screening, based on data analysis and identifying the specific needs of the target population.

8. Contributing to the development of a more efficient and accessible screening program that meets the needs of women and ensures the early detection of breast cancer.

Importance of the Study:

Our study aims to explore the perception and access of Romanian women to breast cancer screening. By identifying barriers and motivators, we can propose practical solutions to improve participation rates, and implicitly, reduce the incidence and mortality associated with breast cancer. Additionally, the results will contribute to optimizing public health policies and guide future interventions aimed at increasing the accessibility and efficiency of screening programs. Furthermore, these results can serve to inform patients, offering them a better understanding of general perceptions and the importance of early detection.

Chapter 4: General Research Methodology

This research was structured into two complementary studies, each with its own specific methods and objectives, but together contributing to a deep understanding of Romanian women's participation in breast cancer screening and the factors that influence this behavior.

Study I: Retrospective Observational Study on Participation in Mammography
The first study was retrospective in nature, analyzing the clinical data of a sample of 1,704 patients who underwent mammography at the "Alessandrescu-Rusescu" National Institute for Mother and Child Health between 2019 and 2021.

Study II: Barriers to Regular Breast Cancer Screening in Romanian Women
The second study was prospective, focusing on identifying the barriers and motivational factors that influence women's participation in regular breast cancer screening. From the population of 1,704 patients included in the main study, a subgroup of 100 women was selected to

complete two essential questionnaires aimed at gaining a deeper understanding of the barriers to screening participation.

Integration of the Studies and General Contribution

The methodology used in these two complementary studies allowed for the collection of comprehensive data on Romanian women's participation in breast cancer screening. Study I provided a solid foundation of clinical and demographic data, while Study II deepened the understanding of socio-economic barriers and the impact of quality of life on adherence to screening. Together, these studies offer an integrated and well-grounded perspective on how various factors influence behaviors related to breast cancer prevention, contributing to the formulation of practical recommendations for improving access to and participation in screening programs.

Chapter 5. Study I – Retrospective Observational Study on Participation in Mammography: Analysis of Clinical Data at the National Institute for Mother and Child Health 2019-2021

5.1. Introduction (Hypotheses and Specific Objectives)

Hypotheses and Objectives

- **Hypothesis 1**: Participation in mammographic breast cancer screening is influenced by socio-demographic factors such as age, education level, residence, and family history of cancer.
- **Hypothesis 2**: Women with a family member diagnosed with breast cancer before the age of 50 are more likely to participate in screening, being more informed and aware of the risks.

- **Hypothesis 3**: Opportunistic screening, as opposed to organized screening, attracts a specific patient profile, often with pre-existing symptoms or better awareness of the importance of early diagnosis.
- **Hypothesis 4**: Breast symptoms are a major determinant in women's decision to undergo mammography, particularly among younger women who may not realize the importance of screening in the absence of symptoms.

Study Objectives:

1. Evaluate the participation rate in mammography screening among women in the studied sample.
2. Identify socio-demographic and clinical factors influencing participation in screening.
3. Analyze breast biopsies and their correlation with the presence of symptoms and the obtained results (benign/malignant).
4. Propose practical measures to increase participation rates in breast cancer screening programs.

Inclusion and Exclusion Criteria:

- **Inclusion Criteria**: Women who underwent mammography at the National Institute for Mother and Child Health "Alessandrescu-Rusescu" between 2019-2021, either for screening or due to symptoms.
- **Exclusion Criteria**: Patients with incomplete or inconsistent data, i.e., those who did not complete the required forms or whose medical records lack essential information for analysis (such as age, family history, or mammogram results).

5.2. Materials and Methods

The study included a sample of 1,704 patients who underwent mammography at the "Alessandrescu-Rusescu" National Institute for Mother and Child Health over a 3-year period, from 2019 to 2021.

Statistical analysis was performed using IBM SPSS Statistics 25, and results were illustrated using Microsoft Office Excel/Word 2021. Quantitative variables were tested for distribution using the Shapiro-Wilk test and expressed as means with standard deviations or medians with interpercentile ranges. Independent quantitative variables with non-parametric distribution were tested between groups using the Mann-Whitney U test. Qualitative variables were expressed in absolute or percentage form, and differences between groups were tested using Fisher's Exact Test or Pearson's Chi-Square Test. Z-tests with Bonferroni correction were used to detail the results obtained in contingency tables.

5.3. Results

There were 1,704 patients who presented for mammograms. Personal data were recorded for 99.8% of them (1,701 patients). The mean age was 50.97 ± 8.91 years, with a median of 50 years. The minimum age was 21 years, and the maximum age was 85 years.

The comparison of the patients' ages who underwent mammograms in relation to the presence of symptoms at presentation showed that the age distribution between groups was non-parametric according to the Shapiro-Wilk test ($p<0.05$). The differences between groups were statistically significant according to the Mann-Whitney U test ($p<0.001$), showing that patients with symptoms had a significantly lower age (median = 49, IQR = 44-54.75) compared to patients without symptoms (median = 50, IQR = 45-56).

For 1,702 patients, the place of residence was known. The data showed that the majority of patients came from Bucharest (43.5%), Argeș County (12.8%), Prahova County (6.6%), Ilfov County (6%), and Dâmbovița County (5.5%).

The distribution of patients who underwent mammograms and had a family history of cancer in relation to the age of diagnosis of family members: for 222 patients (86.71%), the ages at diagnosis were known. Among these, the majority (59%) had a family member diagnosed with breast/ovarian cancer at age 50 or older.

The distribution of patients who underwent mammograms in relation to past investigations and age: the differences between groups were statistically significant according to Fisher's test

(p=0.031), with patients aged 50 years or older being significantly more associated with having undergone past medical investigations (52.3% vs. 46.6%).

The distribution of patients who underwent mammograms with hereditary cancer history in relation to the age of family members at diagnosis and the existence of past investigations: the differences between groups were statistically significant according to Fisher's test (p=0.016), showing that patients who had undergone past medical investigations had significantly more frequently family members diagnosed with cancer under the age of 50 (31.9% vs. 17.6%).

5.5. Conclusions

- **15% of the patients** reported a family history of cancer, with the majority being associated with breast or ovarian cancer. Women with a family history of early diagnosis were more aware of the risks and more proactive in monitoring their health.
- **Women under the age of 40** more frequently had a history of biopsies, suggesting that a strong family history and the presence of symptoms lead to more invasive investigations in this age group.
- **Ultrasound** is perceived as more comfortable and less invasive than mammography, which explains why it is preferred, especially among younger women.
- The majority of patients came from **Bucharest and neighboring counties**, reflecting the recognition of the quality and expertise of the referral center in the capital, but also highlighting possible deficiencies in access to screening services in other counties.
- There was **no significant correlation** between hyperestrogenic status and the presence of symptoms at the time of presenting for a mammogram, highlighting that hyperestrogenic status does not significantly influence the appearance of breast symptoms.
- **Regular monitoring** of women with risk factors, even in the absence of symptoms, remains essential for the early detection of breast lesions.

Chapter 6. Study II – Barriers to Regular Breast Cancer Screening in Women in Romania: A Prospective Study on Socio-Economic Determinants and Quality of Life

6.1. Introduction (Hypotheses and Specific Objectives)

Hypothesis 1: Women from rural areas have a lower participation rate in breast cancer screening compared to those from urban areas due to limited access to healthcare services and a generally lower quality of life.

Hypothesis 2: The level of education significantly influences the likelihood of undergoing regular mammograms; women with higher education levels have greater adherence to screening programs.

Hypothesis 3: Regular participation in gynecological visits is an important predictor of adherence to breast cancer screening programs.

Inclusion Criteria: Participants who fully completed both questionnaires (socio-demographic and WHOQOL-Bref).

Exclusion Criteria: Participants who did not fully complete the questionnaires. Women with cognitive or physical limitations that would prevent them from properly completing the questionnaires.

Primary objectives of the study were:

1. Validation of the use of the WHOQOL-Bref quality of life questionnaire with these patients and investigating the existence of an association between self-preventive behavior (regular mammography) for the early detection of breast cancer and women's quality of life, measured using the WHOQOL-Bref questionnaire.
2. Identification of socio-economic and demographic factors that influence adherence to breast cancer screening among women in Romania; evaluation of the impact of quality of life on the decision to participate in screening, using WHOQOL-Bref scores.

Secondary objectives of the study were:

1. Investigating the existence of associations between other demographic characteristics and preventive behavior for breast cancer detection, and investigating the existence of predictors for women's self-preventive behavior, related to the annual visit to the gynecologist.
2. Analysis of specific reasons why women in Romania do not participate in regular breast cancer screening and identifying solutions to increase participation.

6.2. Materials and Methods

From a population of 1,704 patients included in our primary study, a subgroup of 100 women was selected who completed two essential questionnaires for a deeper understanding of the barriers to screening participation.

For statistical analysis, the software programs used were **JASP 0.18.3 R** © JASP Team (2024), **JASP (Version 0.18.3)**[Computer software], and **R version 4.4** Copyright (C) 2024 The R Foundation for Statistical Computing, R Core Team (2024). **R: A language and environment for statistical computing.** R Foundation for Statistical Computing, Vienna, Austria.

6.3. Results

The significance level αα of the study was set at 0.05, and p-values less than 0.05 were considered statistically significant.

Marginally non-significant, patients without a personal history (PH) of breast cancer had odds of not undergoing regular mammograms almost 2.5 times higher than those with a known history of breast cancer. Although an odds ratio (OR) could not be calculated, a strong association was observed between having an ultrasound and mammography: all patients who did not undergo breast ultrasounds also did not have regular mammograms (Table VI.17).

Patients who do not visit a gynecologist regularly (annually) had odds 4 times higher of not undergoing regular mammograms (Table VI.17; Figure 6.2). Patients from rural areas had lower scores than urban patients on the overall WHOQOL score, indicating a lower quality of life.

Descriptive Statistical Analysis: The mean and standard deviation (SD) were calculated for continuous variables, and absolute and relative frequencies for categorical variables:

- **Geographic Distribution:** 34% of patients were from rural areas, and 66% from urban areas.
- **Educational Level:** 43% of participants completed secondary education, 14% completed tertiary education, and 43% had higher education (Table VI.24).
- **Family and Personal History:** 16% reported a family history of breast cancer, 5% of ovarian cancer; 17% of patients had a personal history of breast cancer, 5% of ovarian cancer, and 4% reported other types of cancer.
- **Screening Practices:** 87% of patients had previously undergone breast ultrasound; 50% practiced regular breast self-exams, 38% did so occasionally, and 12% never practiced it.
- **Awareness and Adherence:** 93% of patients felt they were informed about the importance of breast screening, but only 35% regularly underwent mammograms; 64% were informed by a healthcare provider, with the rest receiving information from other sources.
- **Reasons for Not Regularly Undergoing Mammograms:** 42% of participants did not consider mammography important due to the lack of symptoms, 12% had difficulties accessing services, and the rest cited financial reasons, fear of pain or radiation, and lack of trust in the healthcare system.
- **Determinants for Undergoing Mammography:** The majority of patients (42%) indicated they would undergo regular mammograms if they had easy access, including receiving a written invitation; 27% mentioned cost-free access, 21% mentioned additional information, 12% sought a pain- or radiation-free method, and 8% desired greater trust in the healthcare system.

6.5. Conclusions

- **Rural-Urban Disparities:** Our study highlighted significant differences between women in rural and urban areas regarding access to breast cancer screening.
- **Determinants of Screening Adherence:** Patients with a personal history of breast cancer, those who undergo breast ultrasounds, or those who regularly attend gynecological consultations are more likely to have regular mammograms. Conversely, women without a prior diagnosis of breast cancer had 2.5 times higher odds of not undergoing regular mammograms, while those who do not regularly visit a gynecologist had 4 times higher odds of not participating in screening.
- **Importance of Risk Perception and Education:** Education and risk perception play an essential role in the decision to participate in screening. Informed women, especially those with higher education levels, showed greater adherence to screening programs. This underscores the need for effective, targeted awareness campaigns tailored to the education level of the target population.
- **Solutions to Improve Screening Access:** The results suggest that personalized invitations and written recommendations, combined with easier access to healthcare services, could significantly increase participation rates in breast cancer screening. Additionally, adequate information, especially in rural areas and among those with lower educational levels, is essential to ensure early detection and improve prognosis.
- **Recommendations for Health Policies:** Based on the results, it is recommended to develop public health policies aimed at reducing disparities between rural and urban areas and improving access to screening. These policies should include culturally and socially adapted interventions, as well as facilitating access to healthcare services through improved infrastructure and adequate financial resources.

Chapter 7: Conclusions and personal contributions

Conclusions

Our study has made a significant contribution to understanding the challenges and barriers encountered in implementing mammographic screening for breast cancer in Romania, both through the retrospective analysis of clinical data from the National Institute for Mother and Child Health and the investigation of socio-economic perspectives and the quality of life of women.

1. **Inequalities in Access to Mammographic Screening:** The studies conducted revealed significant disparities in participation in mammographic screening between women in rural and urban areas. Women from rural areas had less access to mammography, which was associated with a lower perceived quality of life and insufficient education about the importance of screening. This disparity highlights the need to improve medical infrastructure in rural areas and implement tailored educational programs to raise awareness and increase access to healthcare services.
2. **Demographic Profile and Screening Behavior:** The average age of women who participated in mammographic screening in our study was approximately 51 years, suggesting that most women in Romania become more aware of the need for breast screening at this age. However, the wide age range, from 21 to 85 years, reflects considerable diversity within the studied population and indicates that some women become concerned with breast health at much younger ages, possibly due to specific risk factors.
3. **The Importance of Education and Risk Perception:** Results showed that education level and perception of breast cancer risk are key determinants of screening adherence. Women with higher education levels and those informed about breast cancer risks demonstrated higher participation in screening programs. This underscores the need for well-structured public information campaigns aimed at improving knowledge levels, particularly among vulnerable groups.
4. **The Role of Symptoms in Presenting for Mammography:** Approximately 41.9% of the women who underwent mammograms reported symptoms, highlighting that the presence of symptoms is a major determining factor in the decision to seek

investigations. This indicates a tendency to delay screening until symptoms appear, which can delay early diagnosis and reduce the chances of successful treatment.

5. **Lack of an Organized National Screening Program:** Romania currently lacks an organized national screening program for breast cancer, contributing to inequalities in access to early diagnosis. Opportunistic screening, while available, fails to effectively cover the target population, leading to late-stage disease diagnoses. It is imperative to develop a national screening program that ensures equal access to healthcare services for all women, regardless of residence or socio-economic status.
6. **The Importance of Social Support and Health Perception:** Assessing quality of life using the WHOQOL-Bref questionnaire revealed that social support and health perception are important factors in the decision to participate in screening. Women who benefit from adequate social support and perceive themselves to be in good health are more likely to participate in screening, while the lack of such support can be a significant barrier.
7. **Validation of the WHOQOL-Bref Questionnaire in the Context of Breast Cancer:** Our research also validated the use of the WHOQOL-Bref questionnaire in evaluating the quality of life of women in the context of breast cancer screening. This tool proved useful in correlating socio-economic status and quality of life with health-related behaviors, offering a new perspective on how these variables influence screening participation. The validation of this questionnaire in our specific context enriches the research tools usable in the oncology field.

Personal Contributions

1. **Comprehensive Approach to the Issue of Mammographic Screening:** I approached the subject from a complex perspective, analyzing both clinical data from a retrospective study and socio-economic factors and quality of life through a prospective study. This holistic approach enabled a deeper understanding of the barriers and motivational factors for screening participation, addressing both medical and social-psychological aspects.
2. **Identification and Detailed Analysis of Socio-Economic Factors:** I contributed to identifying specific factors that influence adherence to mammographic screening, such as education level, place of residence, and social support. By correlating these factors

with the data obtained from the WHOQOL-Bref questionnaires, I highlighted how quality of life influences the health behaviors of women in Romania.

3. **Validation of the WHOQOL-Bref Questionnaire in the Context of Breast Cancer:** One of my significant personal contributions lies in validating the use of the WHOQOL-Bref questionnaire in the specific context of breast cancer screening. This tool was validated to assess the quality of life of women in relation to health decisions, providing a useful instrument for future research and interventions in this field.
4. **Proposal of Practical Measures and Health Policies:** Based on the obtained results, I formulated clear recommendations for improving access to mammographic screening, including the development of an organized national screening program, the creation of tailored public awareness campaigns, and facilitating access to healthcare services in rural areas. These recommendations have the potential to influence public health policies and contribute to reducing breast cancer mortality in Romania.
5. **Contribution to the Specialized Literature:** My research provides a significant contribution to the specialized literature by highlighting regional and socio-economic differences that influence the preventive behavior of women in Romania. This data is valuable for developing personalized interventions that improve mammographic screening participation and reduce inequalities in access to early diagnosis.
6. **Methodological Innovation:** I integrated the use of the WHOQOL-Bref questionnaire into a breast cancer screening context, representing an innovative approach to evaluating the impact of quality of life on health decisions. This methodological aspect can be replicated in future research to explore the relationship between quality of life and other preventive behaviors.

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Published Articles Based on the Studies Conducted in the Doctoral Thesis

1) Mihai AM, Ianculescu LM, Crețoiu D, Suciu N, Breast cancer screening in Romania: challenges and opportunities for early detection.. Acta Endocrinologica. Manuscript ID-4048-AEB-09-2024 (ORIGINAL PAPER) – (cap 5.4.; pg 96).

2) Mihai AM, Ianculescu LM, Cretoiu D, et al. In vitro fertilization impact on the risk of breast cancer. Arch Clin Cases. 2024; 11(3):73-82. doi: 10.22551/2024.44.1103.10292 – (cap 5.4.; pg 94).

2) Mihai AM, Ianculescu LM, Crețoiu D, Suciu N, Primary Breast Tuberculosis Mimicking Breast Cancer: An Original Study of Imaging Findings and Differential Diagnosis Challenges, Journal of Medicine and Life DOI 10.25122/jml-2024-0333 (ORIGINAL PAPER) – (cap 5.4.; pg 91).

3) Mihai AM, Ianculescu LM, Suciu N, MiRNAs as potential biomarkers in early breast cancer detection: a systematic review. Journal of Medicine and Life, doi: 10.25122/jml-2024-0322 – (cap 1.8.; pg. 33).