UNIVERSITAT DE BARCELONA

Prevalence of silent breast cancer in autopsy specimens: study of the diseases held by image-guided biopsies

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Doctoral Program of Biomedicine at the University of Barcelona

Memorandum submitted by:

Zacharoula Sidiropoulou

to qualify for the degree of PhD from the University of Barcelona

This work has been performed at the Hospital São Francisco Xavier, Lisbon, Portugal in conjunction with the Instituto National de Medicina Legal e Ciencias Forenses, Lisbon, Portugal.

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Per la present em complau donar el meu vist-i-plau a la presentació i defensa de la Tesis doctoral de la qual soc Co-director:

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Σα βγεις στον πηγαιμό για την Ιθάκη,
να εύχεσαι νάναι μακρύς ο δρόμος,
γεμάτος περιπέτειες, γεμάτος γνώσεις.
Τους Λαιστρυγόνας και τους Κύκλωπας,
τον θυμωμένο Ποσειδώνα μη φοβάσαι,
τέτοια στον δρόμο σου ποτέ σου δεν θα βρεις,
αν μέν' η σκέψις σου υψηλή, αν εκλεκτή
συγκίνησις το πνεύμα και το σώμα σου αγγίζει.
Τους Λαιστρυγόνας και τους Κύκλωπας,
τον άγριο Ποσειδώνα δεν θα συναντήσεις,
αν δεν τους κουβανείς μες στην ψυχή σου,
αν η ψυχή σου δεν τους στήνει εμπρός σου.

Να εύχεσαι νάναι μακρύς ο δρόμος.
Πολλά τα καλοκαιρινά πρωιά να είναι
που με τι ευχαρίστησι, με τι χαρά
θα μπαίνεις σε λιμένας πρωτοειδωμένους·
να σταματήσεις σ' εμπορεία Φοινικικά,
και τες καλές πραγμάτειες ν' αποκτήσεις,
σεντέφια και κοράλλια, κεχριμπάρια κ' έβενους,
και ηδονικά μυρωδικά κάθε λογής,
όσο μπορείς πιο άφθονα ηδονικά μυρωδικά·
σε πόλεις Αιγυπτιακές πολλές να πας,
να μάθεις και να μάθεις απ' τους σπουδασμένους.

Πάντα στον νου σου νάχεις την Ιθάκη.
Το φθάσιμον εκεί είν' ο προορισμός σου.
Αλλά μη βιάζεις το ταξείδι διόλου.
Καλλίτερα χρόνια πολλά να διαρκέσει·
και γέρος πια ν' αράξεις στο νησί,
πλούσιος με όσα κέρδισες στον δρόμο,
μη προσδοκώντας πλούτη να σε δώσει η Ιθάκη.

Η Ιθάκη σ' έδωσε τ' ωραίο ταξείδι.
Χωρίς αυτήν δεν θάβγαινες στον δρόμο.
Άλλα δεν έχει να σε δώσει πια.

Κι αν πτωχική την βρεις, η Ιθάκη δεν σε γέλασε.
Έτσι σοφός που έγινες, με τόση πείρα,
ήδη θα το κατάλαβες η Ιθάκες τι σημαίνουν.

Κωνσταντινος Καβαφης, Οκτώβριος του 1910

As you set out for Ithaka
hope your road is a long one,
full of adventure, full of discovery.
Laistrygonians, Cyclops,
angry Poseidon—don't be afraid of them:
you'll never find things like that on your way
as long as you keep your thoughts raised high,
as long as a rare excitement
stirs your spirit and your body.
Laistrygonians, Cyclops,
wild Poseidon—you won't encounter them
unless you bring them along inside your soul,
unless your soul sets them up in front of you.

Hope your road is a long one.
May there be many summer mornings when,
with what pleasure, what joy,
you enter harbors you're seeing for the first time;
may you stop at Phoenician trading stations
to buy fine things,
mother of pearl and coral, amber and ebony,
sensual perfume of every kind—
as many sensual perfumes as you can;
and may you visit many Egyptian cities
to learn and go on learning from their scholars.

Keep Ithaka always in your mind.
Arriving there is what you're destined for.
But don't hurry the journey at all.
Better if it lasts for years,
so you're old by the time you reach the island,
wealthy with all you've gained on the way,
not expecting Ithaka to make you rich.

Ithaka gave you the marvelous journey.
Without her you wouldn't have set out.
She has nothing left to give you now.

And if you find her poor, Ithaka won't have fooled you.
Wise as you will have become, so full of experience,
you'll have understood by then what these Ithakas mean.

C. P. Cavafy, "The City" from *C.P. Cavafy: Collected Poems.*
Translated by Edmund Keeley and Philip Sherrard.

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And what a journey, and how many people have “sailed” and accompanied me all these years of Ithaka´s quest…
Authorizations and more authorizations, conditioning, transportation, accommodation, collection, analysis and statistics.
To the technicians, medical doctors, residents, hospital auxiliary staff, legal medicine department residents, surgery residents, pathology “freaks”, cleaning staff that discharged specimens.
To my department’s chief and my hospital´s board of administration.
To my three pilots, Dr Gascón, Dr. Cardoso and Dr. Carbó
To my reviewers
To my family
To each one of all you individually and to all of us like a team, my sincere thank, this work is also yours.

The great tragedy of Science — the slaying of a beautiful hypothesis by an ugly fact”

Thomas Henry Huxley

BUT

“The good thing about science is that it's true whether or not you believe in it.”

Neil G Tyson

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Articles

The present Thesis is presented in the classic format and the pilot study has been published:

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List of Abbreviations

WHO (World Health Organization)

BRCA 1 and 2 (Breast cancer 1 and 2 gene)

BI-RADS (Breast Imaging-Reporting and Data System)

RAS (H or K Ras proteins)

MYC (Myelocytomatosis homolog oncogene)

ER (Estrogen receptor)

PR (Progesterone receptor)

AR (Androgen receptor)

HER2 (Human epidermal growth factor receptor)

TNBC (Triple negative breast cancer)

TNM (TNM Classification of Malignant Tumors)

AJCC (American Joint Committee on Cancer)

T (Size or direct extent of the primary tumor)

N (Degree of spread to regional lymph nodes)

M (Presence of distant metastasis)

OS (Overall survival)

G (Grade)

DEG (Differentially expressed genes)

bsMRM (Bilateral subcutaneous modified radical mastectomy)

MBC (Male breast cancer)

FBC (Female breast cancer)

RT (Radiotherapy)

Abstract

Breast cancer epidemiological patterns vary in European countries, presenting different incidence rates (49-148 new cases per 100,000 women) with a narrow but still variable range of mortality (15-36 new cases per 100,000 women). In Portugal, female breast cancer incidence is increasing while mortality is gradually decreasing, with 118.5 and 30.4 cases per 100,000 women, respectively. Regarding male breast cancer, a rare disease comprising ~1% of breast cancers, data are generally scant. The reduction in breast cancer mortality is not only due to the early detection of the disease but is, in almost equal parts, the result of both the advances in screening and molecular medicine and the development of new therapies. This study aimed to quantify the actual number of breast cancer present in both genders by determining the prevalence of silent breast cancer in corpses. We quantified the imaging-identified cancers that were not clinically manifested, with the thesis hypothesis that the natural reservoir of silent breast cancer is greater than the actual incidence of the disease, a hypothesis that was not confirmed.

Resum

Els patrons epidemiològics del càncer de mama varien als països europeus, presentant taxes d'incidència diferents (49-148 casos nous per cada 100.000 dones) amb un rang de mortalitat estret però variable (15-36 casos nous per cada 100.000 dones). A Portugal, la incidència de càncer de mama femení augmenta, mentre que la mortalitat disminueix gradualment, amb 118,5 i 30,4 casos per cada 100.000 dones, respectivament. Pel que fa al càncer de mama masculí, una malaltia rara que comprèn aproximadament l'1% dels càncers de mama, les dades solen ser escasses. Pel que fa al càncer de mama masculí, una malaltia rara que comprèn aproximadament l'1% dels càncers de mama, les dades solen ser escasses. La reducció de la mortalitat per càncer de mama no només es deu a la detecció precoç de la malaltia, sinó que és, en parts gairebé iguals, el resultat tant dels avenços en cribratge i medicina molecular com del desenvolupament de noves teràpies Aquest estudi tenia com a objectiu quantificar el nombre real de càncer de mama present en ambdós gèneres determinant la prevalença del càncer de mama silenciós en cadàvers. Es van quantificar els càncers identificats per imatge que no es van manifestar clínicament, amb la hipòtesi de la tesi que el dipòsit natural de càncer de mama silenciós és superior a la incidència real de la malaltia, hipòtesi que no es va confirmar.

1 Introduction

1.1 Cancer

Cancer, (in Greek **Καρκίνος**), is a word of Pre-Greek origin (a hypothetical language conjectured to have been spoken in prehistoric Greece before the arrival of Proto-Greek speakers, and used to explain the large number of non-Indo-European words found in Ancient Greek), used by the Greek physician Hippocrates 400 BCE to refer to the shell-like surface, leglike filaments, and sharp pain often associated with tumors. It refers to more than 100 distinct diseases characterized by the uncontrolled growth of abnormal cells in the body.

Though cancer has been known since antiquity, some of the most significant advances in scientists' understanding of it have been made since the middle of the 20th century. Those advances led to major improvements in cancer treatment, mainly through the development of methods for timely and accurate diagnosis, selective surgery, radiation therapy, chemotherapeutic drugs, and targeted therapies (agents designed against specific molecules involved in cancer).

Advances in treatment have succeeded in bringing about a decrease in cancer deaths, though mainly in developed countries. Indeed, cancer remains a major cause of sickness and death throughout the world. By 2012 the number of new cases diagnosed annually had risen to more than 14 million, more than half of them belonged to less-developed countries, and by 2015 the number of deaths from cancer had reached 8.8 million worldwide. About 70 percent of cancer deaths were in low- and middle-income countries.

The World Health Organization (WHO) has estimated that the global cancer burden could be reduced by 30 to 50 percent through prevention strategies, particularly by avoiding known risk factors. Besides, laboratory investigations aimed at understanding the causes and mechanisms of cancer have maintained optimism that the disease can be controlled. Through breakthroughs in cell biology, genetics, and biotechnology, researchers have gained a fundamental understanding of what occurs within cells to cause them to become cancerous. The conceptual gains are steadily being converted into actual gains in the practice of cancer diagnosis and treatment, with notable progress toward personalized cancer medicine, in which therapy is tailored to individuals according to biological anomalies unique to their disease. Personalized cancer medicine is considered the most promising area of progress yet for modern cancer therapy.

Cancer or malignant tumors or malignant neoplasms (from Greek **νεο-**, "new," and **πλάσμα,** "formation"), are abnormal growths of cells arising from malfunctions in the regulatory mechanisms that oversee the cells' growth and development (Costa, s.d.). Thus, cancer can be described as an abnormal and uncontrolled proliferation of cells. The cancerous cells often spread into the surrounding tissue or metastasize to distant organs through the blood or the lymphatic system (Rusciano, 1992) (Fidler, 1989). As shown in figure 1, the first step of the cancer formation is the accumulation of genetic mutations, referred to as the "Initiation" phase. "Initiators," which cause or promote genetic mutations, include hormones, chemicals, radiations, infections, and hypoxia (Weinberg, 1988) (Nelson, 2004). Genetic mutations can take place in pro-oncogenic genes such as *R.A.S.* (Downward, 2003) and *M.Y.C.* (Finver, 1988) or tumor suppressor genes such as *BRCA1*, *BRCA2,* and *TP53* (Friedenson, 2007) (Baker, 1990). Generally, cancer development requires the accumulation of multiple genetic aberrations (Devilee, 1994) (Bieche, 1995). Afterward, the mutated cells can stay in a dormant phase or become proliferative. The second step of cancer formation, the "Promotion" phase, includes hyperplasia (increase in the number of cells), dysplasia (phenotypic changes in cells), *in situ* carcinoma (early-stage cancer), and finally, invasive carcinoma (spread to the surrounding tissues) (Harvey Lodish, 2000).

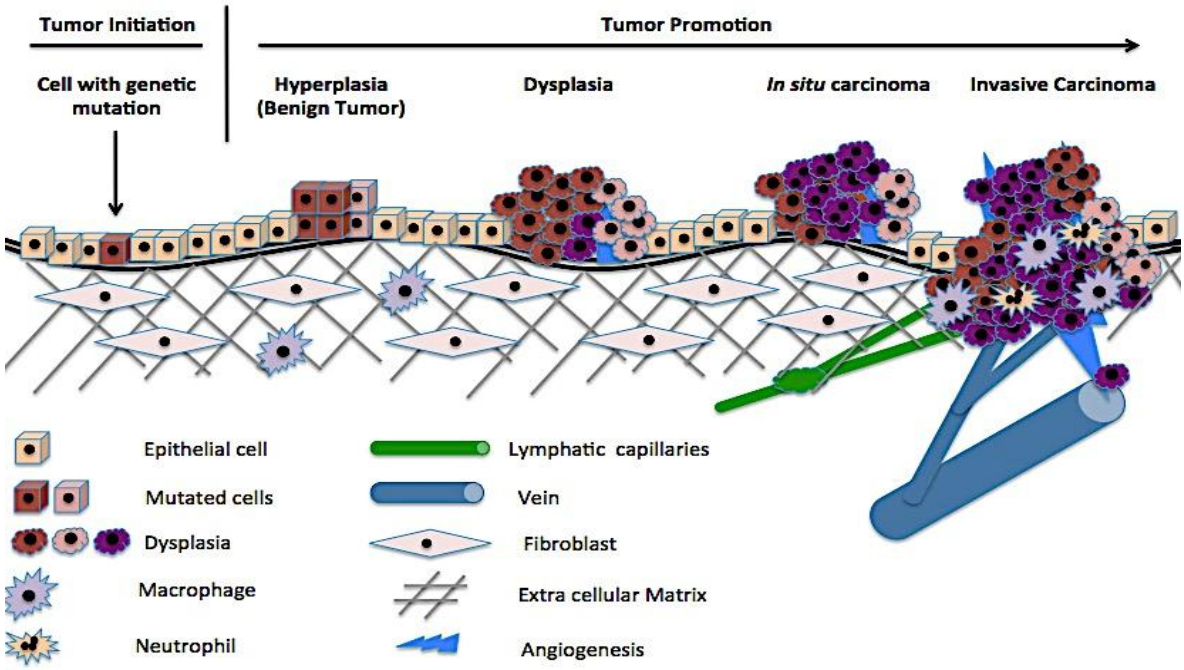


Figure 1. Stages of tumor development from normal cells to metastasis.

The development of cancer begins when a single mutated cell starts proliferating abnormally. Additional mutations followed by the selection of more rapidly proliferating altered cells within the population lead to cancer progression and then invasion to the surrounding connective

tissues. The altered cells can spread to distant organs through blood and lymphatic vessels. To date, six hallmarks of cancer have been described by which cancer cells uphold abnormal growth and escape growth suppressor mechanisms (Hanahan, 2011). These include sustaining of proliferating signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis (Hanahan, 2011).

1.2 Breast cancer

1.2.1 Definition

Breast cancer is a malignant tumor arising from epithelial cells of glandular milk ducts or lobules of the breast (Benson, 2009). It is classified as either non-invasive (carcinoma *in situ*) or invasive, depending on whether the tumor has started to grow outside the basal membrane. Invasive carcinomas are cancers in which malignant cells diffuse to surrounding connective tissues and metastasize to the body's distant organs. Around two-thirds of breast carcinomas arise from epithelial cells of the ducts, called ductal carcinoma, and around one-third from lobules called lobular carcinoma (Malhotra, 2010). Other less common histological groups are identified as inflammatory, medullary, apocrine, mucinous, and tubular carcinomas, as shown in Figure 2 (Malhotra, 2010).

1.2.2 Epidemiology

Breast cancer is the most frequently diagnosed malignancy in women worldwide, with an estimated one and a half million new cases each year and approximately half a million deaths per year (Ferlay, 2015). The incidence rate of breast cancer is steadily increasing worldwide and varies almost four-fold across different regions. The prevalence of breast carcinoma varies from 27 per 100,000 in Middle Africa and Eastern Asia to 92 per 100,000 in North America (Ferlay, 2015). The dissimilarities in pervasiveness can be attributed to differences in age distribution, diet, lifestyle, ethnicity, genetic background, and other breast cancer risk factors among populations.

Male breast cancer accounts for less than one percent of all cancers in men and less than one percent of all breast cancers. However, the incidence of male breast cancer is rising and reaching 15% in some patient groups over the course of their lives (AJ., 2017 Aug).

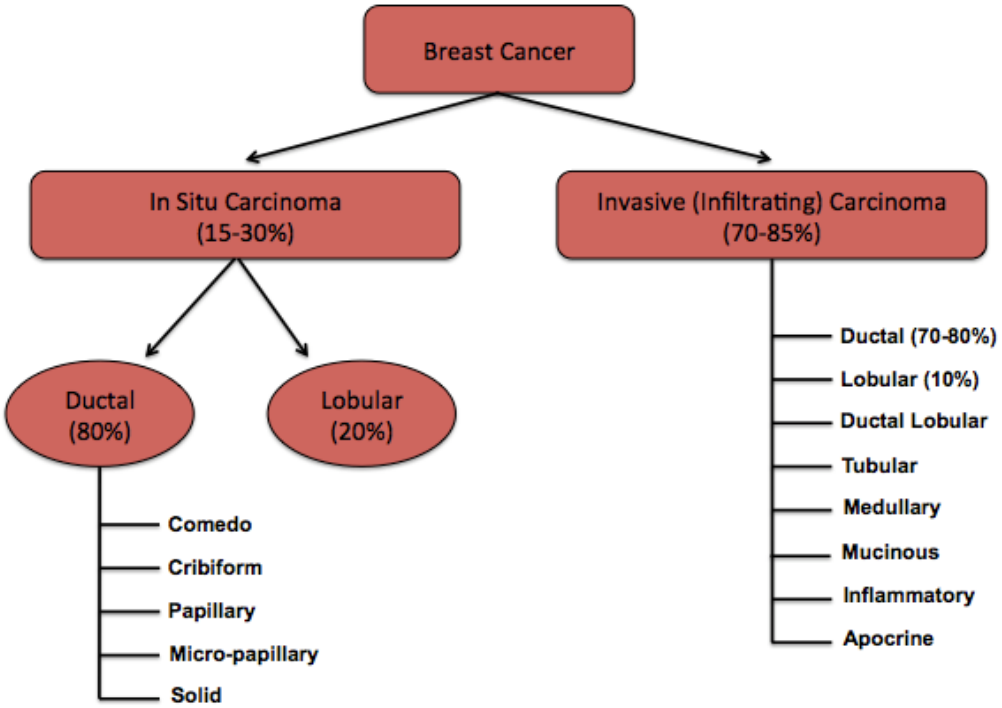


Figure 2. Histological stratification of breast cancer. The majority of breast carcinomas arise from ductal epithelial cells and tend to involve the surrounding connective tissues (invasive ductal carcinoma) and metastasize to the distant organs of the body.

1.2.3 Treatment

Traditionally, surgery is the first choice for patients with operable primary breast cancer (Matsen, 2013). Breast-conserving surgery is preferred, followed by local radiation treatment (Fisher, 2002). This treatment is curative for a large group of patients with breast cancer (Sacks, 1993). To eradicate potentially undetectable micro-metastases after surgery, patients often receive adjuvant therapy, including chemo, endocrine, and/or targeted therapies. Nevertheless, depending on the breast cancer subgroup, some patients may receive neoadjuvant therapy (Matsen, 2013). An additional advantage of this treatment is that it allows the study of the tumor response to the selected therapy.

During the past 30 years, breast cancer treatment has undertaken various approaches, yet the tendency is towards the less invasive but more efficient methods.

The St Gallen's Early Breast Cancer consensus statement in 2019: *"After "no tumor on ink" had finally been firmly established in 2017 as the standard for unifocal residual breast cancers and breast-conserving procedures, this year, a majority of the panel voted that such an approach may also be used for multifocal residual disease (provided that breast radiotherapy is planned) (yes 83%)"* (Harbeck, 2019), might had seemed "shocking" to the fathers of the radical mastectomy, Paré and Servetus, back in 1509 (Freeman, et al., 2018). Even though the first oncologic surgeons of the history, Λεωνιδας (Leonidas) (b. 200) and later Παῦλος

Αἰγινήτης (Paul of Aegina) (b. 625) and Lafranc of Milan (b. 1250) had already recommended tumor excision and cautery as a treatment for breast cancer.

At present, patients that traditionally were candidates only to palliative therapy (metastatic ones), may become *"A.B.C. patients with stable disease, being treated as a "chronic condition",* and *"should have the option to undergo breast reconstruction, if clinically appropriate"* (F. Cardoso, 2020). Thus, a collaborative effort among multiple subspecialties should be the standard of care for all breast cancer patients (Tracy-Ann Moo, 2018 Jul).

1.2.4 Biomarkers in breast cancer

The term "biomarker," a portmanteau of "biological marker," refers to a broad subcategory of medical signs, that is, objective indications of a medical state which can be measured accurately and reproducibly from outside the patient (Strimbu K, 2010,Nov). When used as outcomes in clinical trials, biomarkers are considered surrogate endpoints; they act as surrogates or substitutes for clinically meaningful endpoints. However, not all biomarkers are surrogate endpoints, nor are they all intended to be. Surrogate endpoints are a small subset of well-characterized biomarkers with well-evaluated clinical relevance (Group, 2001). To be considered a surrogate endpoint, there must be solid scientific evidence (e.g., epidemiological, therapeutic, and/or pathophysiological) that a biomarker consistently and accurately predicts a clinical outcome, either a benefit or harm. In this sense, a surrogate endpoint is a biomarker that can be trusted to serve as a stand-in for, but not as a replacement of, a clinical endpoint (Strimbu K, 2010,Nov).

A tumor biomarker is defined as a molecule produced by a tumor or in response to a tumor (Mishra, 2010) (Terms., s.d.). Biomarkers can be detected from any tissue in the body, including the breast. They may have prognostic, diagnostic and/or predictive values (Vivanco, 2010), and are defined by their specificity, that is, the proportion of control (normal) individuals who test negative for the biomarker, and sensitivity, that is, the proportion of individuals with the confirmed disease who test positive for the biomarker.

- **Diagnostic (screening) biomarker**
  Is defined as a marker used to detect and identify a given type of cancer in an individual. These markers are expected to have high specificity and sensitivity; for example, the presence of Bence – Jones protein in urine remains one of the strongest diagnostic indicators of multiple myeloma.

- **Prognostic biomarker**

  This type of marker is used once the disease status has been established. These biomarkers are expected to predict the probable course of the disease including its recurrence, and they therefore have an important influence on the aggressiveness of therapy. For example, in testicular teratoma, human chorionic gonadotropin and alfa-fetoprotein levels can discriminate two groups with different survival rates.
- **Stratification (predictive) biomarker**

  This type of marker serves to predict the response to a drug before treatment is started. This marker classifies individuals as likely responders or nonresponders to a particular treatment. These biomarkers mainly arise from array-type experiments that make it possible to predict clinical outcome from the molecular characteristics of a patient's tumor. (Sinobiological, 2020)

Prognostic biomarkers foretell the natural disease course regardless of treatment, while predictive biomarkers foresee the response of a patient to a specific treatment (Weigel, 2010). The expression levels of hormone receptors such as ERα and P.R. are good examples of weak prognostic but strong predictive biomarkers (Radhakrishna, 2015). In comparison, the overexpression of HER2 is a good example of both a strong prognostic and a strong predictive biomarker (Radhakrishna, 2015).

In addition to the established biomarkers, a large number of other biomarkers have already been proposed, most of which could not be validated and qualified practically for clinical use. Biomarkers must overcome many practical hurdles and pass five conceptual phases before they are applied in the clinics. These five steps include I) preclinical exploratory, II) clinical assay and validation, III) retrospective longitudinal, IV) prospective screening and V) cancer control (Ludwig, 2005).

1.2.5 Established classifications in breast cancer

To specify the precise prognosis and plan an effective therapy, breast cancer classification is of utmost importance. Therefore, in the following section, the most established classifications in breast cancer, including molecular subtypes of breast cancer, T.N.M. (Tumor, Node, Metastases) staging system, and grading, are described.

1.2.5.1 Molecular subtypes of breast cancer

Breast tumors can be classified into four distinct subtypes using four well-known biomarkers, including ERα, PR, HER2, and Ki-67 (Figure 3) (Sorlie, 2001). This molecular subtype classification is often a key reference for prognosis and choice of therapeutic strategy (Parker,

2009). Luminal A is the most common subtype that is ERα-positive, PR-positive, HER2-negative, has low expression of Ki-67, and offers promising outcomes with hormonal therapy (Cheang, 2009). Luminal B is similar to luminal A but has a high expression of Ki-67—a proliferation-ted gene and is more aggressive than luminal A (Cheang, 2009) (Heitz, 2009). Patients with luminal B subtype can benefit from hormonal therapy combined with treatment with anti-HER2 antibody Trastuzumab, depending on the expression of HER2 or not (Onitilo, 2009) (Yersal, 2014). Finally, basal-like breast cancer, similar to triple-negative breast cancer (T.N.B.C.), is a subtype with a poor prognosis due to the lack of specific drug targets (Heitz, 2009). Chemotherapy is the primary treatment for this subtype (Senkus, 2013).

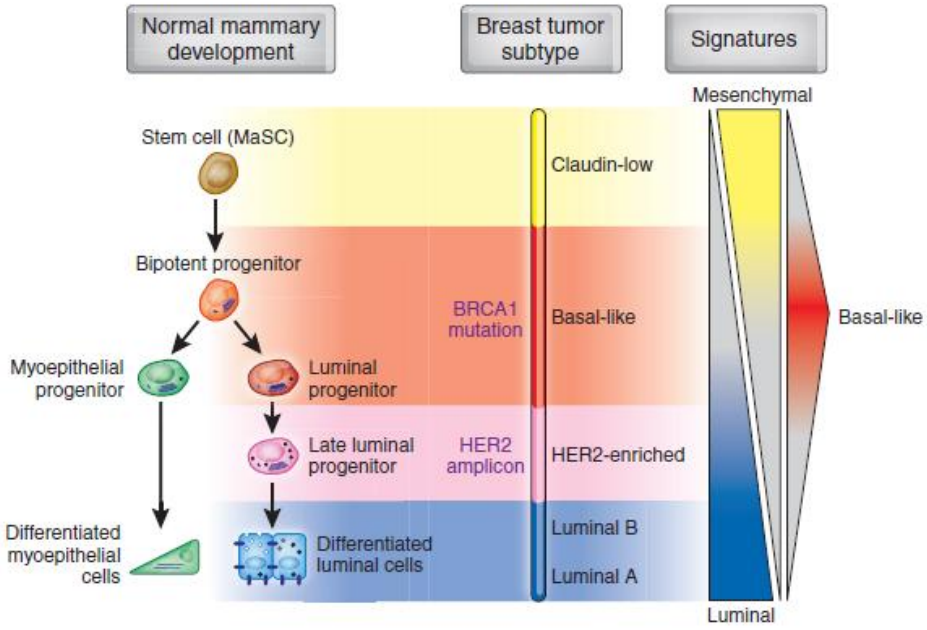


Figure 3. Model of the human mammary epithelial hierarchy linked to cancer subtype (Perou, august 2009)

Since the earliest models of 2006, an effort has been made to define molecular breast cancer subtyping in a precise way; however, no clear classification exists yet. For instance, a new molecular subgroup, the Claudin-low carcinomas, merged in the triple-negative breast cancer subtype in 2010 (Prat, 2010).

In conclusion, since 1991 and the beginning of histologic classification, passing through molecular classification, microarray-based gene expression signatures, molecular surrogates, risk prediction tests, we stand since 2012 in the gene mutational profiling and the genomic landscape of the breast cancer era (Pereira B, 2016). Yet to this day, ER, PR, and HER2 status are the major clinical decision-making role players. Together with histologic grade/mitotic count, these three biomarkers can be used to define luminal, HER2, and T.N.

subtypes. It is not clear whether there is any need to proceed to further classifications, given the state of the art of the systemic therapy we can provide (Schmitt, 2016).

1.2.5.2 TNM staging system

The T.N.M. staging system declared by the American Joint Committee on Cancer (A.J.C.C.) is based on anatomical properties of the tumor (Edge, 2010). T.N.M. classification uses a combination of tumor size (T), lymph node involvement (N), and presence or absence of metasstasis (M) (Sobin, 2003). This classification system provides a basis for survival prediction (prognosis), choice of initial therapeutic approaches, and evaluation of therapeutic results (Sobin, 2003).

The last T.N.M. classification, as described in Figure 4, has been published in 2017 (Hortobagyi GN, 2017).

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)	Ductal carcinoma in situ
Tis (Paget)	Paget disease not associated with invasive carcinoma or DCIS
T1	Tumor size ≤ 20 mm
T1mi	Tumor size ≤ 1 mm
T1a	Tumor size > 1 mm but ≤ 5 mm
T1b	Tumor size > 5 mm but ≤ 10 mm
T1c	Tumor size > 10 mm but ≤ 20 mm
T2	Tumor size > 20 mm but ≤ 50 mm
T3	Tumor size > 50 mm
T4	Tumor with direct extension to the chest wall and/or the skin with macroscopic changes
T4a	Tumor with chest wall invasion
T4b	Tumor with macroscopic skin changes including ulceration and/or satellite skin nodules and/or edema
T4c	Tumor with criteria of both T4a and T4b
T4d	Inflammatory carcinoma

Figure 4. T.N.M. classification for breast cancer staging, 2017

The details relating to the last version of National Comprehensive Cancer Network (N.C.C.N.; version 6/2020) guidelines are presented in Figure 5 and 6.

TNM	Grade	HER2	ER	PR	Stage
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	
				Negative	IB
	G2	Positive	Positive	Positive	IA
				Negative	
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	
				Negative	IB
	G3	Positive	Positive	Positive	IA
				Negative	
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	IB
				Negative	

TNM	Grade	HER2	ER	PR	Stage
T0 N1** M0 T1* N1** M0 T2 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	IIB
	G3	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IIB
				Negative	
			Negative	Positive	
				Negative	

Conti

Figure 5. N.C.C.N. staging guidlines for breast cancer, version 6/2020

TNM	Grade	HER2	ER	PR	Stage
T1 N0 M0 T2 N0 M0	Any	Negative	Positive	Any	IA

Figure 6. N.C.C.N. staging guidlines for breast cancer (when oncotype DX score is less than 11), version 6/2020

The inclusion of molecular subtyping and consensual biological markers (tumor grade, ER, PR, and HER2 status) were additional independent predictors for survival compared to the 7th A.J.C.C. staging system. When adjusted for grade, E.R., PR, and HER2 status in the 7th A.J.C.C. staging system, stage I.I.I.C. patients (adjusted HR=18.54, 95% CI=16.62–20.69, P<0.001) had superior (and not inferior) prognosis to stage I.I.I.B. patients (adjusted H.R. =20.09, 95% CI=17.90–22.55, P<0.001) for breast cancer-specific survival (B.C.S.S.). For overall survival (O.S.), the estimates were similar. Results demonstrated that the prognostic accuracy of the 8th A.J.C.C. prognostic staging system utilizing tumor grade, E.R., PR, and HER2 status as biologic staging factors could be considered superior to the 7th staging system (Figure 7).

8th AJCC prognostic staging system	7th AJCC staging system													
	IA		IB		IIA		IIB		IIIA		IIIB		IIIC	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
IA	66,171	39.4	3,386	2.0										
IB	12,972	7.7	809	0.5	22,902	13.6	2,303	1.4	504	0.3				
IIA	9,842	5.9	372	0.2	6,776	4.0			954	0.6				
IIB					4,524	2.7	90	0.1	4,785	2.8				
IIIA					8,922	5.3	2,721	1.6	449	0.3	192	0.1	272	0.2
IIIB							1,459	0.9	3,784	2.3	1,173	0.7	1,819	1.1
IIIC							2,989	1.8	2,421	1.4	2,371	1.4	3,114	1.9

Figure 7. 7th and 8th A.J.C.C. editions of prognostic staging systems for breast cancer (Shao N, 2019).

1.2.5.3 Tumor grade

Tumor grade classifies tumor tissues based on the abnormality of the tumor cells microscopically (Elston, 1991). It is used as a prognostic indicator of how quickly a tumor will grow and spread (Elston, 1991). Tumor grade represents the potential aggressiveness of a tumor, taking into consideration the glandular/tubular formation, nuclear pleomorphism (variability in the size and shape of nuclei and nucleoli), and mitotic (cell division) count (Elston, 1984). It classifies the tumor into three different grades, G1, G2, and G3. G1 represents low grade and well-differentiated, G2 represents moderately differentiated, and G3 indicates high grade and poorly differentiated tumor (Elston, 1984). In recent works, efforts have been concentrated on studying the grade-specific expression profiles of genes in breast cancer and finding the differentially expressed genes (D.E.G.s), which are also highly connected in the interaction network. According to Jayanthi et al., these hub genes are supposed to be significant in breast cancer progression and can be potential targets for breast cancer diagnosis and prognosis. The expression of UBE2C and CCNB2 genes gradually increases and is strongly correlated with breast cancer progression from grade 1 to grade 3; hence, these genes are characterized as prognostic markers. The expression, survival, and gene set enrichment analysis on all the genes of the grade 3 network suggests that CCNB1, CDK1, KIF2C, NDC80, UBE2C, and CCNB2 genes could be the potential targets for early breast cancer diagnosis and therapy (V.S.P.K. Sankara Aditya Jayanthi, 2019).

2 Objectives

2.1 Introduction

Breast cancer epidemiological patterns vary in European countries (Ferlay J, 2013), presenting different incidence rates (49-148 new cases per 100,000 women) with a narrower but still variable range of mortality (15-36 new cases per 100,000 women).

In Portugal, there has been a gradual and progressive increase in female breast cancer incidence and a continuing decrease in the mortality rate. According to the latest published data, the incidence and mortality rate in the country is 118.5 and 30.4 cases per 100,000 women, respectively, as per the statistics provided by the Directorate-General of Health (Direção-GeneraldaSaúde,2016;see https://www.dgs.pt/em-destaque/portugal-doencas-oncologicas-em-numeros-201511.aspx). Pursuant to the same report, the national screening program covers 67.70% of the target population, with a population adhesion rate of 60.89% (www.dgs.pt). Nevertheless, breast cancer incidence and mortality patterns vary significantly among different regions within Portugal. Furthermore, the capital area of the country (Lisbon) is not officially screened, and the majority of the population is followed in private or general practice settings.

Male breast cancer is a rare disease, comprising ~1% of breast cancers. Therefore, data are generally scant on this issue. One national study reported the diagnosis and treatment of 166 cases of male patients with breast cancer in Portugal between 1970 and 2013 (https://fenix.tecnico.ulisboa.pt/downloadFile/395145917396/resumo.pdf.). Portugal is a participant in the International Male Breast Cancer Program, coordinated by the European Organization for Research and Treatment of Cancer (E.O.R.T.C.) and runs in conjunction with the Breast International Group (BIG) and the North American Breast Cancer Group (N.A.B.C.G.) networks.

By increasing public awareness and improving screening programs, the early detection of breast cancer has been made possible, resulting in an increase in the incidence of small breast tumors. However, the incidence of advanced metastatic breast cancer remains stable. Approximately 10-15% of breast cancers in Portugal are diagnosed at stage IV. Almost one-third of the early breast cancers that are detected relapse eventually. Data have suggested that the reduction in breast cancer mortality is not only due to the early detection of the disease but is, in almost equal part, a consequence of screening and the advances that have been made in terms of molecular medicine and the development of novel therapies (Clinical

Science Symposium: New Insights into Epidemiology and Outcomes, E.C.C.O., abs. no. O-410, 2014; http://ec.europa.eu/eurostat/statistics-explained/index.php/Cancer_statistics.).

The aim of the present study, the first one to appraise breast tissue via imaging by means of orienting the biopsy incision, is to quantify the actual number of cases of breast cancer present in both sexes by calculating the prevalence of silent breast cancer in corpses. The intention was to quantify the cases of existing cancers that had not clinically manifested themselves. The results of the pilot study are consequently shown hereby.

In the international literature, there are only five publications (Bhathal PS, 1985) (Bartow SA, 1987) (Nielsen M, 1987) (Welch HG, 1997) (Stalsberg H, 2015) based on medico-legal autopsies that were designed to define the 'natural reservoir' of the disease.

2.2 Literature review

In the present study, a thorough MEDLINE database search (from 1953 to 2016) was performed using the medical subject heading (MeSH) terms of ‘breast’ AND ‘autopsy/ies’. After excluding case reports, hospital autopsies, breast benign disease, and series over autopsies in patients with breast cancer, five publications (2-6) were identified, one of them being a meta-analysis, four of the papers were published between 1966-1997.

Table 1 summarises the five relevant studies that were identified. The most recent of the studies, published in 2015 by Stalsberg et al. (5), did not enable an improved evaluation of the ‘silent breast cancer’ phenomenon because it was not designed to characterize the disease ‘reservoir’ in the study population: The sample size remained small, the age limits were outside the target population, and the biopsy technique was neither oriented nor extensive.

Although (Nielsen M, 1987) concluded that *‘to definitively characterise the ductal carcinoma in situ (DCis) reservoir, a large prospective study of the age-specific prevalence of occult breast cancer is sorely needed,’* hardly any studies have been performed since 1987 despite controversies surrounding breast cancer screening and eventual overdiagnosis. Therefore, the current review emphasizes the need for such a broad study (Sidiropoulou, 2017).

Year	Author	Study	Females	Males	Ages	Biopsy technique	Samples	Cis*	IC*	AH*
1985	P.S. Bhathall	forensic	207	none	15-97	fixation, 3 mm, random	11	12.1%	1.4%	13%
1987	S. Bartow	forensic	490	none	15-98	fixation, 5 mm slices, random or selected	9	0	1.8%	10%
1987	M.Nielsen	forensic	110	none	20-54	radiography,fixation, 5mm slices, gross and histology	275	14.7%	0.9%	12%
1997	H. Welch	meta-analisys 1966-1997	852	none	15-98	none		8.9%	1.3%	
2015	H.Stalsberg	forensic	54	none	15-60	central sagital fixed, 8 blocks	8	0	0.05%	0.01%

Table 1. Literature Review. *Cis: in situ carcinoma, IC: invasive carcinoma, AH: atypical hyperplasia

2.3 Objectives

The present study aims:

- to determine silent breast cancer prevalence in both genders
- to identify the specific profiles that influence the clinical manifestation of the disease and,
- to characterize the age distribution of the silent breast cancer in the population under study.

2.4 Study design

The samples comprising the study population were obtained from the National Institute of Legal Medicine and Forensic Science in Lisbon, following a proper tissue collection authorization procedure.

The advantage of forensic autopsies stems from two major factors: unexpected deaths and the relatively uniform age distribution of the population under study, as opposed to hospital samples (Table 2):

Age	Number of corpses
30-40	74
40-50	120
50-60	186
60-70	127
70-80	149
80-90	96
>90	1

Table 2. Age distribution of forensic autopsies performed in 2014 (National Institute of Forensic Science)

The most commonly used research methods include quantitative and qualitative methods. (Dawson, 2009) highlighted that quantitative research is usually used to achieve numerical statistics using well-structured questionnaires. Quantitative research methods are very important because they help predict the relationship between variables, attain generalizability, and replicate the study findings. Quantitative research uses instruments such as surveys to collect primary data from the study participants to test the research hypotheses and answer the research questions. The deductive approach goes hand in hand with the quantitative research methods as inferences obtained by testing the research hypotheses of the sample population lead to the general inferences to the population with the same characteristics (Lincoln, 1985).

Quantitative studies are very important because they allow one to determine the relationship between independent and dependent variables and achieve the study's goal (Berg, 2004). This type of research also seeks to determine or establish facts, test hypotheses, and make study predictions. According to Vanderstoep & Johnson (Vanderstoep, 2009) quantitative research is advantageous because it yields accurate results that can be used to reflect the general population from which the sample was drawn. Furthermore, the result of the quantitative study is objective because the researcher remains detached when gaining, analyzing, and interpreting the research data (Nykiel, 2007). Therefore, the present study employed a quantitative research design to achieve its goals.

2.5 Sampling procedure

Probability and non-probability are the two main sampling techniques; the first one is known as choosing a random sample from a large population, while the latter one is regarded as a purposive sample created by targeted members of the population (Cohen, 2007). This study employed the random (probability) sampling approach. The random sample can represent the whole researched population since it does not focus on the particular group of the population.

2.6 Sample size

The study employed Cochran's (Cochran, 1977) sample size estimation procedure where the target population is infinite. The sample size formula is:

$$n_0 = \frac{z^2 pq}{e^2}$$

Where n_0 is the sample size, z is the selected critical value of desired confidence interval (95%), p is the estimated proportion of an attribute that is present, q = 1-p, and e is the

desired level of precision (0.05). For instance, the approximate overall incidence of breast cancer in the Portuguese population is 0.12% (118.5 in 100,000 women).

Therefore, the sample size calculated at 95% confidence interval, 0.12 proportion, and precision level of 0.05 will be:

$$n_0 = \frac{1.96^2(0.12) * (1 - 0.12)}{0.05^2}$$

Thus, the estimated population size = 27 cadavers are needed to achieve the null hypothesis in the male gender and 182 in the female gender.

2.7 Data collection

The data collection process of the cadavers included patients' profile, gland characterization, lesion size, histological type, and molecular surrogates. Cadavers profile included age, ethnicity, comorbidities, medications, cause of death, breast screening adhesion, and breast cancer risk factors. Gland's characteristics included dimensions, weight, and size.

2.8 Data analysis

The quantitative statistical method of analysis was based on the overall multi-dimension constructs measurements for every factor, descriptive statistics, regression, and parametric as well as non-parametric tests. The regression statistics will be used to determine the correlation between the multi-dimension construct assessment and each factor, as well as the actual percentage of people with breast cancer. Moreover, the line fit plot will be employed to obtain illustrations based on the correlation and to provide the relationship between each factor. Further, the descriptive statistical analysis can be performed to provide the comparisons of age, ethnicity, and risks of breast cancer. The predicting factors of breast cancer will be determined using logistic regression.

3 Methodology

The study group consisted of a series of consecutive medico-legal autopsies on fresh Portuguese cadaver performed from July 2016 to December 2019 at the National Institute of Legal Medicine and Forensic Science, Lisbon, Portugal.

The criteria for exclusion were age younger than 40 years, the autopsy performed in less than 48 hours after death, extensive injury to one or both breasts, and known or clinically evident breast cancer. Once the eligibility criteria were met, and the sample collection authorization was obtained, a bilateral subcutaneous modified radical mastectomy (bsMRM) was performed (Figure 8) through a Douformentel incision (allowing the subsequent reconstruction, previous to corpses release) in each fresh cadaver at the National Institute of Legal Medicine and Forensic Science.

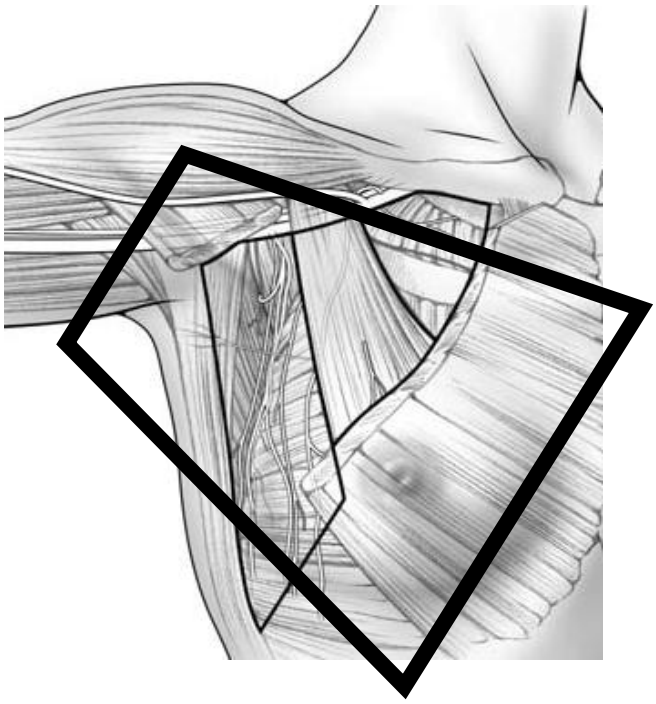


Figure 8. Excised area from corpses for analysis (Jatoi, 2006)

General information, such as age, height, weight, and body mass index (B.M.I.), was obtained from the cadaver's referring file when available, while past medical history data was not included due to inadequate collection.

Each specimen was properly identified in means of spatial orientation and, after conditioning in sealed bags (Figure 9), was transported within an appropriate container to the Hospital São Francisco Xavier (Lisbon, Portugal), and submitted to measuring (three-dimensions), waiting, inspection, palpation, ultrasound (Figure 10), and mammography by breast radiologists and breast surgeon.

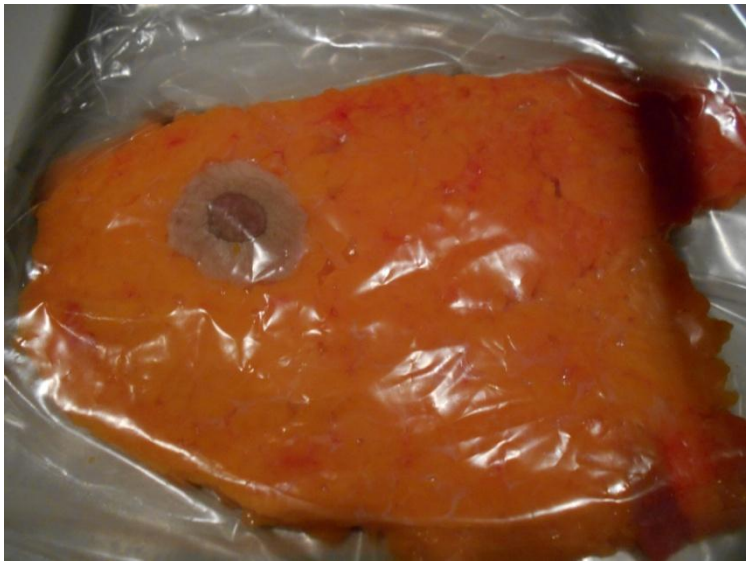


Figure 9. Left male breast sample

The collected tissues were imaged using the G.E. Healthcare digital mammography system, Senographe Essential™ (G.E. Healthcare Bio Sciences, Pittsburgh, PA, U.S.A.; Figure 11), with an X-ray beam of 27 kV (range, 60 70 mA) and 10 15 decanewtons (daN) compression, depending on tissue density and size (Figure 12). The visualization screen had a resolution of five megapixels (G.E. Healthcare LOGIQ™ S7 Expert ultrasound system, with a medium frequency of 9 15 MHz; G.E. Healthcare Bio Sciences).

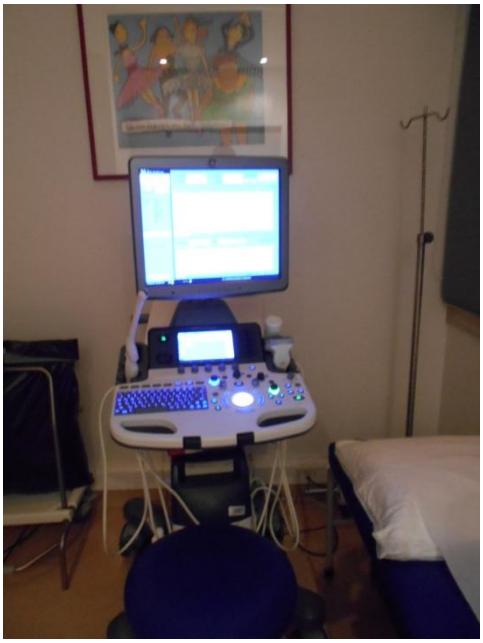


Figure 10. Ultrasound system used for analyses

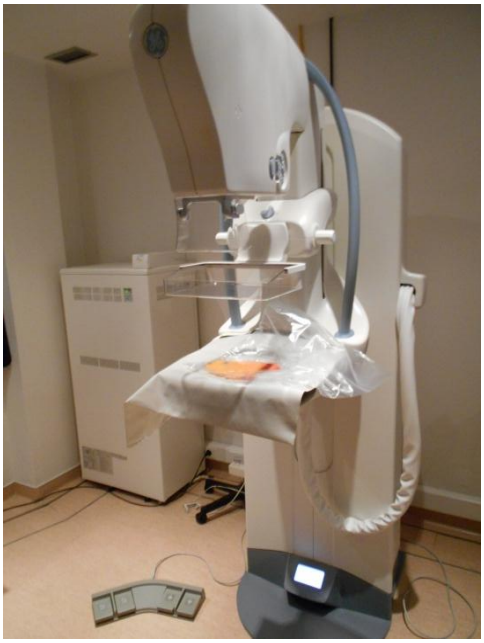


Figure 11. Mammograph employed in the study

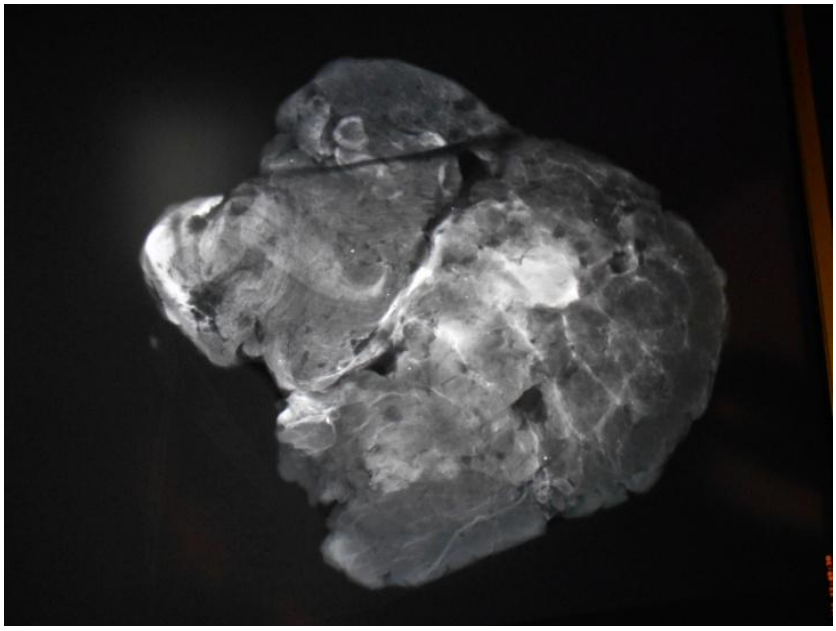


Figure 12. Sample's mammogram

Breast tissue, classified as Breast Imaging Reporting and Data System (BI-RADS) category three or higher, was submitted to wire-guided or direct excisional surgical biopsy by the author. According to the 5th edition of the ACR BI-RADS Atlas, ACR BI-RADS (ACR, s.d.) system used:

- 0: Incomplete
- 1: Negative
- 2: Benign
- 3: Probably benign
- 4: Suspicious
    - 4A: low suspicion for malignancy, about 2%
    - 4B: intermediate suspicion of malignancy, about 10%
    - 4C: moderate concern, but not classic for malignancy, about 50%
- 5: Highly suggestive of malignancy
- 6: Known biopsy – proven malignancy

BI-RADS 0 refers to an incomplete evaluation with further imaging required, such as additional mammographic views, including spot compression or magnification and or ultrasound. BI-RADS 1 refers to a negative examination, meaning that there are no masses, suspicious calcifications, or areas of architectural distortion. There can be no description of a finding in the report if it is categorized as a BI-RADS 1. BI-RADS 2 is consistent with benign findings that include secretory calcifications, simple cysts, fat-containing lesions, calcified fibroadenomas, implants, and intramammary lymph nodes. BI-RADS 3 is probably benign and should be followed up at shorter intervals to determine stability; the risk of malignancy is below 2%. There are very strict classifications to qualify a finding in the BI-RADS 3 category: a non-palpable, circumscribed mass on a baseline mammogram; a focal asymmetry, which becomes less dense on spot compression images, or a solitary group of punctate

calcifications. Any findings other than this cannot be placed in the category 3. BI-RADS 4 is a suspicious abnormality, which can represent the chance of being malignant (in percent). The BI-RADS category 4 is subdivided into a, b, and c. The subcategory of (a) has a low probability of malignancy with a 2% to 10% chance of malignancy. The subcategory of (b) has an intermediate change of malignancy ranging from 10% to 50%. The subcategory of (c) has a high probability of malignancy ranging from 50% to 95%. BI-RADS 5 is highly suggestive of malignancy more than 95% (Magny, et al., 2020)

The samples were subsequently analyzed in the pathology department by an experienced breast pathologist.

3.1 Samples

In the pre-analytical phase, breast biopsies were fixed in 10% buffered formalin (JTBaker) for 24 hours, and lumpectomy specimens were fixed for 48 to 72 hours at room temperature (20°C). Formalin-fixed, paraffin (VWR International, EUA) embedded tissues were processed in Sakura's "Tissue-Tek VIP" and cut into 3 µm sections, one cut per adhesive slide (Superfrost Plus Gold - Thermo Scientific, EUA), with respective positive control. Tissue section adhesion time and temperature were held constant for 1 hour at 70ºC.

Following these procedures, the slide was subjected to labeling by the immunocytochemistry (ICC) method.

3.2 ICC Procedure

The ICC panel of primary antibodies used against Ki67 (clone 30-9, Cat. 790-4286), ER (clone SP1, Cat. 790-4324), and PR (clone 1E2, Cat.790-2223) were performed in the BenchMark ULTRA using Optiview DAB IHC Detection Kit (Cat. 760-700), for Ki67 and Ultraview Universal DAB Detection Kit (Cat. 760-500), for ER and PR, all from Ventana Medical Systems, Tucson, USA.

The slides were observed by a surgical pathologist under an optical microscope.

3.2.1 Interpretation of ER and PR Staining

Immunocytochemically stained slides were evaluated for the presence of positive reaction, cellular localization (only nuclear staining was considered positive), the pattern of staining (focal or diffuse), and intensity of the reaction in individual tumor cells (strong or weak). The percentage of immunoreactive cells was determined by visual estimation, and quantitation was provided by reporting the percentage of positive cells (any positive nuclear reaction for

ER and PR was recorded as positive). Carcinomas with <1% positive cells were considered negative for ER and PR.

Appropriate positive controls were stained concurrently with the patient slides on the same slide.

3.2.2 Interpretation of Ki67 Staining

Ki67 score is defined as the percentage of positively stained cells among the total number of malignant cells scored. The score was determined by manually counting the positive tumor cells in three high-power fields (40x objective) and calculating the average percentage of positive tumor cells. Only nuclear staining was considered positive; the staining intensity was considered irrelevant.

3.3 Pilot study/Feasibility report

The pilot study (Sidiropoulou Z, 2017) includes the results of the first seven bilateral modified radical mastectomies performed on each gender (Table 3 and 4).

Age	Race	Cause of death	BMI	Breast	Weight (gr)	Size	Palpation	BI-RADS	Ecography	Mamograpfy	Quadrant	Histology
37	Negroid	Asphyxiation	27.68	RB	NA	17x33	N	2	Intramammary lymph nodes	ID	EU	
				LB	NA	23x38	N	2	Intramammary lymph nodes	ID	UT	
74	Caucasian	Stroke	NA	RB	NA	NA	N	2	Axillary lymph nodes	mics	disperse	
				LB	NA	NA	N	2	Axillary lymph nodes	mics	disperse	
86	Caucasian	Peritonitis	27.34	RB	NA	NA	N	1	0		0	
				LB	NA	NA	N	1	0		0	
63	Caucasian	Heart attack	25.403	RB	780	23x23	N	1	0		0	
				LB	940	28x25	N	1	0		0	
48	Caucasian	Meningitis	23.94	RB	147	14x13	N	1	0		0	
				LB	180	23x16	P	4a	3 Intramammary lymph nodes		UT	W
48	Caucasian	Cranial Trauma	30.72	RB	NA	NA	N	1	0		0	
				LB	NA	NA	N	1	0		0	
57	Caucasian	Under Investigation	NA	RB	207	17x14	N	1	0		0	
				LB	250	26x13	N	1	0		0	

Table 3. Male breast pilot study. Results of the first seven bilateral modified radical mastectomies performed on male corpses.

Age	Race	Cause of death	BMI	Breast	Weight (gr)	Size	Palpation	BI-RADS	Ecography	Mamograpfy	Quadrant
61	Caucasian	Tromboembolism	31.1	RB	NA	NA	N	2	0	miCs	Disperse
				LB	NA	NA	N	2	0	miCs + macroCal	Disperse
85	Caucasian	Intoxication	30.8	RB	NA	NA	N	2	0	miCs	Disperse
				LB	NA	NA	N	2	0	miCs	Disperse
74	Caucasian	W	39.7	RB	2500	32x26	N	2	Cysts	plasmacytic mastitis	UI/EU
				LB	1900	27x24	N	2	Ductal Ectasia	miCs	Disperse
61	Caucasian	Heart attack	37.5	RB	1330	27x21	N	1	0	0	
				LB	1450	28x26	N	1	0	0	
45	Caucasian	W	27.2	RB	1190	29x24	N	1	0	0	
				LB	1230	28x25	N	2	Microcysts	0	EU
45	Caucasian	Heart attack	30.2	RB	960	30x21	N	1	0	0	
				LB	990	30x20	N	1	0	0	
94	Caucasian	Respiratory failure	22.3	RB	420	18x16	N	1	0	0	
				LB	490	23x14	N	1	0	0	

Table 4. Female breast pilot study. Results of the first seven bilateral modified radical mastectomies performed on male corpses.

During the same period, futility testing was performed on female gender data, which concluded that since the approximate overall incidence of breast cancer in the Portuguese population is 0.12% (118.5 in 100,000 women), even if only one case (0.26 percent) is detected, it can validate the current study's initial hypothesis, that is, the prevalence of silent breast cancer is higher than the actual incidence.

Table 5 presents the inputs regarding estimated proportion, desired precision, and confidence interval. Moreover, Table 6 describes the results, required sample size required to simulate the null hypothesis scenario, that is, silent breast cancer prevalence equals breast cancer incidence in the Portuguese female population.

Estimated Proportion	0.12
Desired precision of estimate	0.05
Confidence level	0.95

Table 5. Inputs regarding estimated proportion, desired precision, and confidence interval

Large population	163

Table 6. Sample size size required for specified inputs

At that point, we were able to state that:

- It is feasible to execute the prevalence definition by extending our time frame up to 36 months as the actual rate of recruitment is lower than initially anticipated.
- The tissues collected from fresh cadavers can be analyzed through imaging without tissue degradation up to 48 hours post-collection.
- The corpse's specificities in terms of gynecologic/obstetric or medication and comorbidities profile cannot be established for legal reasons (no access to personal files). As a result, determining potential protective or harmful factors was not going to be possible.

4 Results

4.1 Silent male breast cancer

Breast cancer epidemiological patterns (Ferlay J, 2013) differ across European countries, with varying incidence rates (49–148 new cases per 100,000 women) and a narrower but still variable range of mortality (15–36 new cases per 100,000 women). Breast cancer also affects men. However, male breast cancer is a rare disease, comprising ~1% of breast cancers, and data are generally scant about this ailment.

The aim of the present study was to quantify the actual number of cases of breast cancer in both sexes by calculating the prevalence of silent breast cancer in corpses. The intention was to quantify the cases of existing cancers that had not clinically manifested themselves by using imaging methods.

In this chapter, the male study's findings are presented.

4.1.1 Results

All 74 cases were submitted to bsMRM and proceeded to tissue evaluation. The average post-mortem to biopsy duration was 18 hours. Age at death ranged from 40 to 91 years, with a mean age of 63.9 years (Figure 13).

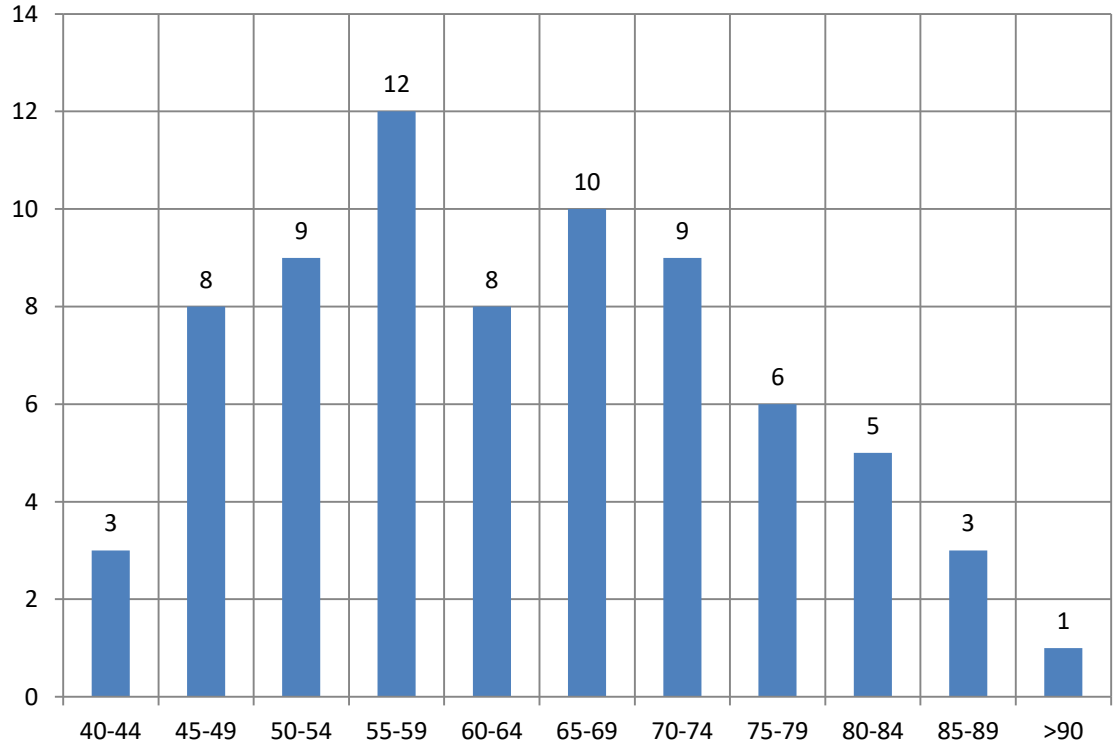


Figure 13. Age distribution of the male corpses. Age groups are presented on x-axis while y-axis denotes the number of corpses.

The mean BMI was 28.63kg/m^2; out of 74 cadavers, 90.54% were Caucasoid, six of Negroid, and one of Asiatic ethnicity. Of the 74 cases, 23 (31.08%) died suddenly from acute heart failure (myocardial infarction; Table 7; Figure 14), while the most interesting data is the diagnosis of four gastrointestinal tract silent adenocarcinomas (two colons, one gastric, and one pancreatic) and one lymphatic system neoplasm.

Cause of death	**Number of corpses**
Acute myocardial infarction	23
Acute pulmonary embolism	7
Hypovolemic shock	7
Aspiration	6
Asfixiation	5
Viral pneumonia	5
Subarachnoid hemorrhage	4
Acute alcohol intoxication	3
Hypertrophic cardiomyopathy	3
Hemopericardium/tamponade	2
Acute cerebrovascular accident	2
Peritonitis post right hemicolectomy	1
Left colon adenocarcinoma	1
Right colon metastatic adenocarcinoma	1
Pancreatic metastatic adenocarcinoma	1
Gastric adenocarcinoma	1
Splenic lymphoma	1
Viral meningitis	1
Total	**74**

Table 7. Cause of death/autopsy findings of the cases. Four cases of gastrointestinal tract silent adenocarcinomas (two colons, one gastric, and one pancreatic) and one case of lymphatic system neoplasm were diagnosed.

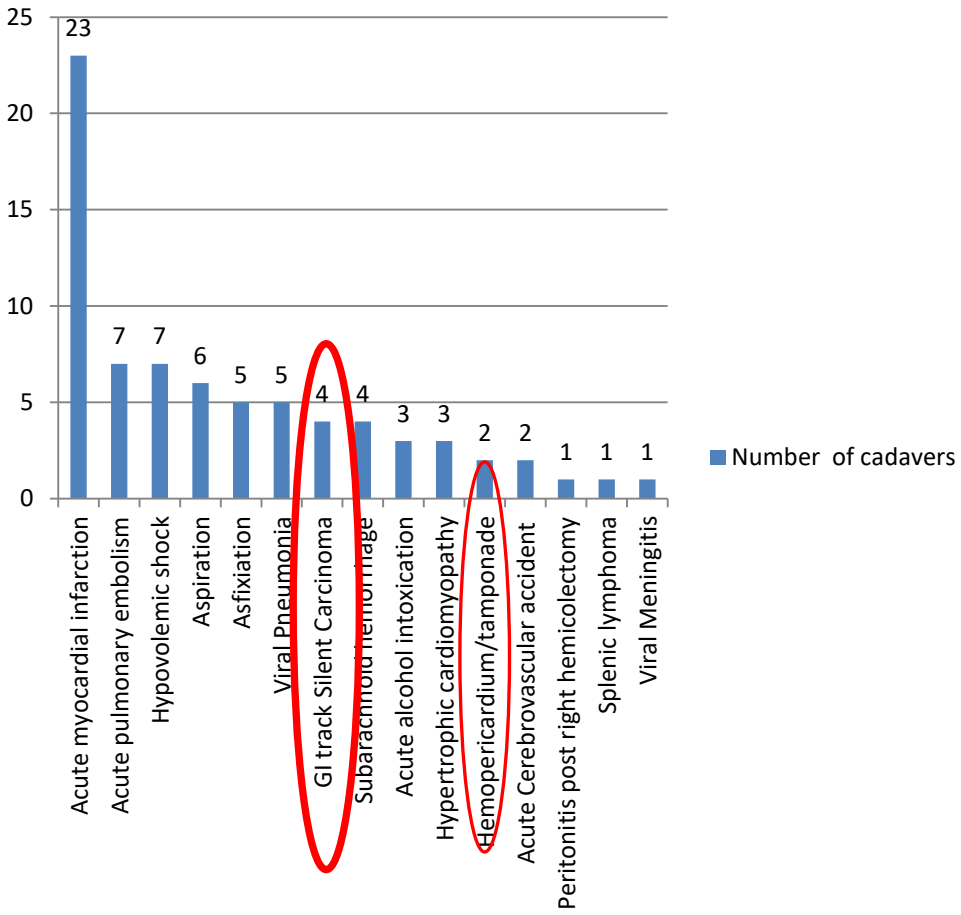


Figure 14. Cause of death/autopsy findings of the cases. The x-axis presents the causes of death, while the y-axis shows the number of cases in each cause of death category.

No case of breast cancer was detected among the analyzed cadavers. None of the corpses had a history or scars of breast surgery, nor did they have a confirmed diagnosis or clinical signs of BC.

The mean weight of processed breast tissue was 842.10 g/cadaver, with mean dimensions of medio-lateral 23.46 cm, supero-inferior 16.37 cm, and antero-posterior 0.83 cm per tissue (Figure 15). There appeared to be no relationship between BMI and breast tissue weight.

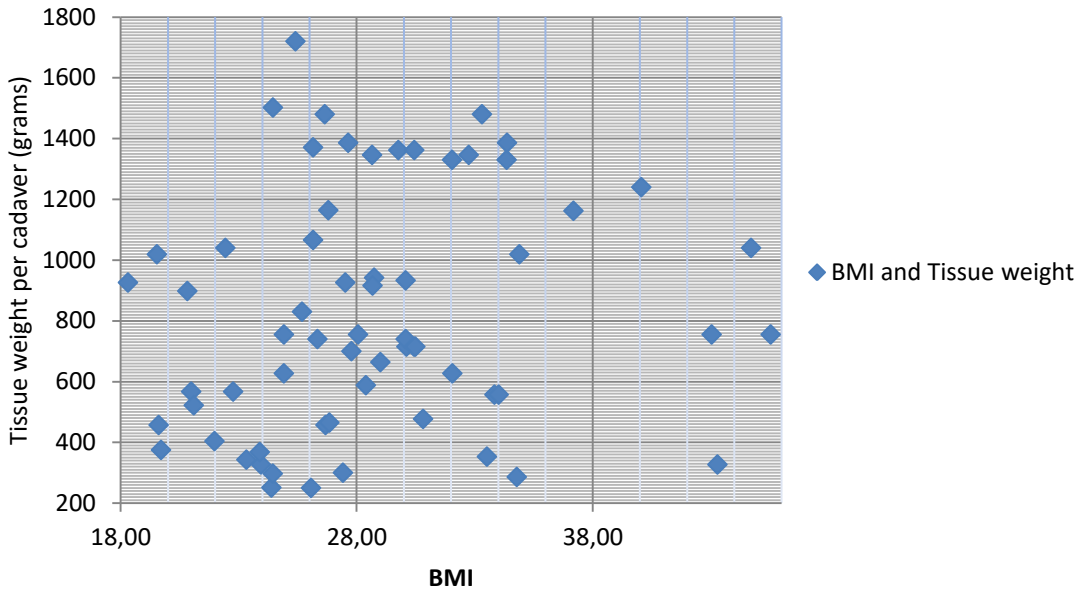
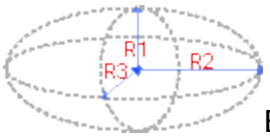


Figure 15. BMI and mean tissue weight/cadaver. X-axis presents BMI values vs. tissue weight per cadaver on the y-axis. There appeared to be no relationship between these two traits.

In volumetric terms, the breast tissue was submitted to imaging, and the following calculus was used to approximate its shape to a hemi-ellipsoid:



Ellipsoid dimensions and ellipsoid Formula (Knud Thomsen):

$$V = \frac{4}{3}\pi R_1 R_2 R_3$$ divided by 2.

The total breast tissue volume elaborated was 102774,08 cm^3 (102.77L). The correlation between BMI and Total Breast Volume (TBV) is depicted in Figure 16. There appears to be no correlation (correlation index of 0.176279) between TBV and BMI.

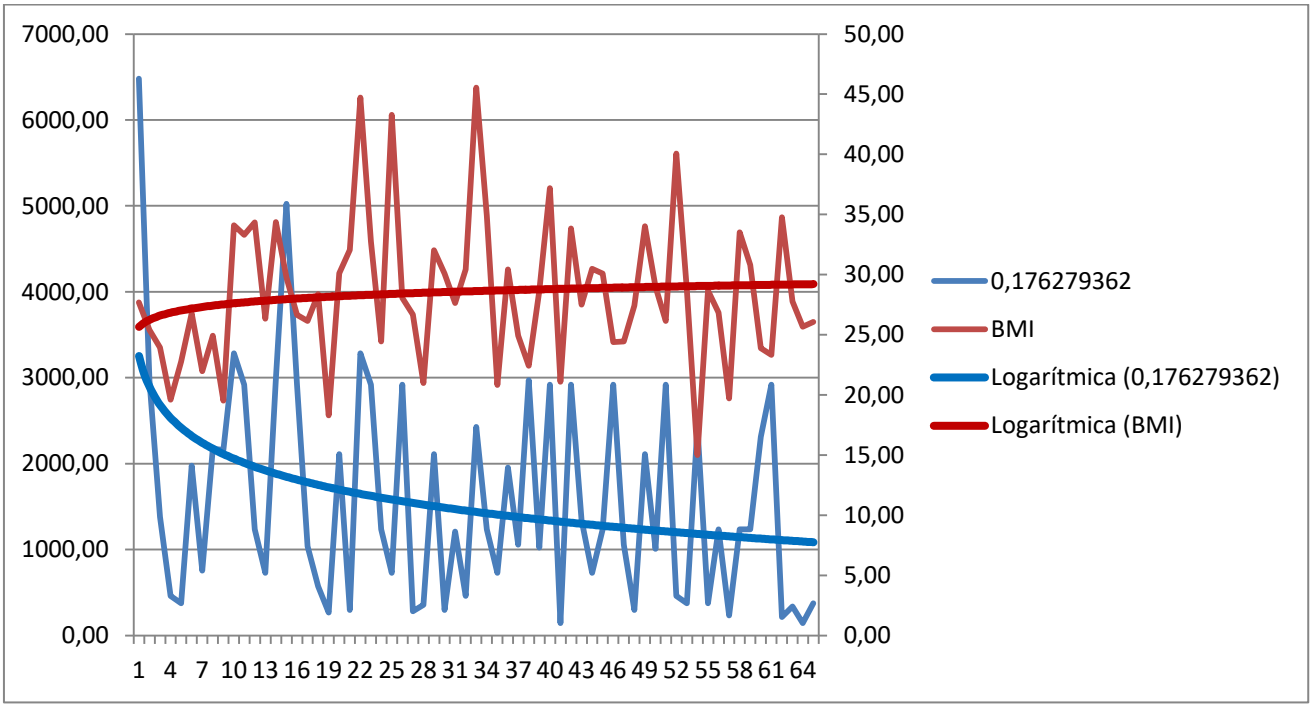


Figure 16. BMI and TBV. A correlation index of 0.176279 was noticed between the two parameters.

Breast Density and BMI also do not appear to have any correlation, presenting a negative correlation index of -0.13 (Figure 17).

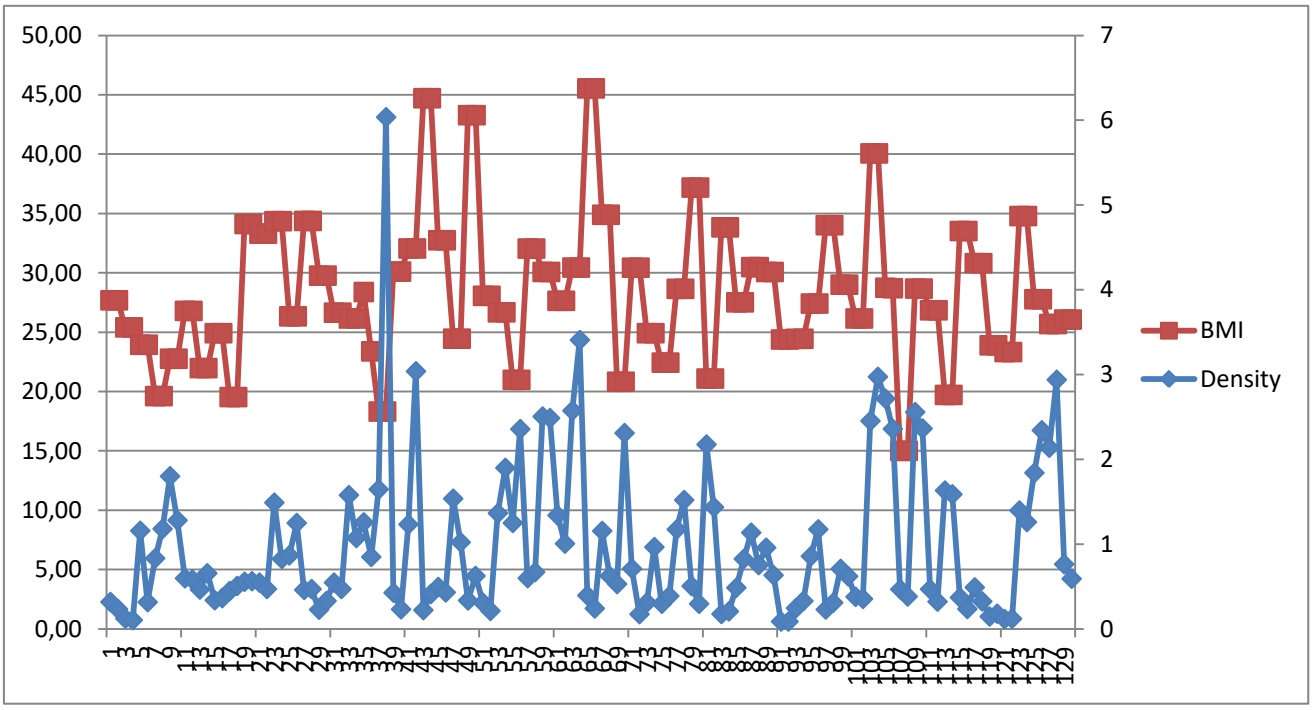


Figure 17. BMI and breast density. Red line denotes BMI values, while blue line shows density. A negative correlation index of -0.13 was noticed between the two traits.

BI-RADS classification indicated 1 in 129 breast samples (87.16%), 2 in 18 breast samples (12.16%), and 4a in 1 (0.67%) breast sample (Figure 18).

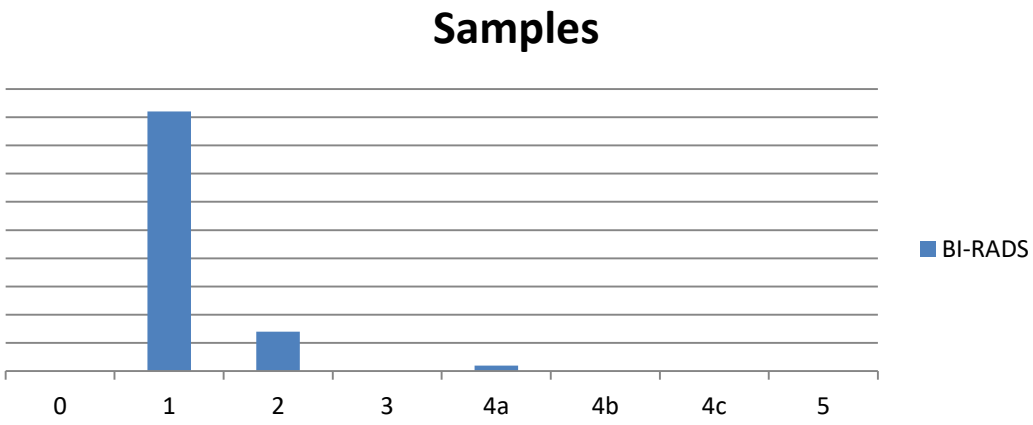


Figure 18. BI-RADS classification of the samples

Benign microcalcifications were detected in nine glands, dispersed in six cases, and localized in the remaining three. Benign macrocalcifications were detected in only five cases, localized in upper quadrants, while three cases had both types of benign calcifications. Moreover, intramammary lymph nodes were found in six cases (five cadavers, one biopsied included), while benign multiple axillary lymph nodes were present in seven cases (six cadavers).

The biopsied cadaver was a 47-year-old Caucasoid male who died from viral meningitis associated with a respiratory infection. The left breast ecography revealed three intramammary nodules in the upper quadrants transition, classified as BI-RADS 4a (imaging of lymph nodes with thickened cortical).

The pathology report confirmed "reactive intramammary lymph nodes with no neoplastic lesion."

No other biopsy was performed.

4.1.2 Correlation analyses

Correlation analysis was conducted on SPSS to determine the relationship of the gland's classification (BI-RADS system) with age, weight, height, and BMI of the male corpses. The correlation was tested at a 95% confidence interval (CI), and a significant value (2-tailed) was used as a criterion to decide the significance of the relationship between the two variables. If the significance value is .05 or less, it indicates a significant relationship, and a greater value than .05 implies an insignificant relationship. Nonetheless, the Pearson correlation value was

used to determine whether the relationship was negative or positive (based on the presence or absence of the negative sign).

The correlation matrix shown in Table 8 presents the correlation of glands (BI-RADS) with age, weight, height, and BMI of male corpses. The results indicated the glands (BI-RADS) have a significant relationship with the weight and BMI of male corpses as their respective significance values were (.020) and (.028), which were less than (.05). However, based on negative signs of their Pearson correlation values, the relationship was significantly negative. The results also illustrated that glands (BI-RADS) have an insignificant relationship with the age and height of male corpses as their respective significance values were (.170) and (.346), which were more than (.05). Thus, the gland (BI-RADS) found in male corpses increases as their weight and BMI decrease. Hence, higher BI-RADS is found in thinner individuals, which is probably due to the low sampling volume.

		1	2	3	4	5
Glands (BI-RADS)	Pearson Correlation	1	-.113	-.202*	.078	-.182*
	Sig. (2-tailed)		.170	.020	.346	.028
Age	Pearson Correlation		1	-.223**	-.130	-.302**
	Sig. (2-tailed)			.010	.115	.000
Weight	Pearson Correlation			1	.054	.863**
	Sig. (2-tailed)				.538	.000
Height	Pearson Correlation				1	-.229**
	Sig. (2-tailed)					.005
BMI	Pearson Correlation					1
	Sig. (2-tailed)					

Table 8. Correlation of Glands (BI-RADS) with age, weight, height, and BMI of male corpses

Moreover, a second correlation analysis was conducted to determine the relationship of the cause of death with the results of mammography, ecography, and glands (BI-RADS) on male corpses, as depicted in Table 9. The results indicated the cause of death has a significant positive relationship with mammography, with a significance value of.027 and a positive Pearson correlation value of .568. However, the cause of death has an insignificant relationship with ecography and glands (BI-RADS) of male corpses as their respective significance values were (.732) and (.085) which were greater than (.05). The results depicted that the cause of death was insignificantly related to ecography and gland's BI-RADS of male

corpses. Thus, the ecography findings (calcifications) and gland's BI-RADS did not correlate with the cause of death of the male corpses examined in this research. The cause of death and mammography findings might imply vascular calcification and consequent ischemic strokes or heart ischemic disease, data not uniformly supported by other studies.

		1	2	3	4
Cause of death	Pearson Correlation	1	.568	.134	-.142
	Sig. (2-tailed)		.027	.732	.085
Mammography	Pearson Correlation		1	1.000	-.206
	Sig. (2-tailed)			.000	.462
Ecography	Pearson Correlation			1	-.550
	Sig. (2-tailed)				.125
Glands (BI-RADS)	Pearson Correlation				1
	Sig. (2-tailed)				

Table 9. Correlation of cause of death with the results of mammography, ecography, and gland´s BI-RADS of male corpses

4.1.3 Hypothesis testing

The study's goal was to quantify the number of male silent breast cancers that aren't clinically manifested but can be identified through imaging analysis. The null hypothesis stated that the natural reservoir of silent breast cancer is not superior to the actual incidence of the disease. The alternative hypothesis stated that the natural reservoir of silent breast cancer is superior to the actual incidence of the disease.

The hypothesis was tested in the first period with 27 recruited male gender cadavers (Sidiropoulou Z et al, 2019). The findings did not identify any silent breast cancer despite the fact that male breast cancer's molecular surrogate (usually ER, PR, and AR positive, Luminal B-like/HER2-negative, and 56% patients of T1 tumors) generally has a good prognosis; its late detection and consequent treatment dictates the disease course (5.1% with metastatic disease [M1] and OS 2.6 years).

Cross tabulation analysis was conducted on SPSS to test the null hypothesis. The glands' results were expressed in seven BI-RADS categories. BI-RADS 1 shows negative examination, while BI-RADS 2 is consistent with benign findings. BI-RADS 3 is probably benign and should have shortened interval follow-up to determine stability; the risk of malignancy is below 2%. BI-RADS 4 is a suspicious abnormality, which can represent the chance of being malignant (in percent). The BI-RADS category 4 is subdivided into a, b, and

c. The subcategory of (a) has a low probability of malignancy with a 2% to 10% chance of malignancy. The (b) subcategory has an intermediate risk of malignancy ranging from 10% to 50%. In comparison, the subcategory of (c) has a high probability of malignancy ranging from 50% to 95%. BI-RADS 5 is highly suggestive of malignancy more than 95%). In the cross tabulation analysis, the BI-RADS 4a: probably benign, has a low probability of malignancy, indication for biopsy was only one observation (0.67%); that is, less than 1%. Therefore, it was automatically ignored by the SPSS while performing the cross tabulation analysis. The cross tabulation results of the gland's BI-RADS against the male corpses' mammography are given in Table 10.

			Mammography				
			ID	mics	mics + MacroC	MacroC	Total
Glands	Bi-RADS 1: no alterations found	Count	0	2	3	2	7
		% within Glands	.0%	28.6%	42.9%	28.6%	100.0%
		% of Total	.0%	13.3%	20.0%	13.3%	46.7%
	BI-RADS 2: benign findings	Count	1	3	2	2	8
		% within Glands	12.5%	37.5%	25.0%	25.0%	100.0%
		% of Total	6.7%	20.0%	13.3%	13.3%	53.3%
Total		Count	1	5	5	4	15
		% within Glands	6.7%	33.3%	33.3%	26.7%	100.0%
		% of Total	6.7%	33.3%	33.3%	26.7%	100.0%

Table 10. Gland's (BI-RADS) × mammography cross tabulation. The cross tabulation was conducted using SPSS.

The mammography results showed that male corpses samples had 'microcalcifications,' 'both microcalcifications and macrocalcifications,' and 'macrocalcifications'. The majority, *viz*. 37.5% of the male corpses were found to have 'microcalcifications,' 25% had 'macrocalcifications,' and 25% had 'microcalcifications and macrocalcifications.'

The cross tabulation results of the gland's BI-RADS against the ecography of the male corpses are presented in Table 11. According to the ecography results and BI-RADS classifications of 1 or 2, 25% of the male corpses had 'Intrammary lymph nodes,' while the majority, 75%, had 'Axillary lymph nodes. While in BI-RADS 2 cases 80% of the male corpses were found to have 'Intramammary lymph nodes, and 20% were found to have 'Intramammary lymph nodes based on ecography results.

			Ecography		
			Intramammary lymphnodes	Axilary lypmhnodes	Total
Glands	Bi-RADS 1: no alterations found	Count	1	3	4
		% within Glands	25.0%	75.0%	100.0%
		% of Total	11.1%	33.3%	44.4%
	BI-RADS 2: benign findings	Count	4	1	5
		% within Glands	80.0%	20.0%	100.0%
		% of Total	44.4%	11.1%	55.6%
Total		Count	5	4	9
		% within Glands	55.6%	44.4%	100.0%
		% of Total	55.6%	44.4%	100.0%

Table 11. Glands (BI-RADS) × Ecography cross tabulation among the male corpses

Based on cross tabulation results, it was evident that no malignancy signs were found by breast ecography and mammography in the male corpses. However, to statically validate these findings, the level of significance was evaluated by correlation analysis. The correlations of the gland's BI-RADS with the results of ecography and mammography are shown in Table 12. The correlations of gland's BI-RADS with the results of ecography and mammography were insignificant as their respective (2-tailed) significance values were .125 and .462, *viz*. greater than .05. Consequently, in male breast evaluation, BI-RADS classification obtained by ecography and mammography cannot be used as a screening method (as suspicious findings are so scant) in the general population, as expected.

		1	2	3
Glands (Bi-RADS)	Pearson Correlation	1	-.550	-.206
	Sig. (2-tailed)		.125	.462
Ecography	Pearson Correlation		1	1.000**
	Sig. (2-tailed)			.000
Mammography	Pearson Correlation			1
	Sig. (2-tailed)			

Table 12. Correlations of glands BI-RADS with the results of ecography and mammography

The statistical analysis found no significant incidence or suspicion of breast cancer in the male corpses, implying that the rate of male breast cancer is not superior to the actual incidence in the general population.

Therefore:

We can conclude that the actual cases of male breast cancer manifest themselves, and thus, we accept the null hypothesis that the natural reservoir of silent breast cancer is not superior to the actual incidence of the disease.

4.2 Silent female breast cancer

Breast cancer epidemiological patterns (Ferlay J, 2013) vary in European countries, presenting different incidence rates (49–148 new cases per 100,000 women) with a narrower but still variable range of mortality (15–36 new cases per 100,000 women).

The aim of the present study was to quantify the actual number of cases of breast cancer present in both sexes using imaging analysis by calculating the prevalence of silent breast cancer in corpses. The intention was to quantify the cases of existing cancers, including those that had not clinically manifested themselves.

In the present chapter, the female study's findings are analyzed.

4.2.1 Results

All 217 cases have been submitted to bsMRM and proceeded to tissue evaluation. The average post-mortem to biopsy duration was of 18 hours. Age at death ranged from 40 to 91 years, with a mean age of 65.53 years (Figure 19).

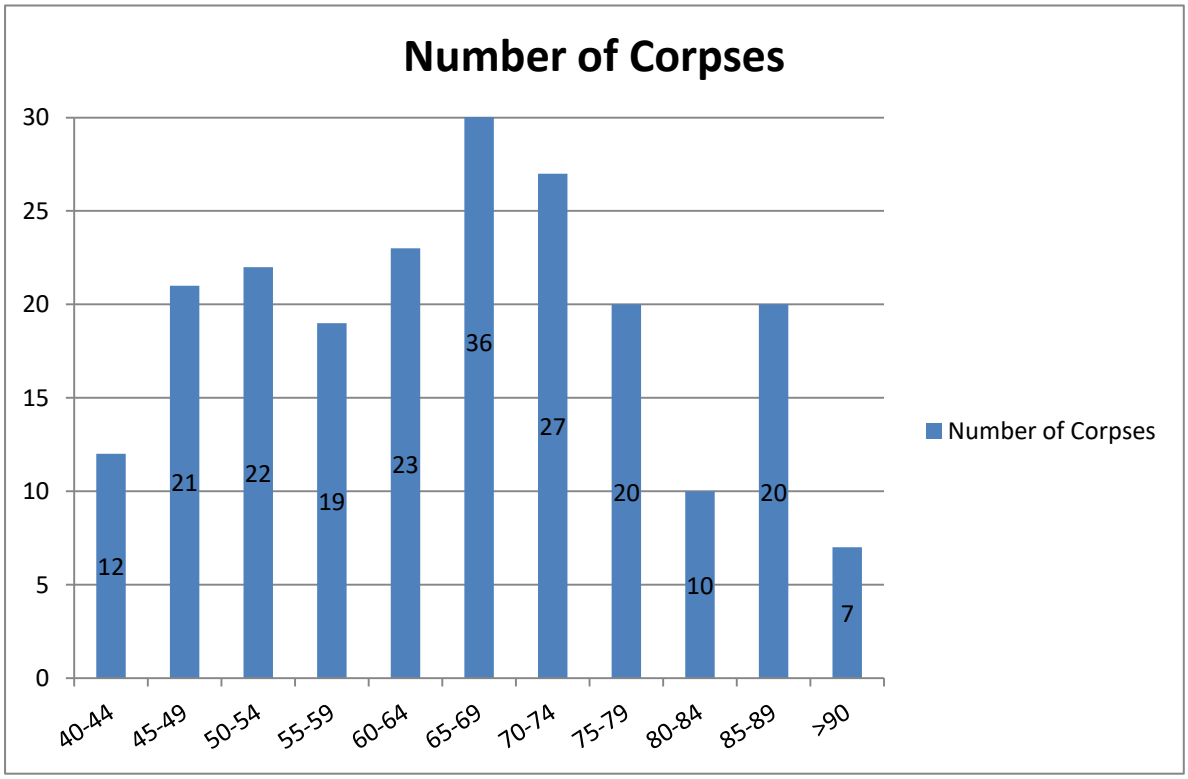


Figure 19. Age distribution of the female corpses. Age groups are presented on the x-axis while the y-axis denotes the number of corpses. The highest number of corpses related to 65-69 years of age.

Mean BMI was 24.89 kg/m^2; out of 271 cadavers, 94% were Caucasoid, and 13 of Negroid ethnicity (06%). Of the 271 cases, 65 (31.08%) died suddenly from acute heart failure (myocardial infarction; Table 13). Interestingly, eight gastrointestinal tract silent adenocarcinomas (seven colons and once gastric) and one silent ovarian adenocarcinoma were diagnosed; Figure 20).

Cause of death	Number of corpses
Acute myocardial infarction	65
Acute Cerebrovascular accident	45
Hipovolemic shock	20
Viral Pneumonia	16
Head trauma Subarachnoid hemorrhage	14
Hypoxic encephalopathy	8
Poisoning	8
Aspiration	7
Acute alcohol intoxication	4
Acute pulmonary embolism	4
Asfixiation	4
Right colon adenocarcinoma	3
Diabetic ketoacidosis	2
Lung adenocarcinoma	2
Peritonitis	2
Peritonitis post left hemicolectomy	2
Viral Meningitis	2
Bacterial menignitis	1
Bacterial pneumonia	1
Gastric adenocarcinoma perf	1
Hepatic metastasis of left colon adenocarcinoma	1
Hypertrophic cardiomyopathy	1
Left colon adenocarcinoma perfuration	1
Left colon metastatic adenocarcinoma	1
Ovarian metastatic adenocarcinoma	1
Peritonitis post right hemicolectomy	1

Table 13. Cause of death/autopsy findings of the cases. 31.08% of the cases died suddenly from acute heart failure

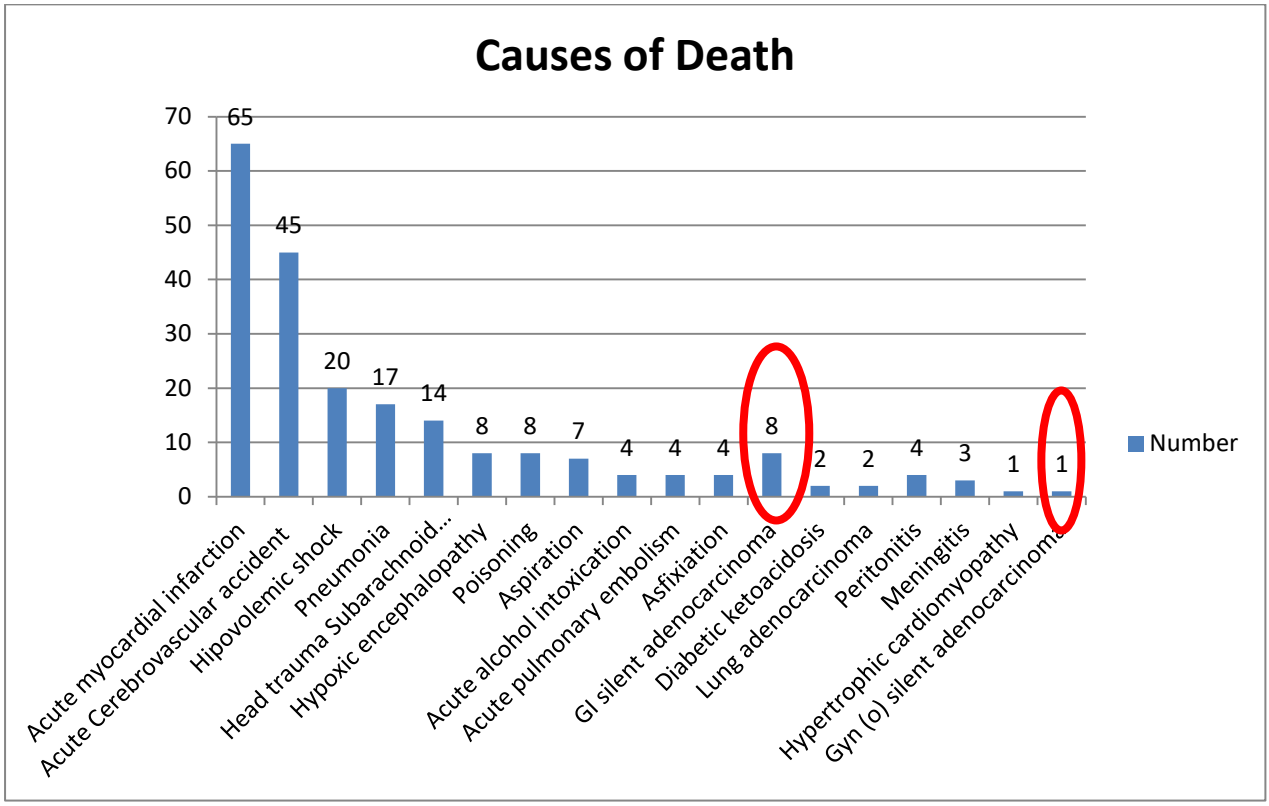


Figure 20. Cause of death/autopsy findings of the cases. The y-axis denotes the number of cases belonging to each cause of death. Eight cases of gastrointestinal tract silent adenocarcinomas and one case of silent ovarian adenocarcinoma were diagnosed.

No Breast cancer was detected. None of these people had a history or scars of breast surgery, nor did they have a confirmed diagnosis or clinical signs of BC.

Mean breast tissue weight processed was 2005.244 g/cadaver, and the dimensions were: medio-lateral 25.97 cm, supero-inferior 22.87 cm, and antero-posterior 3.39 cm per tissue (Figure 21). Moreover, it seemed that there was a weak correlation between BMI and breast tissue weight (correlation index of 0.076 and covar index of 277.836).

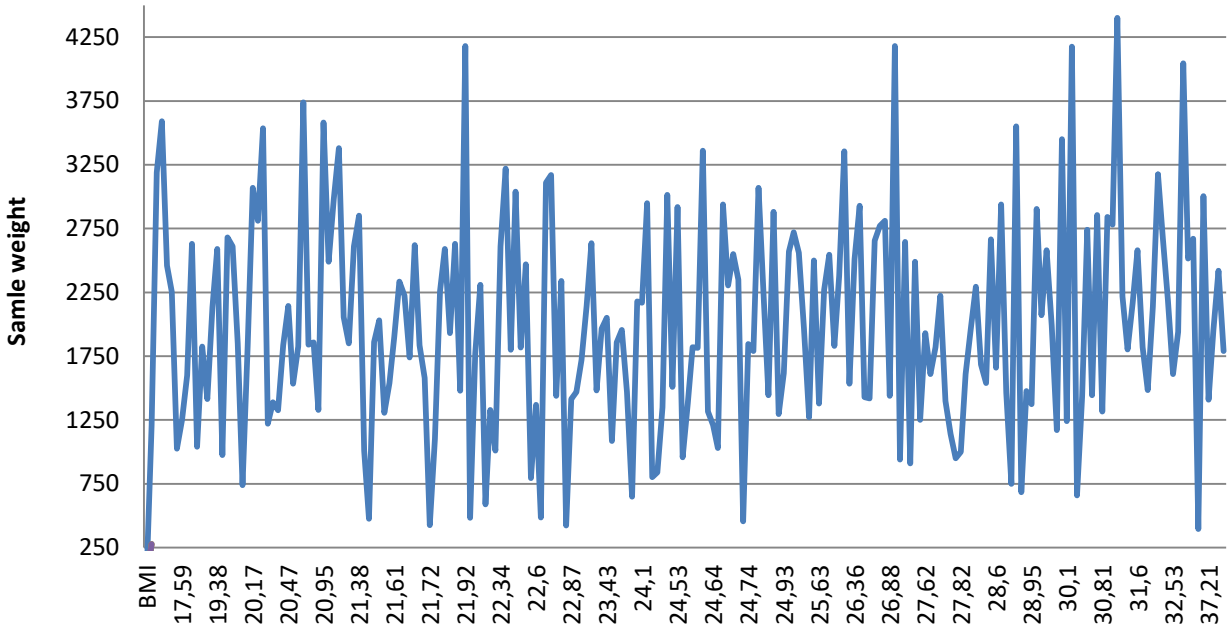
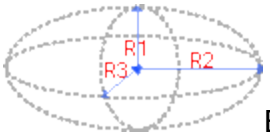


Figure 21. BMI and mean tissue weight/cadaver. BMI is presented on the x-axis and breast weights on the y-axis. Only a weak correlation between BMI and breast tissue weight was observed.

In volumetric terms, the breast tissue was submitted to imaging, and in order to approximate its shape to a hemi-ellipsoid, the following calculus was applied:



Ellipsoid dimensions and ellipsoid Formula (Knud Thomsen):

$$V = \frac{4}{3}\pi R_1 R_2 R_3$$ divided by 2.

The total breast tissue volume elaborated was 836821.9 cm^3 (836,822L). The correlation between BMI and Total Breast Volume (TBV) is presented in Figure 22. The total volume of breast tissue created was 836821.9 cm3 (836,822L). The observed correlation between BMI and TBV is depicted in the following graph (Figure 22). Breast volume and BMI appear not to correlate (correlation index of 0.008).

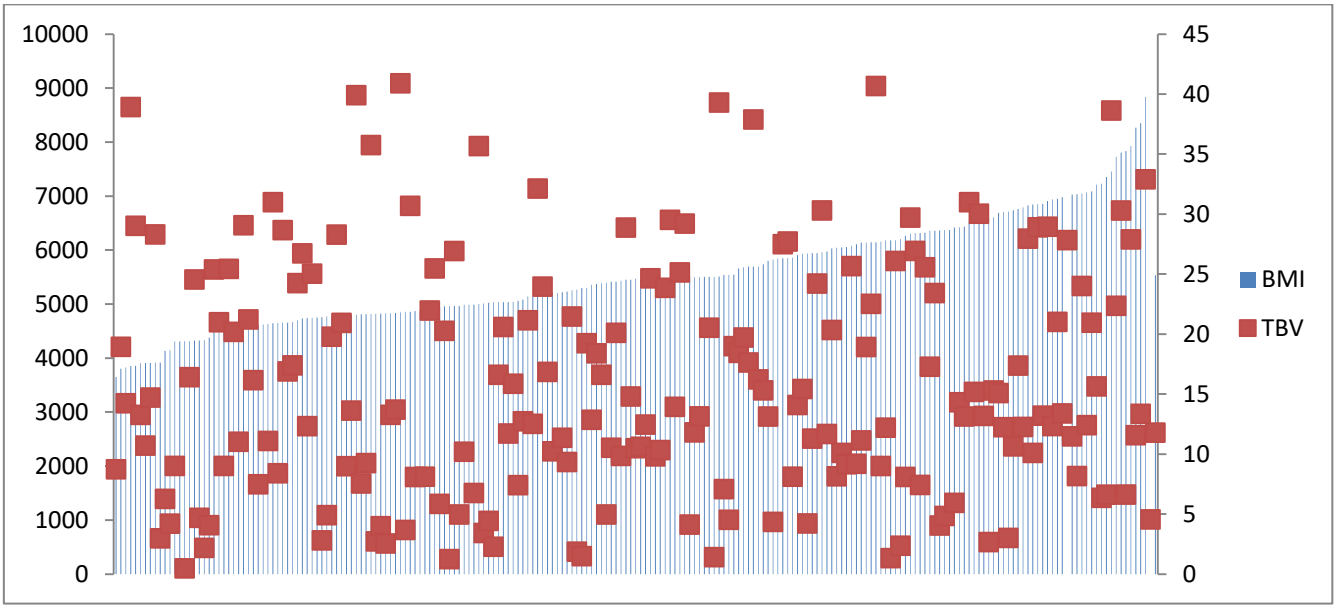


Figure 22. Correlation between BMI and total breast volume. BMI is represented by blue columns and TBV using red color. Apparently, there was no correlation between the two parameters.

Breast density and BMI appear to have a minor correlation, with a correlation index of 0.02 and a covar index of 0.09 (Figure 23).

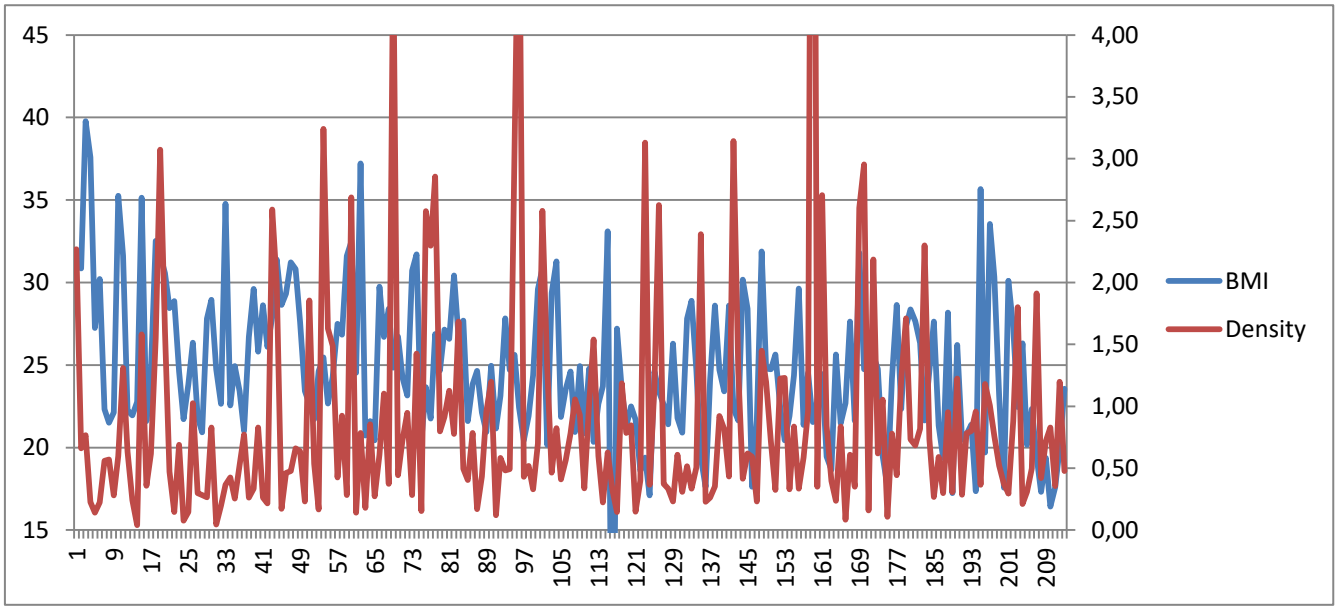


Figure 23. BMI and breast density. BMI is represented by blue lines and breast density by red. A minor correlation between the parameters was noticed.

BI-RADS classification revealed alteration 1 in 236 (54.50%), 2 in 189 (43.6%), and 3 in 0 (0%; as per the study protocol, BI-RADS 3 alteration is detected, it should be classified as 4a and subjected to biopsy because there do not exist the chance of 6 months control), 4a in 5 (1.15%), and 4b in 3 breast samples (0.69%; Figure 24).

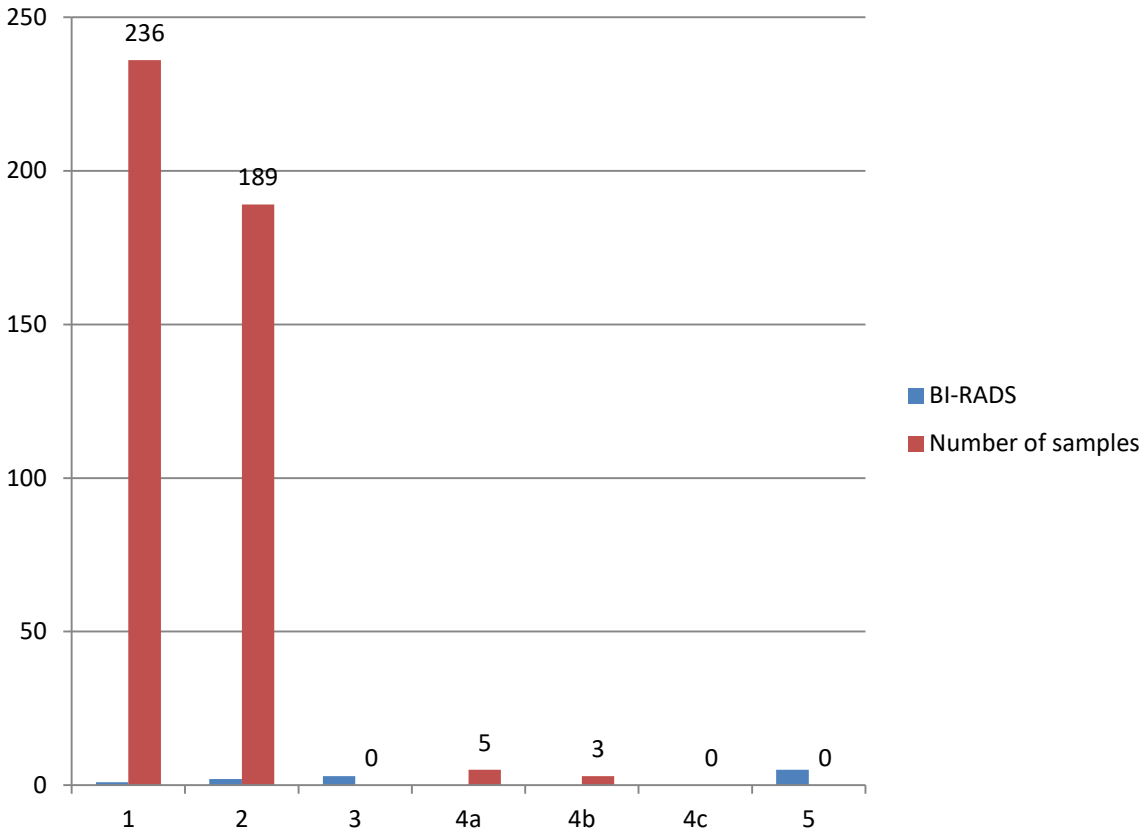


Figure 24. Samples and their BI-RADS classification. The x-axis denotes the classes of samples and the y-axis indicates the number of samples in each class.

In general, as shown in Table 14 and Figure 25, an objective examination (OE), that is, inspection and palpation, even if performed by an exclusively dedicated breast surgeon, cannot be used to detect breast alterations.

BI-RADS	Normal OE	Pathologic OE
1	236	0
2	209	1
4a	2	3
4b	1	2

Table 14. BI-RADS classes and number of objective examinations.

There was one false-positive result: pathologic OE with no imaging correspondence (0.23% more biopsies) and three false negatives, normal OE where biopsy has been performed for imaging alterations of 4a and 4b (missing the rest of 37.5% of breast changes). This finding points out that an objective exam with a high false-negative rate cannot be used as a screening method.

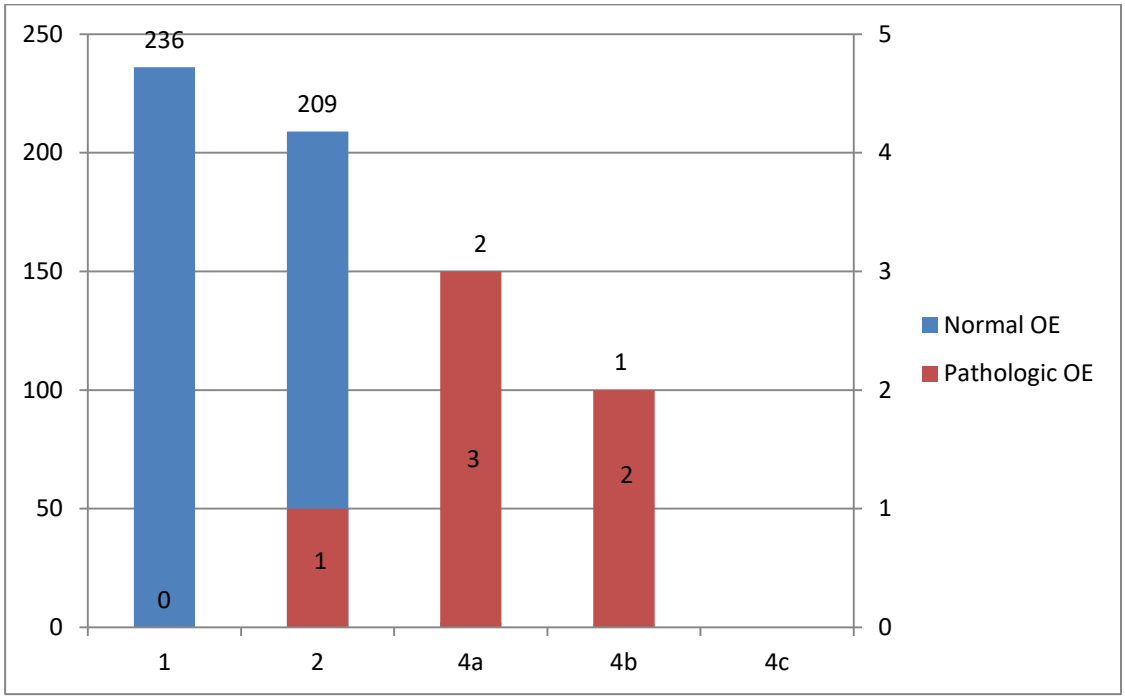


Figure 25. Imaging versus objective examinations. Normal OE is represented by blue color while pathologic OE by red. It was evident that OE has high false-negative rate.

The mammographic analysis of the samples revealed benign microcalcifications in 42 cases, 35 of which were dispersed and seven were localized (Figure 26). Moreover, benign macrocalcifications were detected in 13 cases, mostly localized in the upper quadrants. Furthermore, in 28 cases, both types of benign calcifications were present. Besides, plasma cell mastitis was found in eight cases.

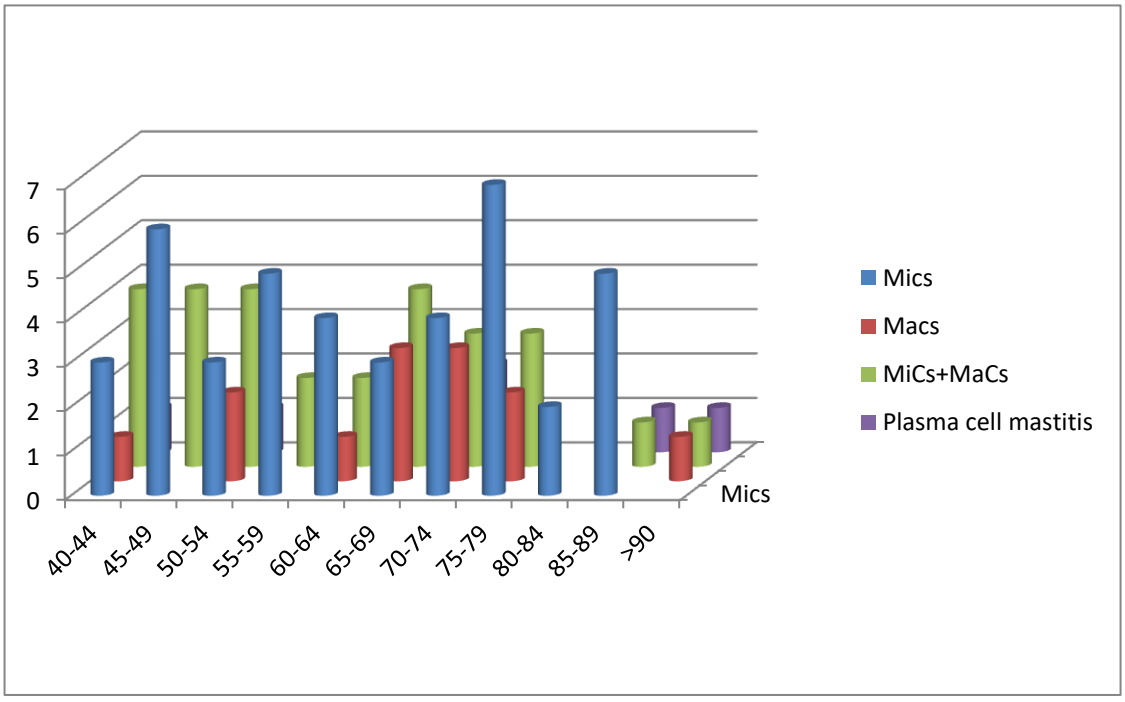


Figure 26. Mamographic analysis of the BI-RADS 2 specimens. Age groups are presented on the x-axis and the number of cases on the y-axis. Microcalcifications are represented by different colors.

The samples' ecography revealed cysts in 14 cases, ductal ectasia in 13 cases, both types of lesions in eight cases, lipomas in three cases, and steatonecrotic lesions in five cases (Figure 27). Moreover, six cases had benign axillary adenomegalies, and two had intramammary adenomegalies.

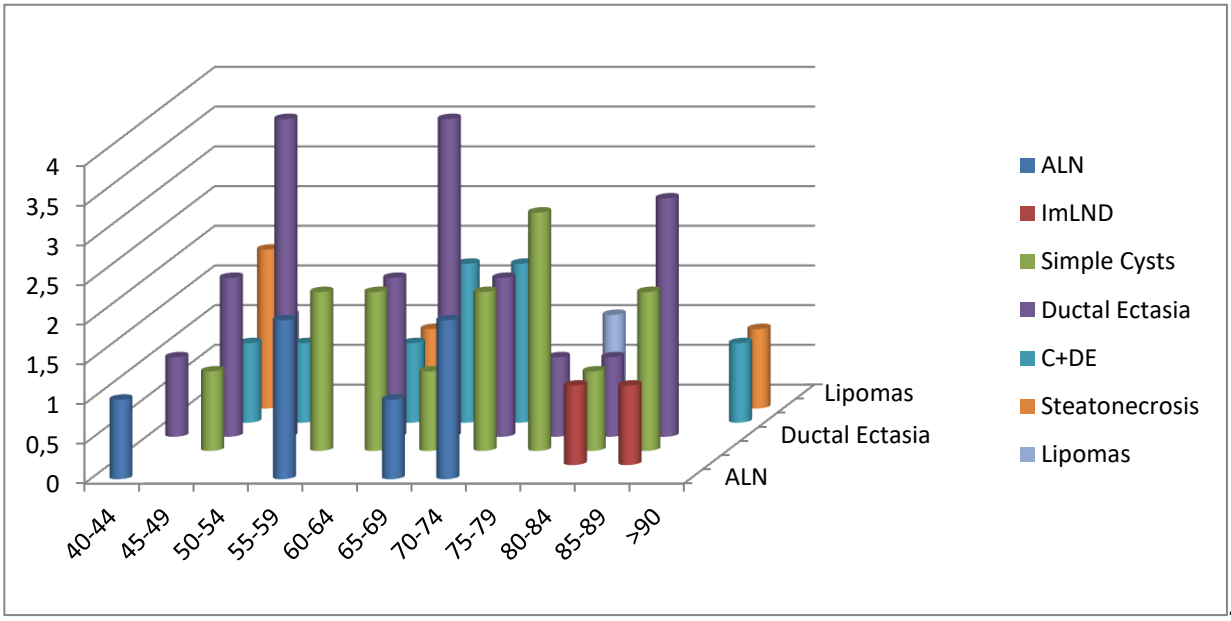


Figure 27. Ecographic analysis of the BI-RADS 2 specimens. Age groups are presented on the x-axis and the number of cases on the y-axis.

Table 15 presents the details of excisional biopsies performed on corpses. Moreover, graphic representation of biopsies and their age-related distribution is presented in Figure 28. Concerned 4a (five cases) and 4b BI-RADS (three cases) classification changes were noticed.

Age	Corpses	Eco	Mamo	Bi-rads	Histology
40-44	1	25mm	miCs	4b	FbrQ
45-49					
50-54					
55-59	2	0,8-10		4a/4a	FAD/steaton
60-64					
65-69	1	40		4b	FbrQ
70-74					
75-79	3	25/15/0,8		4b/4a/4a	Calcif Cyst/Hamartoma/FAD
80-84	1	18	miCs	4a	FbrQ
85-89					
>90					

Table 15. Biopsied corpses with respect to different age groups.

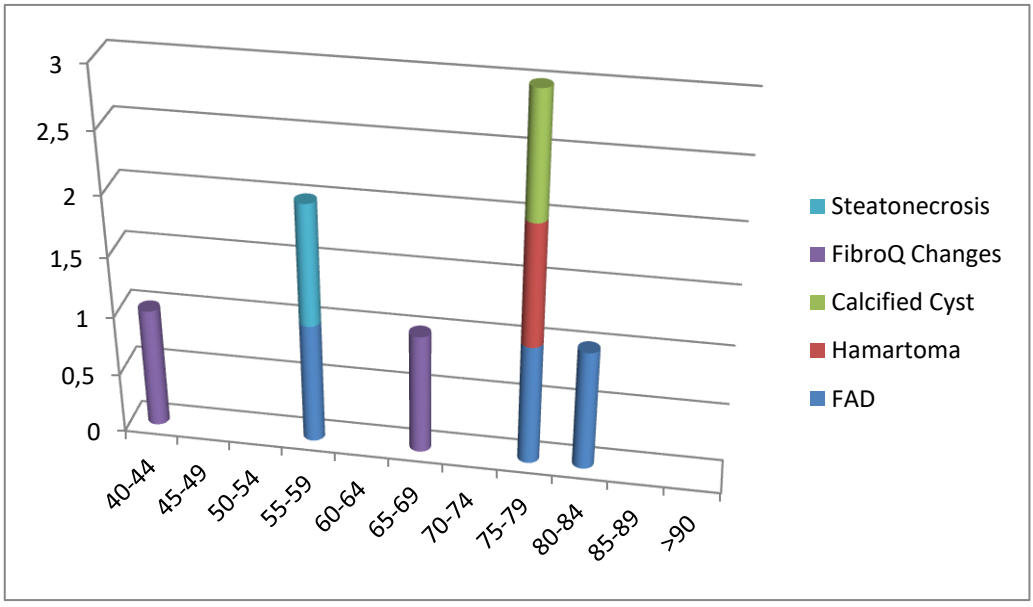


Figure 28. Graphic representation of biopsies and their age-related distribution. Age groups are presented on the x-axis and the number of cases on the y-axis.

The biopsied cadavers were:

1. A 42-years-old Negroid female with a pathologic left breast palpation and 4b BI-RADS due to a 25 mm ill-defined lesion in the upper quadrants. Histology was of fibroquistic changes in the area.
2. A 43-years-old Caucasoid female with normal left breast palpation and a 4b BI-RADS due to a vague nodular, ill-defined area of the inner quadrants. Histological analysis was of fibroquistic changes.
3. A 55-years-old Caucasoid female with pathologic right breast palpation and 4b BI-RADS due to a nodular lesion in the inner quadrants. Histology was of a 10 mm steatonecrosis area.
4. A 57-years-old Caucasoid female with normal right breast palpation and 4a BI-RADS due to a 0.8mm nodular lesion in the inner quadrants. Histology was of simple fibroadenoma.
5. A 75-years-old Caucasoid female with a pathologic left breast palpation and 4b BI-RADS due to an external quadrant nodular lesion associated with microcalcifications. Histology was of a 10 mm calcified fibroadenoma and intraductal microcalcification.

6. A 76-years-old Caucasoid female with a pathologic right breast palpation and 4a BI-RADS because of a nodular lesion in the central quadrants associated with macrocalcifications. Histology was of a 25 mm partially calcified microcyst.
7. A 79-years-old Caucasoid female with a pathologic right breast palpation and 4a BI-RADS due to a nodular lesion in the external quadrants associated with macrocalcifications. Histology was of a 25 mm hamartoma.
8. An 80-years-old Caucasoid female with normal left breast palpation and 4a BI-RADS due to a nodular lesion in the external quadrants associated with macrocalcifications. Histology analysis was of fibroquistic changes.

No other biopsy has been performed, and no silent breast cancer was detected.

4.2.2 Correlation analyses

Correlation analysis was conducted on SPSS to determine the relationship of the gland's BI-RADS with age, weight, and BMI of the female corpses. The correlation was tested at a 95% confidence interval (CI), and the significance value (2-tailed) was used as a criterion to decide whether the relationship between variables was significant or not. The correlation matrix is given in Table 16. The results indicated that the variable gland's BI-RADS has a significant relationship with the BMI of the female corpses as the significance value of the relationship was .031, that is, less than .05. Based on positive signs of the Pearson correlation value, the relationship was significantly positive. As a result, the BI-RADS grade found in the female corpses increases as their BMI rises. The results also demonstrated an insignificant relationship of the gland's BI-RADS with age and weight of female corpses; the respective significance values were .860 and .441, *viz*. higher than .05. Hence, the age and weight of female corpses are unrelated.

		1	2	3	4
Gland's BI-RADS	Pearson Correlation	1	-.008	-.037	.143
	Sig. (2-tailed)		.860	.441	.031
Age	Pearson Correlation		1	-.030	.008
	Sig. (2-tailed)			.542	.902
Weight	Pearson Correlation			1	.175
	Sig. (2-tailed)				.009
BMI	Pearson Correlation				1
	Sig. (2-tailed)				

Table 16. Correlation of gland's Bi-RADS with age, weight, and BMI of female corpses.

The correlation analysis was also conducted to determine the relationship of the cause of death with the results of mammography, ecography, and gland's BI-RADS of female corpses, as shown below in Table 17. The results indicated the cause of death has an insignificant correlation with mammography, ecography, and gland's Bi-RADS of female corpses as their respective significance values were .058, .333, and .067 (greater than .05). Thus, the results of mammography, ecography, and gland's BI-RADS had no correlation with the cause of death of the female corpses examined in this research.

		1	2	3	4
Cause of death	Pearson Correlation	1	.164	-.094	-.088
	Sig. (2-tailed)		.058	.333	.067
Mammography	Pearson Correlation		1	-.003	.127
	Sig. (2-tailed)			.985	.143
Ecography	Pearson Correlation			1	.328
	Sig. (2-tailed)				.001
Glands (Bi-RADS)	Pearson Correlation				1
	Sig. (2-tailed)				

Table 17. Correlation of cause of death with the results of mammography, ecography, and gland's Bi-RADS of female corpses

4.2.3 Hypothesis testing

The study intended to quantify the existing female silent breast cancers that had not yet manifested clinically. The null hypothesis stated that the natural reservoir of silent breast cancer is not superior to the actual incidence of the diseases. The alternative hypothesis stated that the natural reservoir of silent breast cancer is superior to the actual incidence of the disease.

The null hypothesis was to be tested in the female gender once 163 samples were obtained; however, since distributions do not follow a Gaussian curve, we proceeded to further collections to achieve a sample size that allows the thesis hypothesis to be tested and verified.

The cross tabulation analysis was performed in SPSS to test the null hypothesis. The gland's BI-RADS results were expressed in seven BI-RADS categories, namely;

- BI-RADS 1: negative
  - Symmetrical and no masses, architectural distortion, or suspicious calcifications
- BI-RADS 2: benign
  - 0% probability of malignancy
- BI-RADS 3: probably benign
  - <2% probability of malignancy
  - Short interval follow-up suggested
- BI-RADS 4: suspicious for malignancy
  - BI-RADS 4A: low suspicion for malignancy (2-9%)
  - BI-RADS 4B: moderate suspicion for malignancy (10-49%)
  - BI-RADS 4C: high suspicion for malignancy (50-94%)
  - Biopsy
- BI-RADS 5: highly suggestive of malignancy
  - >95% probability of malignancy

The cross-tabulation results of the gland's BI-RADS against the mammography of female corpses are shown in Table 18.

			Mammography						
			Plasma cell mastitis	miCs	miCs + macroCal	MacroCal	Macroc	Nodular	Total
Glands (BI-RADS)	BI-RADS 2: benign findings	Count	9	64	38	17	1	0	129
		% within Glands (Bi-RADS)	7.0%	49.6%	29.5%	13.2%	.8%	.0%	100.0%
		% of Total	6.7%	47.4%	28.1%	12.6%	.7%	.0%	95.6%
	BI-RADS 4a: low suspicion for malignancy (2-9%)	Count	0	2	0	1	0	1	4
		% within Glands (Bi-RADS)	.0%	50.0%	.0%	25.0%	.0%	25.0%	100.0%
		% of Total	.0%	1.5%	.0%	.7%	.0%	.7%	3.0%
	BI-RADS 4b: moderate suspicion for malignancy (10-49%)	Count	0	1	1	0	0	0	2
		% within Glands (Bi-RADS)	.0%	50.0%	50.0%	.0%	.0%	.0%	100.0%
		% of Total	.0%	.7%	.7%	.0%	.0%	.0%	1.5%
Total		Count	9	67	39	18	1	1	135
		% within Glands (Bi-RADS)	6.7%	49.6%	28.9%	13.3%	.7%	.7%	100.0%
		% of Total	6.7%	49.6%	28.9%	13.3%	.7%	.7%	100.0%

Table 18. Glands (BI-RADS) × Mammography Crosstabulation

According to the findings in Table 18, the female corpses' alterations classified as 'Plasma cell mastitis, "miCs,"miCs + macroCal,' 'MacroCal,' 'Macroc,' and 'Nodular.' It was evident that 95.6% of the female corpses had nonsuspicious findings, while only 3% and 1.5% had BI-RADS 4a and BI-RADS 4b, respectively. Based on mammography results, 47.4% of the female corpses with benign findings had 'miCs,' 28.1% had 'MiCs + MacroCal,' 12.6% had 'mics + MacroC,' and 6.7% had plasma cell mastitis. The mammography results supported the null hypothesis discussed above. An insignificant percentage of female corpses needed a biopsy. The results are also diagrammatically represented in Figure 29.

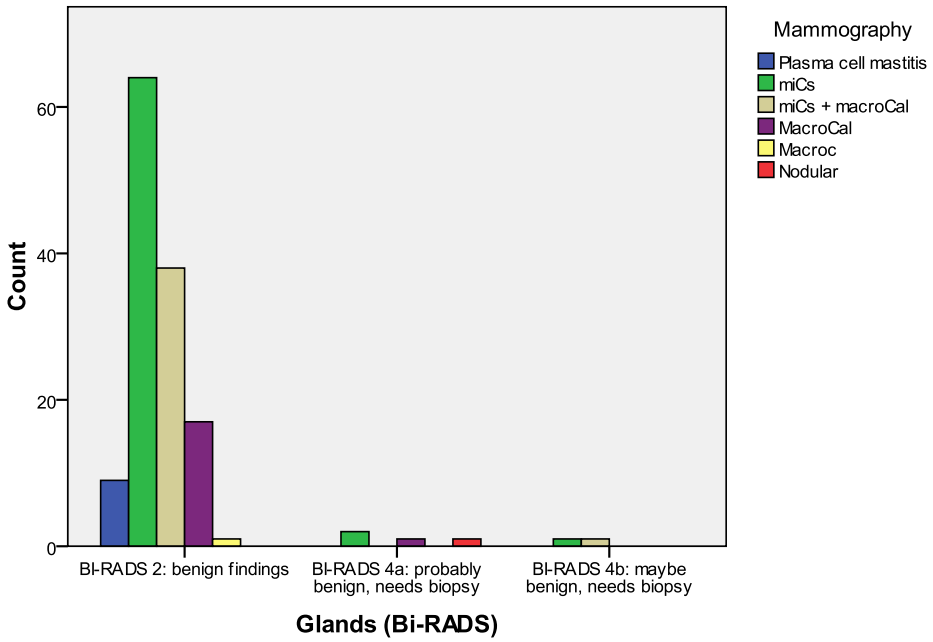


Figure 29. Bar chart of gland's (Bi-RADS) × Mammography crosstabulation. Bi-RADS classes are presented on the x-axis and count on the y-axis.

Subsequently, the gland's BI-RADS results of the female corpses were cross-tabulated against the ecography results (Table 19). The results evinced that 8.3% of the female corpses had no alterations, and 85.2% had benign findings, with only 3.7% having BI-RADS 4a and 2.8% having BI-RADS 4b. Hence, based on ecography results, most of the female corpses with benign findings exhibited simple cysts, simple cyst (micro), ductal ectasia, and simple cyst and ductal ectasia.

			Ecography									Total
			Simple cyst	Simple cyst (micro)	Ductal ectasia	Axilarry lymphnodes	Steaton ecrosis	Intramammary lymphnodes	Lipoma	Nodular lesion	Simple cyst and ductal ectasia	
Glands (Bi-RADS)	Bi-RADS 1: no alterations found	Count	0	0	0	9	0	0	0	0	0	9
		% within Glands (Bi-RADS)	.0%	.0%	.0%	100.0%	.0%	.0%	.0%	.0%	.0%	100.0%
		% of Total	.0%	.0%	.0%	8.3%	.0%	.0%	.0%	.0%	.0%	8.3%
	BI-RADS 2: benign findings	Count	20	18	25	1	6	3	3	1	15	92
		% within Glands (Bi-RADS)	21.7%	19.6%	27.2%	1.1%	6.5%	3.3%	3.3%	1.1%	16.3%	100.0%
		% of Total	18.5%	16.7%	23.1%	.9%	5.6%	2.8%	2.8%	.9%	13.9%	85.2%
	BI-RADS 4a: probably benign, needs biopsy	Count	0	0	0	0	0	0	0	4	0	4
		% within Glands (Bi-RADS)	.0%	.0%	.0%	.0%	.0%	.0%	.0%	100.0%	.0%	100.0%
		% of Total	.0%	.0%	.0%	.0%	.0%	.0%	.0%	3.7%	.0%	3.7%
	BI-RADS 4b: maybe benign, needs biopsy	Count	0	0	0	0	0	0	0	3	0	3
		% within Glands (Bi-RADS)	.0%	.0%	.0%	.0%	.0%	.0%	.0%	100.0%	.0%	100.0%
		% of Total	.0%	.0%	.0%	.0%	.0%	.0%	.0%	2.8%	.0%	2.8%
Total		Count	20	18	25	10	6	3	3	8	15	108
		% within Glands (Bi-RADS)	18.5%	16.7%	23.1%	9.3%	5.6%	2.8%	2.8%	7.4%	13.9%	100.0%
		% of Total	18.5%	16.7%	23.1%	9.3%	5.6%	2.8%	2.8%	7.4%	13.9%	100.0%

Table 19. Gland's Bi-RADS × Ecography crosstabulation. The crosstabulation indicated that most of the female corpses with benign findings exhibited simple cysts.

The gland's BI-RADS and ecography results are presented diagrammatically in Figure 30, given below.

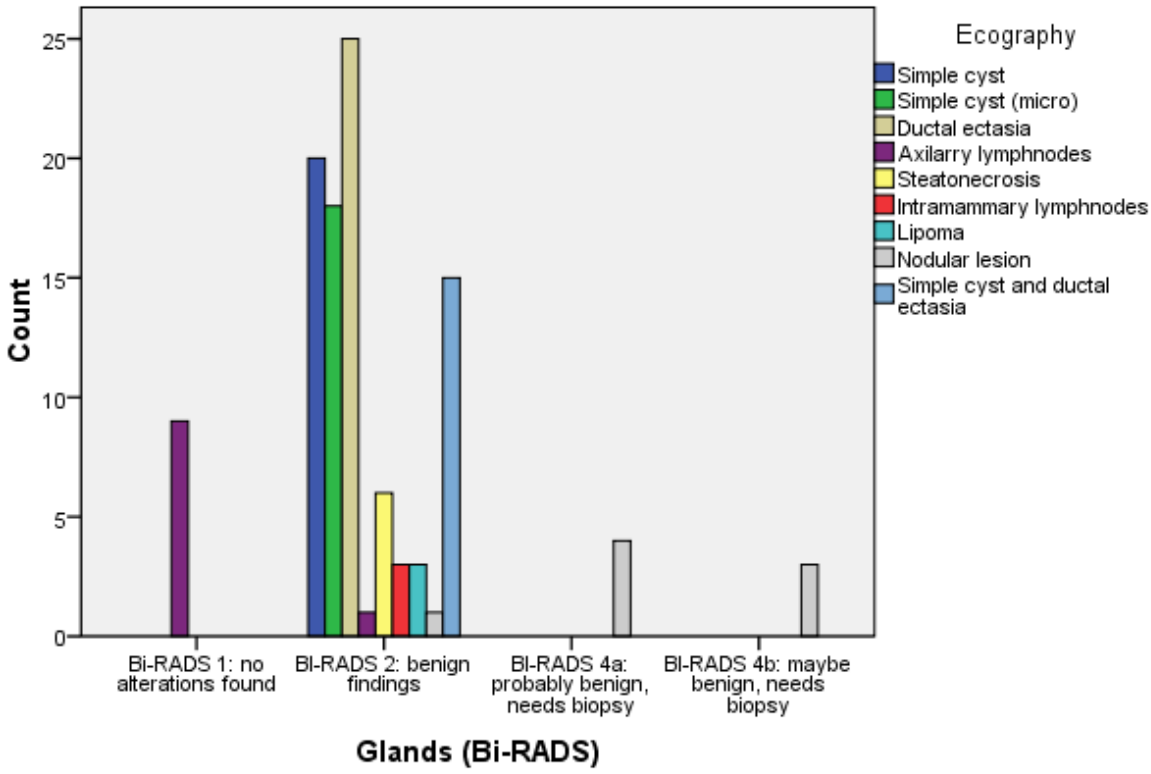


Figure 30. Bar chart of Gland's Bi-RADS × Ecography crosstabulation. Bi-RADS classes are presented on the x-axis and count on the y-axis.

Based on the results of cross-tabulation it was evident that no malignant glands were found by ecography and mammography in the majority of the female corpses. However, to statically validate these findings, the level of significance of this result is evaluated by conducting correlation analysis as detailed below.

The correlations of the gland's Bi-RADS with the results of ecography and mammography are demonstrated in Table 20. The correlation of the gland's Bi-RADS with ecography results was significant as the significance (2-tailed) value was .001 (less than 0.05). Moreover, the Pearson correlation value was positive, indicating that the relationship between the gland's Bi-RADS and ecography results was positive. However, the correlation of the gland's Bi-RADS with mammography results was insignificant because the respective (2-tailed) significance value was .143 (greater than .05). As the correlation value was insignificant, no relationship of the gland's Bi-RADS was found with the results of mammography. It means ecography findings might be useful in screening the general population complementing mammography.

		1	2	3
Glands (Bi-RADS)	Pearson Correlation	1	.328	.127
	Sig. (2-tailed)		.001	.143
Ecography	Pearson Correlation		1	-.003
	Sig. (2-tailed)			.985
Mammography	Pearson Correlation			1
	Sig. (2-tailed)			

Table 20. Correlations of glands with the results of ecography and mammography

The statistical analysis did not find a significant incidence of breast cancer in the female corpses, implying that the image detected silent breast cancer is not superior to the true incidence in the general population.

Therefore:

We can conclude that the actual cases of female breast cancer manifest themselves, and thus, we accept the null hypothesis that the natural reservoir of silent breast cancer is not superior to the actual incidence of the disease.

5 Discussion

5.1 Male brest cancer

5.1.1 Portuguese National Data

Thorough research on available national public databases was conducted yet leading to scant data. Male breast cancer incidence as recorded by the National Oncology Registry (RON; a national platform where all malignancies are individually registered) allowed collecting some data for 2001 to 2010. MBC has been registered for 477 cases (data for the years 2002-2004 is missing). Male breast cancer mortality was assessed using the National Statistics Institute (INE) data. In the following graphic (Figure 31), data show that: a) the incidence of MBC in the Portuguese population is of a medium of 68.14 new cases/year, with no discernible trend (rising, decreasing, or plateau) and b) the mortality rate due to MBC in the same population is 22.8 individuals/year, presenting a slight decrease over the last two and half decades (R^2=0.0196).

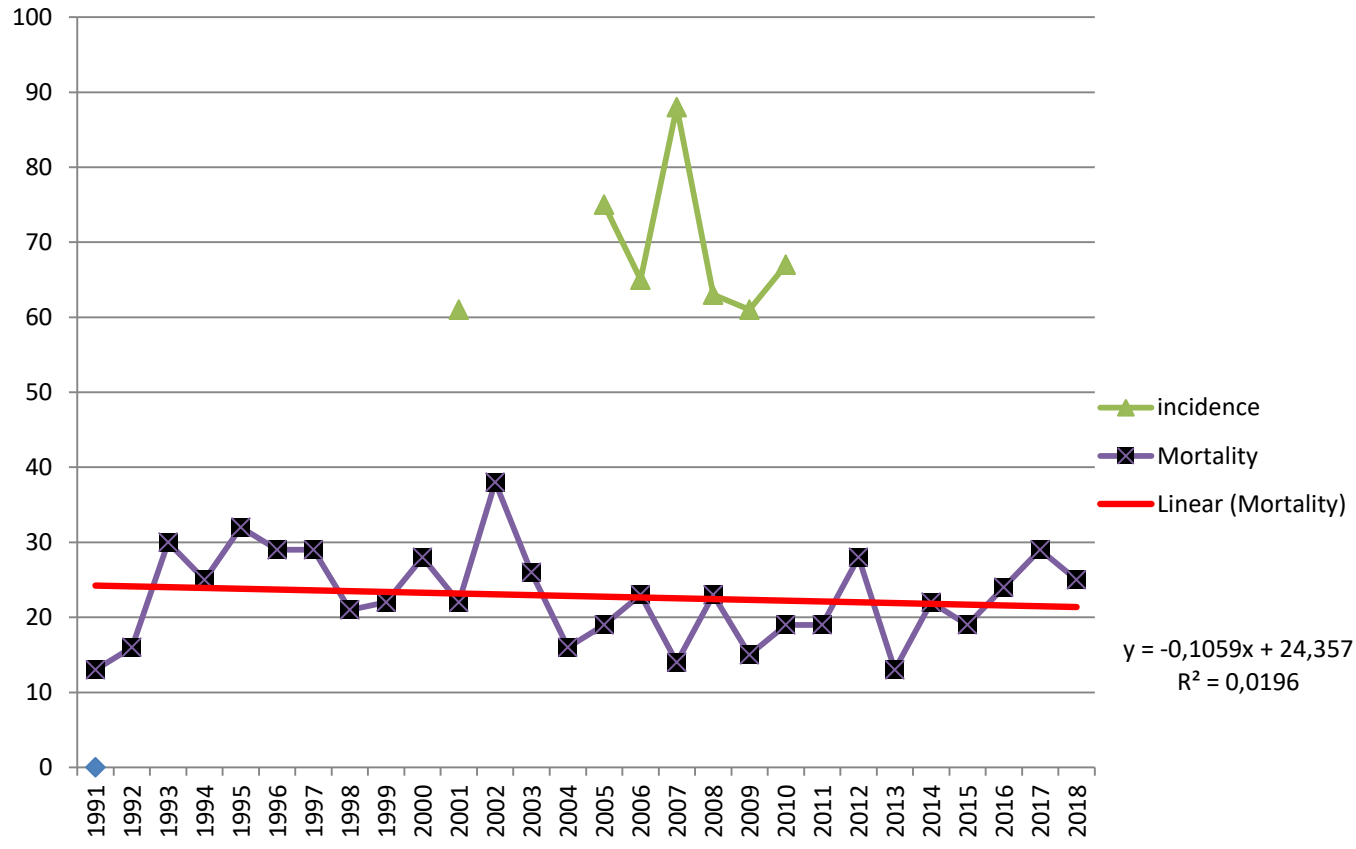


Figure 31. Portuguese MBC data incidence and mortality

5.1.2 Male breast cancer and the state of art

Male Breast Cancer (MBC) is a rare disease that has received little attention in terms of transcriptional profiling or genomic role players. The foundation of male cancer is usually based on the concepts and understanding of female breast cancer (FBC) and the existing literature on female assessment. Over the years, a great deal of effort has been expended in order to answer the question: Is MBC different and more aggressive than FBC? The current review gathered data from the literature on female and male breast cancer from 2000 to 2018 to produce some conclusive results (Garcia-Saenz Ariadna, Apr. 2018)

Male breast cancer, just as FBC, is a heterogeneous disease (Little, 2017), (Deb, 2014), (Rabbee, 2016). According to recent literature and Centre for Disease Control findings, MBC may differ from FBC at the molecular level (Fentiman, 2006). Various studies have established that there are two subgroups of MBC: the luminal M1 and the luminal M2, which are distinct from the currently known subtypes of female breast cancer. Therefore, the novel subsets of the disease vary in males and females, and they have a unique characterization (Fentiman, 2006), (Shahidsales, 2017). Other studies have found that males with breast cancer have a lower chance of survival than females. A survey carried out in the United States between 2004 and 2014 indicated that even though male breast cancer cases are few, the mortality rate is higher than that of female breast cancer cases (Lee, 2009), (Kaneda, 2017).

Women's breast cancer has similarities to the one in males in some aspects. The similarities include the occurrence of invasive ductal carcinoma—frequently of positive hormone receptors ER and PR—as the most common histological type, which is often detected as a sub-areolar lamp, usually painless, with nipple retraction and bleeding (Veena, 2016), (Sharma, 2016). Another significant similarity is that, in both male and female breast cancer, a family history of breast and ovarian cancer is a risk factor of BC development.

As far as differences between male and female breast cancer are concerned, MBC is less common in males than females, accounting for nearly 1% of the total number of FBC (Karangadan, 2016), (Balasundaram, 2017), (Mwakigonja, 2017), (Roed Nielsen, 2016). Secondly, male breast cancer is diagnosed in older men. The mean age of breast cancer diagnosis in men is 67 years, compared to 52 years in women. Moreover, lobular carcinoma is also relatively less common in men (Dwivedi, 2017), (Mann, 2017). Furthermore, the prevalence of germline BRCA2 mutation in male breast cancer patients is 14%, while BRCA1 is less common, occurring at a rate of 4% (Andleeb, 2016), (Deb, 2014). To summarize, it seems that MBC affected patients are older, get diagnosed with a substantial delay (more

than one year in almost half of cases), have a slightly less 5y survival in stages I and II, and even worse in stages III and IV. MBC presents with a higher incidence in advanced stages and axillary evolvement. However, some studies suggest an equal overall disease-specific survival for both sexes, attributing the increased mortality rate in males to other non-cancer-specific mortality. (Fentiman, 2017)

Gender differences are significant at the molecular level, with 95% of MBC being luminal A or B (Ge Y, 2009), (Shaaban, 2012), compared to 73% of female breast cancer (Sorlie T, 2003). Both the HER2 and basal phenotypes are uncommon in men. Genetically, approximately 10% of MBC cases have BRCA2 mutations, while BRCA1 mutations are associated with less than 1%. Male breast cancer has been more linked with BRCA2 mutations, which account for 4–40% of hereditary compared to 5–10% in FBCs (Sousa B., 2013)

The following Figure (32) summarizes the key differences between MBC and FBC (Giordano, 2018).

Factor	Men	Women
Risk of breast cancer (%)		
General population[2]	<1	12
Carrier of *BRCA1* mutation[3,4]	1	65
Carrier of *BRCA2* mutation[3,4]	7	45
Clinical presentation		
Median age at diagnosis (yr)[5]	67	62
Median tumor diameter (mm)[6]	20	15
Nodal involvement (% of patients)[6]	42	33
Pathological characteristics (%)		
Invasive lobular subtype[5]	1	12
Estrogen-receptor–positive[2,7]	99	83
HER2-positive[2,7]	9	17
Androgen-receptor–positive[7,8]	97	61
Somatic mutations[9]	Mutations in DNA-repair genes more likely in men	Loss of 16q and mutations in *PIK3CA* and *TP53* more likely in women
Subtypes (%)[2,7]		
HR-positive, HER2-negative	90	71
HR-positive, HER2-positive	9	12
HR-negative, HER2-positive	<1	5
HR-negative, HER2-negative	<1	12
5-Yr overall survival (%)[6]		
Stage I	87	90
Stage II	74	82
Stage III	57	57
Stage IV	16	19

Fi cer

Cardoso et al. (Cardoso, 2018) reported that while MBC is distinct from FBC, the actual treatment of MBC is based on FBC protocols, with poor outcomes. Their study enrolled 1483 patients, at various participating institutions, with confirmed breast cancer diagnosed between 1990 and 2010. Biological material was handled and analyzed centrally. The findings suggested that most male BC cases were invasive ductal carcinomas, grade 2, and almost always ER+, PR+, and AR+. A trend towards higher OS was observed in patients with highly ER+ disease, highly PR+ disease, and highly AR+ compared with the low expression of the receptor (Allred scores 3–6). HER-2 expression was uncommon, and no association between outcome and HER-2 status was seen. High (≥20%) Ki67 expression was observed in only 24.9% of cases. The majority of patients had a Luminal B-like/HER-2-negative (48.6%) or a Luminal A-like (41.9%) disease. A small number of HER-2+ and triple-negative BC was detected. Although 48.5% of patients had T1 tumors, only 4% had BCs. SLNB has seen a significant trend towards less aggressive axillary nodal management over the years.

Adjuvant radiotherapy (RT) was not delivered to 45% of patients treated with, nor to a significant proportion of patients (30.7%) with node-positive tumors treated with mastectomy. Since current recommendations suggest the use of similar algorithms for RT decision-making in males as in female BC patients, the low rates of adjuvant RT are a major concern as male patients usually have a higher stage at diagnosis. A significant trend toward increased chemotherapy (anthracycline) has been observed over time, with adjuvant ET being administered to only 76.8 percent of patients. *"The reasons for this under-use of an effective and low toxicity therapy are unknown."* fortunately increasing the latest years (Cardoso, 2018).

Another large study by Fei et al. (Fei Wang, et al., 2019) pointed out that male patients with breast cancer significantly differed from their female counterparts by older age at diagnosis, a higher proportion of ER-positive subtype or advanced disease, and less likelihood of receiving conventional treatment. Men had higher mortality than women overall and across disease stages, particularly for ER-positive breast cancer. Clinical and treatment characteristics were the most common factors in sex-based disparity in mortality, but the differences persisted even after adjustment for age, race/ethnicity, clinical and treatment characteristics, and access to care.

5.1.2.1 Epidemiology and Risk factors

As mentioned earlier, male breast cancer is a rare malignancy that represents a small percentage of 0.5 to 1 of all the existing breast cancer cases in the United States (Kornegoor, 2012). The same number applies to the European countries as well (Gomberawalla, 2018).

(Siegel, 2018) estimated 2500 MBC patients in the United States for the year 2018, while 500 men were estimated to die from the disease. According to data from the Surveillance, Epidemiology, and End Results (SEER) program, the age-adjusted incidence rate in the general population increased from 0.85 cases per 100,000 men in 1975 to 1.43 cases per 100,000 in 2011 (Howlader, 2018). The lifetime risk of breast cancer for a man is approximately 1:1000, as compared with 1:8 for a woman (Society, 2018). As is the case with many cancers, breast cancer in men is an age-related disease, with incidence rates rising steadily with age. For men, the average age at diagnosis is approximately five years older than for women (67 years vs. 62 years) (Giordano. SH, 2004). Moreover, Black men appear to be at a greater risk than non-Hispanic white men. (Howlader, 2018) (O'Malley, 2005) Further, men who have a first-degree relative with breast cancer are twice as likely to develop the disease (Brinton, 2008)

Of all the reported new cases of male breast cancer in the United States in 2017, mortality remained high (Kornegoor, 2012). The rate of survivors is almost half the number of those that are affected. Like their female counterparts, the males share similar risk factors like family history, BRCA2 mutation that characterizes male breast cancer, and advancing age. Men with XXY karyotype have a 50-fold increased risk of developing BC (Gomberawalla, 2018) (Streng, 2018). The increased risk appears to be the result of high estrogen compared to androgens due to the low levels of aldosterone and increased gonadotropins. In most cases, as mentioned earlier, the males exhibit positive ER and PR among patients with known receptor status (Eggemann, 2018) (Chang, 2006).

Several genetic conditions increase the likelihood of male breast cancer. Men with higher risk factors, sometimes, never develop the disease. Moreover, most of the patients do not exhibit apparent risk factors. Inherent mutations in the genetic makeup are a major concern in male breast cancer prevalence as men with BRCA2 gene mutations are at a higher risk of developing MBC. The lifetime risk in this scenario is about six out of one hundred. However, the case of BRCA1 mutation is complex since the risk of experiencing the disease is like one in one hundred people. Even though most cases occur in families with a history of breast cancer, some do not have a history of cancer. The mutations in the CHEK2 genes, PTEN genes, and PALB2 types of genes have also been found to be responsible for breast cancers in males.

Mutations in *BRCA* are among the most evident risk factors for breast cancer in men. *BRCA1* and *BRCA2* are tumor-suppressor genes involved in DNA repair; mutations in these genes

are found in 5 to 10% of women with breast cancer and confer a 45 to 65% risk of breast cancer by the age of 70 years (Antoniou. A, 2003). Population-based studies have shown that 0 to 4% of men with breast cancer have *BRCA1* mutations, and 4 to 16% have *BRCA2* mutations (Friedman, 1997) (Ottini. L, 2003) (Basham, 2002) (Ding, 2011). *BRCA* mutations account for a higher percentage of cases in populations with founder mutations; for instance, in Iceland, a *BRCA2* founder mutation is implicated in 40% of cases of male breast cancer. (Thorlacius, 1998) The risk of breast cancer is substantially lower among healthy men with *BRCA* mutations than among healthy women with *BRCA* mutations. Using data from 1939 families in the National Cancer Institute's Cancer Genetics Network, Tai and colleagues evaluated the risk of breast cancer among male carriers of *BRCA* mutations. In 70-year-old men, the estimated cumulative risk of breast cancer was 1.2% for *BRCA1* mutation carriers and 6.8% for *BRCA2* mutation carriers (Tai, 2007). Data on whether the presence of a *BRCA* mutation affects the age at diagnosis or the prognosis are inconsistent (Kwiatkowska, 2003) (Deb, 2012).

Several genes have also been identified that confer a moderate risk of breast cancer for men and women. *CHEK2* encodes a cell-cycle checkpoint kinase involved in DNA-repair pathways. According to a report from the CHEK2– Breast Cancer Consortium, a truncating mutation (*CHEK2**1100delC) in men increases the risk of breast cancer by a factor of 10 compared to men who do not have this mutation (Meijers-Heijboer, 2002). Other case series studies have had inconsistent results and taken as a whole; these studies suggest that the *CHEK2* variant may modestly increase the risk but is unlikely to account for a substantial fraction of cases of breast cancer in men (Neuhausen, 2004) (Syrjäkoski, 2004) (Martínez-Bouzas, 2007)' (Wasielewski, 2009). Moreover, *PALB2* (partner and localizer of *BRCA2*), which encodes a BRCA2-interacting protein, has been shown to confer susceptibility to breast cancer in women (Rahman, 2007). Mutations in *PALB2* have also been reported in men with breast cancer and in families with cases of breast cancer in men, but the prevalence of *PALB2* mutations in men with breast cancer is reported to be only 1 to 2%. (Ding, 2011)' (Erkko, 2007)' (Casadei, 2011)' (Adank, 2011)' (Blanco, 2012). Additionally, single-nucleotide polymorphisms in *CYP17*, *RAD51B*, and chromosomes 2q35, 5p12, 6q25.1, 10q26.13, and 16q12.1 have been linked to increasing the risk of breast cancer in men. (Young, 1999)' (Orr, 2011)' (Orr, 2012) Furthermore, mutations in *PTEN* (resulting in Cowden's disease) and the androgen receptor also prevail in men with breast cancer. (Fackenthal, 2001) (Wooster, 1992)

Radiation exposure has been linked to an increased risk of breast cancer in men. (Thomas, 1994) The most compelling evidence comes from studies of atomic bomb survivors. (Ron,

2005)' (Little, 2017) A cohort of 45,880 Japanese men was followed from 1958 through 1998, and rates of cancer were reported. During the mentioned timeline, the incidence of breast cancer in men increased, with a dose–response relationship between the estimated radiation dose to the breast and the incidence of breast cancer, providing convincing evidence of the link between radiation and breast cancer in men.

Elevated levels of estrogen are also thought to predispose men to breast cancer. The Male Breast Cancer Pooling Project conducted a nested case–control study of estrogen and androgen levels in relation to the risk of breast cancer in men. Although androgen levels were not associated with the risk of breast cancer, circulating estradiol levels were. For men in the highest quartile of estradiol levels vs. those in the lowest quartile, the odds ratio for breast cancer was 2.47 (95% confidence level, 1.10 to 5.58). (Brinton, 2015) Other conditions associated with elevated estrogen levels, including gynecomastia, liver disease, testicular abnormalities, and obesity, are also linked to breast cancer in men. (Brinton, 2014)' (Thomas, 1992)' (Brinton, 2010) Moreover, Klinefelter's syndrome, or the 47, XXY karyotype, is characterized by hypogonadism and low testosterone levels and has been associated with an increased risk of breast cancer in men. According to a study from the Swedish Cancer Registry, the estimated risk of breast cancer among men with Klinefelter's syndrome was increased by a factor of 50, as compared with the risk among men without the syndrome. (Hultborn, 1997) In the UK, a cohort study involving 3518 men with Klinefelter's syndrome showed that the cumulative risk of breast cancer was 0.9% by the age of 75 years. (Swerdlow, 2005) The increased risk may be related to a high estrogen to androgen ratio in affected men.

5.1.2.2 Established biomarkers

5.1.2.2.1 Estrogen receptor (ER)

In male breast cancer classification, the most common and vital biomarker is ER (Estrogen Receptor). The history of ER in MBC dates back to the 1960s when it was first identified in female breast cancer for clinical management. ER is a primary indicator of endocrine responsiveness and is a prognostic factor for both male and female early recurrence. In male breast carcinogenesis, ER plays an essential role. Information on breast carcinogenesis is crucial as it forms the mainstay of breast cancer endocrine therapy. According to a recent gene profiling on male breast cancer, various authors (Chikaraddi, 2012) (Moghadasi, 2018) (Soliman, 2014) (Roed Nielsen, 2016) argue that the ER status is a primary determinant of the portrait of breast cancer. Recent studies show that the increased rates in older adults, especially those over the age of fifty-five years. The latest statistics show that the amount is

up to 55% of the males over sixty-five years of age. In male BC, ER-positive tumors are generally less aggressive, well-differentiated, and have a better outcome. Despite criticism for limited prognostic value, practitioners consider ER as the most valuable single predictive factor for male breast cancer identification (Gogra. A, 2015). Simply put, ER-negative tumors almost never respond to endocrine therapy, whereas ER-positive tumors have a 50 percent chance of responding to an anti-estrogen.

5.1.2.2.2 Progesterone receptor (PR)

According to some studies (Lacle MM, 2015) (Reis, 2011), the goal of endocrine therapy is to induce PR (Progesterone Receptor), which translates into active ER signaling. It has been suggested that a positive PR tumor has a 75% chance of causing breast cancer in men. However, this assertion is questioned (Kornegoor, 2012), and it seems that there is insufficient evidence to support the predictive role of the same. Some scholars continually examine the classification role of PR as its evidence does not conclusively predict ER on the endocrine therapeutic response. For example, the PR positive tumors do not reflect the ER-negative but show 10% of the original tumor depending on the method used to detect the outcome. Hence, it is apparent that a strong PR positive reflected on ER-negative may be a false discovery of ER negativity commonly occurring in routine practice in male breast cancer. Male breast cancer ER-negative and PR positive patients benefit from endocrine therapy. However, the treatment would be most likely excluded if the decision lies on the status of ER alone.

5.1.2.2.3 Androgen receptor (AR)

Androgen receptor (AR) is a member of the nuclear steroid receptor subfamily with functional and structural similarities to ER and is involved in the regulation of cell proliferation (Labrie F, 2003) (Macedo LF, 2006) (Di Monaco M, 1995). Androgens exert anti-mitogenic effects in breast cancer cell lines and cause regression of breast tumors in rats. An increased risk of breast cancer has been observed in patients with hypoandrogenism (Bieche I, 2001) (Khalkhali-Ellis Z, 2004). Researchers report AR expression in 60–80% of the cases. Moreover, its positive correlation with ER, an association with a better outcome, and a prediction of response to anti-androgen or anti-estrogen treatment in female breast cancer cases are also reported (Zhao TP, 1988) (Gucalp A, 2012)

AR expression is common in breast cancer, and it conveys a survival advantage in women (Park, 2011) (Schippinger, 2006) (Vera-Badillo, 2013) (McNamara, 2013). However, the data for AR expression and effects on survival in men is less clear (Rayson D, 1998) (Kwiatkowska, 2003). AR positivity has been detected in 34–81% of male BC (Kidwai N,

2004). AR targeting has been a subject of interest since the 1940s, when case reports of the use of orchiectomy for treating male breast cancer were published (J H Farrow, 1942). In the 1970s, Lippman (Lippman, 1976) and colleagues tested anti-androgens in five human breast cancer cell lines and showed that some breast cancer cell lines depended on AR signaling. Recent research has confirmed their findings. Using gene expression microarrays, Ni and colleagues (Ni, 2013) discovered that the AR signaling mediates activation of Wnt and HER2 signaling pathways in patients with ER-/HER2+ breast cancer. They also demonstrated that bicalutamide, a non-steroidal anti-androgen therapy used in prostate cancer treatment, significantly inhibited the growth of established ER−/HER2+/AR+ breast cancer xenografts.

The androgen receptor plays a critical role in male breast cancer (Wenhui, 2014). Wenhui et al. (Wenhui, 2014) mentioned that having an idea about endocrine therapy can help treat estrogen receptors for patients who test positive in advanced breast cancer. Moreover, the authors suggested a relationship between male breast cancer treatment and the role of AR in the process. Their study also indicated that the AR expression did not correlate with the T-Stage and other sex hormones receptors. The patients who recorded a positive AR status displayed shorter five-year overall survival; on the other hand, the patients with the AR-negative status manifested a five-year disease-free survival. Tamoxifen therapy was relatively effective, and it yielded a positive response in patients with a negative AR status versus those with a positive status. Thus, research indicates that AR-negative patients respond better to therapy than AR-positive patients.

AR is also employed in subtyping male breast cancer. AR is a hormone receptor representing sex steroid which is expressed to be 90% PR-negative and around 54% ER-negative (Kiluk, 2011). In male breast cancer, AR is a potential therapeutic target and prognostic marker. As mentioned, researchers agree that AR plays an almost equal role as HER2. The researchers classify the PR-ER-tumor into PR-ER-AR+ and hormone receptor-negative carcinomas.

5.1.2.3 MBC sub-types

It was not until recently that the first attempts at MBC sub-classification were made. At first, the genomic profiling of MBC revealed two subgroups, namely, male-simple and male-complex (Le Tourneau, 2015). Male-simple was identified as a disease that occurs exclusively in men. The notion that MBC is a heterogeneous disease was reinforced by the unsupervised hierarchical clustering of gene expression profiling (Vermeulen, 2018). Using this approach, two distinct subtypes were identified and named luminal M1 (70%) and luminal M2 (30%). The groups varied both in terms of underlying biological processes and survival outcomes. Despite

an array of data being interrogated exclusively, to the best of our knowledge, there was no scrutiny on seven gene expression modules and a signature registering the activity of AR, and thus, the study provided further ground to the heterogeneous nature of male breast cancer.

In a gene expression profiling study that was carried out to determine differences between MBC and FBC, the results indicated approximately 1000 differentially expressed genes (M. Callari, 2011). Biologically, the gene set interpretation showed that significantly higher AR-related genes were up-regulated in MBC compared to FBC, suggesting an overall AR activation. By using FBC as a benchmark, it is possible to foresee strategies that could be employed to address the molecular consequences of AR activation in MBC and the therapeutic benefit of its pharmacological inhibition. In FBC cell lines, AR activation has opposite outcomes in relation to the ER status. For ERα-positive cells androgen, treatment exerts effects inhibiting ERα-driven proliferation (T.E. Hickey, 2012). Conversely, activation of AR signaling promotes proliferation in a subset of ER-negative BC (molecular apocrine or luminal androgen receptor) (D.R. Cochrane, 2014).

Early efficacy markers were reported coherently with bicalutamide in ER-negative/AR-positive female breast cancer (A. Gucalp, 2013). This was further supported by results from a phase 2 study with enzalutamide in triple-negative, AR-positive BC patients. Another study found an androgen-driven gene signature that was associated with better clinical outcomes (T.A. Traina, 2015). Despite this, in vivo growth inhibition of ER-positive/AR-positive tumors was discovered with enzalutamide and was associated with the high nuclear AR:ER ratio (D.R. Cochrane, 2014). Generally, the level of segmentation achieved by molecular characterization of female breast cancer, combined with the vast number of cellular and animal models available, allows researchers to decipher the different scenarios in which AR-directed drugs are more likely to be active. Significant breakthroughs have also occurred in gene expression profiling studies for classification purposes in male breast cancer. Therefore, there is a need for rigorous efforts aimed at achieving more granular taxonomy, the establishment of cell lines, and patient-derived xenografts for preclinical trials. These advances will increase the therapeutic potential of androgen receptor targeting agents in male breast cancer.

5.1.2.3.1 Luminal A male breast cancer

Luminal A is the most common subtype of cancer. In this subgroup, the characteristics of cancer are proven by the expression of ERs and PR (progressive receptors). Luminal A breast cancer manifests low-grade tumor and, in almost all cases, lacks HER2/nue proto-oncogene amplification. In addition, the Ki-67 proliferation index is low, which can assist in controlling the

rate at which cancer cells grow. The luminal-A tumor cells in male breast cancer manifest in the inner lining of luminal cells. According to Lacle et al. (Lacle MM, 2015), the percentage of luminal A cancer is between 30 and 70 percent of the total breast cancers. Luminal A cancers grow slowly and are not easy to detect. However, their prognosis has been successful due to the expression of steroid hormone receptors which predict the response to hormonal therapy. Of the four molecular subtypes, luminal A has the best prognosis, with a survival rate that is reasonably high and low to no recurrence incidences.

5.1.2.3.2 Luminal B male breast cancer

The tumor cells in luminal B male BC manifest cancers that begin in the inner cells of the mammary duct (Lacle MM, 2015) (Wang, 2018). In luminal B breast cancer, ER and PR are positive cancer, with high proliferative activities due to the elevated level of Ki between 60-67. Luminal B is a novel subgroup of tumors that typically manifests as mild to high-grade tumors (10, 17, and 19 Ki). In this category, there is no over-expression of HER2/nue with an approximation of 30% HER2-enriched. In comparison to the luminal A category, the prognosis for luminal B cancer is poor. According to the available data in the early 2000s, when the group was defined, the survival rate in this category for up to five years was 40%. The status of the ER determines the success of tamoxifen therapy. It is important to note that the clinical outcome in this subcategory of male breast cancer cannot be determined solely by the ER and PR status, as further analysis of the tumor characteristics and cellular markers is required for a complete assessment.

5.1.2.3.3 HER2-enriched male breast cancer

This subcategory is characterized by ERBB2 overexpression. The ERBB2, also known as HER2/nue gene, can encode any of the four homologous receptors within the epidermal growth factor receptor type 2. The nue is a component of the gene the rat homolog of the HER2 (Kwiatkowski, 2015). HER2-enriched breast cancer is a molecular classification that includes tumors that overexpress HER2/nue and have distinctive features from the luminal and basal molecular subtypes. It is, however, important to highlight that not all HER2-enriched breast cancers display characteristics of HER2/nue overexpression. The tumors in this subtype also overexpress the genes in the ras pathway, which influences cell division and cell signaling and, in the long run, favors tumorigenesis (Lacle MM, 2015). It is evident that HER2-enriched breast cancer exhibits intermediate characteristics of high-grade tumors, meaning an aggressive course (Meijer, 2018). The survival rates are found to be thirty-one percent, while the recurrence rates are about thirty percent. The HER2-enriched breast cancer, according to

most scholars, expresses steroid hormone receptors PR and HR in most cases of MBC (approximately 40 and 30 percent cases, respectively) as compared to the females who manifest ER and PR positive tumor. In other cases, women who demonstrate tumors without ER and PR expression have up to two-fold chances of death.

5.1.2.3.4 HER2-enriched male breast cancer

In this subtype, the most common gene signature is the ER, PR, and HER2 negative types. The biological definition of basal-like cancer embraces not only the absence of PR, HER2/neu, and ER markers but also the overexpression of oncogenes that promote cell carcinogenesis and proliferation. The examples include the c-kit, e-my, and EGFR (epidermal growth factor receptor) genes, and finally, high occurrence of mutation within the p53 gene (Kaneda, 2017) (Kornegoor, 2012). As per some estimates, 12 to 17 percent of female breast cancer is triple-negative, and most of the affected patients are black women. The clinical indication of basal-like phenotype in male breast cancer indicates the presence of a possible germline BRCA1. In other words, the BRCA1-related BC is commonly manifested in non-hereditary breast cancer, supported by the notion that they are often ER-negative than the BRCA1-related breast cancers. Given the underlying genetic susceptibility, this novel subtype is common in black women. Captivatingly, however, unlike non-triple-negative cancers, a linear correlation exists between tumor size and the likelihood of lymph node involvement in the triple-negative subgroup. In general, the curve indicating the possibility of survival for patients with basal-like breast cancer varies at no specific rate. The risk of recurrence under this subtype is highest within one to four years, with a possibility of never recurring after eight years (Johansson I, 2013).

Male breast cancer is a rare disease and accounts for less than one percent of the victims, with only 1/1000000 of the men contracting the disease. Like traditional post-menopausal female breast cancer, male breast cancer has distinct molecular sub-forms, the most common ones being the dominant M1 and the luminal M2. These forms of cancer are quite different from the well-known smaller types of cancer that have been known in women. In many ways, the female subgroup differs from the male subgroup. The well-known novel subgroups are also known to manifest differently and uniquely than the most common male breast cancer. The luminal M2 type has also been proven to demonstrate a higher response to the immune system in relation to the ER type of signaling. At the same time, luminal M1 tumors display the most tumor invasions as well as metastasis signaling and proliferation signaling. The luminal M1 subgroup, in fact, is an aggressive type of cancer, which exhibits highly aggressive MBC tumors.

5.1.2.4 Immunohistochemistry (IHC) based classification of male breast cancer

Independent research groups have attempted to subclassify MBCs into intrinsic subtypes based on IHC, which is also used to describe female breast cancer (Blows FM, 2010) (Ge Y, 2009) (Kornegoor R, 2011) (Nilsson C, 2013) (Shaaban, 2012) (Yu X-F, 2013). The majority of MBC tumors identified in these reports were classified as luminal A (60-98%), which is a subgroup of male breast cancer with one of the best survival rates. According to Blows (2010), 71 percent of female breast cancer cases were classified as luminal A using the definition I. (Eroles P, 2012), also mentioned that expression-based classifications account for 50-60% of luminal A tumors. Based on this information, the use of definition I could be problematic when distinguishing between luminal A and B. Although Ki67 is used in the definition of I and II for separating luminal A and B tumors, comparing studies that do not use a standard protocol for scoring Ki67 is difficult.

While comparing the use of definition, most MBC cases were classified as luminal A compared to FBC (83-98% versus 71%), with the exception of a Chinese study, which had different subgroup distributions. Moreover, HER 2 enriched (0% versus 6%) and basal-like (0-2% versus 16%) tumors were higher in MBC than in FBC. Among women, the worst prognosis was associated with these subgroups (Nilsson, 2013; Ge; 2009; Blows, 2010; Shaaban, 2012). The report by Ye and colleagues was thus surprising in light of males' inferior relative OS and breast cancer-specific survival when compared to females Nilsson, 2011; (Miao H, 2011); (Greif JM, 2012); (Cancerfonden, 2013). According to the studies that have been published so far, using traditional IHC proxy markers in the classification does not capture the aggressive subgroup of MBC. Male and female breast cancers are likely to have different outcomes when subjected to standard treatment therapies. Therefore, there is a need for additional biomarkers that can successfully identify and classify various cases of MBC and help in employing suitable treatment strategies.

5.1.2.5 Genetics and novel directions

Various genetic factors have been reported as important role players in breast cancer. An understanding of these genetic attributes can help in defining novel directions for cancer treatment.

- The *BRCA1* and *BRCA2* genes have long been interrelated with an elevated BC incidence, even in males. By the age of 70, germline PVs/LPVs (pathogenic/likely pathogenic variants) in the *BRCA1* gene are linked to a 57-65% and 1.2% chance of giving rise to breast cancer in females and males, respectively (Tai, et al., 2007)

(Mavaddat, et al., 2013). Likewise, germline PVs/LPVs in the *BRCA2* gene are attributed to a 45–55% and 6.8% chance of developing breast cancer by the age of 70 in females and males, respectively (Tai, et al., 2007) (Mavaddat, et al., 2013). Keeping this in view, men carrying *BRCA1/2* PVs/LPVs should begin undertaking breast scrutiny at 35, which should be done every 6–12 months ((NCCN), 2020). Moreover, men (especially those exhibiting *BRCA2* variant) should undergo an annual prostate cancer clinical screening from the age of 40 years ((NCCN), 2.2019). Furthermore, family history should be considered for melanoma and pancreatic cancer evaluation ((NCCN), 2020).

- *PALB2* produces a protein that interacts with *BRCA2* in homologous recombination. It appears to be one of the most promising genes recognized from NGS research on BC/OC predisposition (Tedaldi et al, 2020). *PALB2* variants also frequently exist in MBC patients (Rizzolo, et al., 2019) (Ding, 2011). In terms of penetrance, a recent analysis of 524 families with *PALB2* variants showed that by the age of 80, females had a BC chance of 53%, and males had a BC risk of 1% (Yang, et al., 2019). By the age of 80, the incidence of OC and pancreatic cancer has been reported to be 5% and 2–3%, respectively, according to the same report. Moreover, Tedaldi et al. (2020) mentioned that a patient with the *PALB2* mutation presented IDC at 75 years of age and had a family history of cancer, with the mother dying of BC at the age of 60. The variant is also borne by the patient's sister, stable and now under a BC vulnerability surveillance program. Their findings support the function of the *PALB2* in male breast cancer predisposition and stress the significance of developing a male carrier surveillance protocol.
- The *CHEK2* is another gene related to breast cancer. It produces a tumor suppressor protein linked with the DNA damage repair mechanisms. The germline variations of *CHEK2* are involved in enhancing the risks of breast cancer for females (Adank, 2011) (Walsh, et al., 2006) by approximately 20–44% over the course of carriers' lives (Tedaldi, et al., 2014). Moreover, other cancers, such as colorectal, prostate, and gastric, have also been related to *CHEK2* PVs/LPVs (Cybulski, et al., . 2004). The *CHEK2* variant c.1100delC was linked with 2-3 times increased risk of BC in women and a ten-fold increment in BC risk in males. Surprisingly, genetic testing of the parents revealed that the variant was carried by the mother as well as a brother of the patient, both of whom were healthy. According to the researchers, this finding supports the *CHEK2* variant's mild penetrance while also implying that *CHEK2* alterations are linked to BC risk in both men and women.

- In the same report of Tedaldi et al. (2020), a PV was recognized in the *ATM* gene, which codes a protein associated with DNA repair and cell cycle regulation. The germline alterations of this genetic factor are linked to the elevated breast cancer risk in females by 15–60% (Marabelli, et al., 2016). Earlier, *ATM* alterations were also documented in male breast cancer (Fostira, et al., 2018). The investigation by Tedaldi et al. (2020) proposed that the patient carrying the *ATM* variant exhibited IDC at 38 years of age and had a family history of the father's death due to melanoma at the age of 65. Because of this patient's young age at cancer onset and the repeated identification of *ATM* alterations in male patients, the function of this gene in cancer predisposition should be studied further.
- A PV has also been discovered in the *RAD51C* gene, which codes for a homologous recombination protein. Variants with *RAD51C* mutations have been linked to an elevated risk of OC, but the risk of BC for variant carriers is debatable. In the case of MBC, *RAD51C* variants were initially thought to be unrelated, but a review of a broad cohort of MBC patients recently discovered PVs in the *RAD51C* and *RAD51D* genes. A patient with the *RAD51C* mutation displayed IDC at 59 years of age and had a sibling who died of breast cancer when she was 55. Thus, the results support the inclusion of the *RAD51C* gene in a panel for assessing breast cancer danger in males as well as female carriers (Tedaldi et al, 2020).
- B-cell CLL/lymphoma 2 genes (*Bcl2*) encodes a crucial outer mitochondrial membrane that inhibits apoptosis in a number of organisms. This gene's anti-apoptotic roles in lymphoma are well established. It is commonly believed to have important prognostic significance in cases of FBC. Likewise, *Bcl2* expression was also observed in the majority of MBC patients. Nevertheless, investigators argue that *Bcl2* is unrelated to major shifts in clinicopathologic variables, for instance, tumor size and mitotic degree (Sharifi, 2014). The biological mechanisms underlying *Bcl2'*s role as a predictive biomarker in MBC are still unknown.

  Bcl2's function as a tumor-suppressor was identified in a range of tumors, including BC. However, there has been a number of conflicting reports about this gene. *Bcl2* may play the role of a tumor suppressor or an oncogene in certain kinds of cells under particular circumstances (Manikandan, 2008). It is commonly assumed that the gene's tumor-suppressing role is highly prominent in BC. The *Bcl2* expression has been tested extensively in FBC cases, and it has been found to have prognostic significance irrespective of the hormonal receptor status (Honma, 2015). Besides that, in FBC, a connection has been proposed between *Bcl2* expression and hormonal receptor

status. Initially, *Bcl2* was assumed to be upregulated by estrogen. In recent trials, a clear connection has been proposed between Bcl2 and estrogen receptor (ER) status ($p = 0.04$) (Seong, 2015). Conversely, there has not been any evidence of a significant inverse association between the expression of *Bcl2* and *p53* accumulation. Furthermore, there are no comprehensive reports specifying the association of *Bcl2* with ER or *p53* in MBC, making it difficult to draw firm conclusions from the current data.

MBC exhibits a higher expression of Bcl2 than FBC (94% versus 68.2%). It is vital to emphasize that the *Bcl2* expression in MBC is not often linked with advantageous clinicopathologic characteristics (Leverson, 2015). By now, there is no sufficient evidence to indicate that HER2 and Bcl2 have a strong association. This lack of proof, in most instances, can be attributed to the fact that a low proportion of tumors (3.3 %) depict the HER2 presence. Furthermore, only a few Bcl2 observational trials have been conducted on small cohorts of MBC patients that show little correlation with survival. A current analysis of 51 males diagnosed with cancer was unable to demonstrate that Bcl2 alone had a major prognostic effect (Vaillant, 2013). The multivariate survival analysis also showed similar results. In a broad sample of 1650 FBC patients, a combination of the mitotic index and Bcl2 expression showed high prognostic value. A similar combination of these two parameters did not indicate a substantial prognostic benefit in MBC (Smerage, 2013). These results are not surprising given that several investigations demonstrated a lack of a substantial link between mitotic indexes and patient survival.

Male and female breast cancers vary significantly in terms of the therapeutic significance of Bcl2 expression and the prognostically optimal mitotic index inceptions. In this backdrop, the biological basis of Bcl2 and MBC relation is unknown (Lacle, 2013). Thus, Bcl2 expression, despite being widespread in MBC, does not appear to be related to major clinicopathologic characteristics. Even when paired with the mitotic index, which is effective in FBC, Bcl2 seems not to have a significant prognostic benefit.

- Multiple sclerosis and male breast cancer: Researchers have looked into the connection between Multiple Sclerosis (MS) and BC for a long time. However, contradictory findings were often observed, necessitating further testing to ascertain this association (Kyritsis, 2016). Numerous reports have suggested that MS patients who take immunosuppressant (IS) drugs have a higher chance of cancer. MS is often characterized by a breakdown of immune self-tolerance of an individual. In the majority

of cases, emancipation causes myelin degeneration and secondary axon injury, primarily in the nervous system. Generally, regulatory T cells (Tregs) inhibit immune system activation and thereby modulate immune responses. Tregs can stimulate tumor growth in patients by interfering with the surveillance mechanisms (Gianfrancesco, 2017). Moreover, Tregs may also suppress the production of certain cancers with inflammatory components in particular circumstances. A high or growing occurrence in some cancers, especially breast and ovarian cancers, has been related to a worse prognosis.

Previous research has shown that Tregs exist in MS patients in comparable numbers to those found in healthy people. Tregs' effector role, on the other hand, has been documented to be compromised in MS patients (Tintore, 2015). Accordingly, variations in the natural killer (NK) cell population are most frequently found in marginal blood incongruence in MS patients. MS is often more prone to evolve in genetically predisposed people following environmental reactions (Sun, 2014). Patient's gender, stress, infections, and climate are among the most well-known causes that raise the incidence of Tregs' adverse effects. Regarding gender, women are considered to have a higher incidence of MS than males. Thus, it is fair to assert that MS does not raise the incidence of male breast cancer in the same way it does in women (Marrie, 2015). In this context, researchers should concentrate on figuring out how to handle MBC patients with MS while preventing the Tregs' harmful impact.

Furthermore, the immune system and neurodegenerative operations that inflict axonal damage and myelin sheath injury are often implicated in the pathogenesis of MS. The connection between immune therapies, MS, and MBC is being investigated (Ragonese, 2017). Contradictory findings have been observed in various studies, which are often linked to inconsistencies in the study design used and the duration of follow-up after participation in research initiatives. The research, nevertheless, reveals that MS does have an impact on the MBC incidence (Roshanisefat, 2015). Many of the questions regarding MBC treatment are still unanswered that should be addressed. For example, the precise impact of immunosuppressive drugs on MBC incidence should be investigated (Lebrun, 2008).

- *PBRM1* (polybromo 1) is a tumor-suppressing gene. It is associated with proliferation, colony formation, and migration (Varela I., 2011). Its activity as a tumor-suppressing factor is evident from the fact that 80% of the genetic alterations in it result in protein's loss of function; such observations were recorded for different kinds of cancers such as breast, ccRCC, and pancreatic cancer. Additionally, another gene, that is, *BAF180,*

was also reported to be associated with altering the *p53* activity (Macher-Goeppinger S., 2015) by inducing *p21* (a p53-target) transcription. This gene is also linked with inhibiting the transcription of 14–3–3σ. Contrary to the roles mentioned above, Murakami et al. (Murakami A., 2017) suggested that the *PBRM1* activity is context-sensitive, and in certain circumstances, this gene may behave as an oncogene instead. The discovery of a germline frameshift deletion in the *EGFR* gene, which encodes the Epidermal Growth Factor Receptor, was a surprising outcome.

The *EGFR* gene variant (c.3538_3541delGAAG) was found in a male breast cancer patient (Lucía Carril-Ajuria, 2020). The variant was also described earlier by Hakimi et al. (Hakimi A.A., 2013), who suggested its detrimental involvement in renal cell carcinoma.

The patient had DCIS at the age of 62 years and non-Hodgkin cancer at 67. No other relatives had the disease making it impractical to investigate segregation, necessitating more research regarding this genetic variant and its association with cancer.

In 78.6% of male breast cancer patients, no PV/LPV is recognized as a genetic contributor. Many of the studies indicate no genetic predisposition to MBC. Nevertheless, there is indeed a possibility of genetic variations in other genes or regulatory regions not included in the relevant studies. Like other types of tumors, MBC is also, apparently, a multifactorial ailment depending upon various behavioral and environmental factors. Thus, the cases in which no hereditary differences have been identified may actually be attributable to genetic predisposition.

- *SETD2* is one of the genetic factors in cancer suppression and may be employed as a marker for prognosis because of its connection with irregular *p53* activity, as suggested by (Rui Chen, 2020). The mentioned gene is involved in various cellular activities. Its genetic alterations disturb associated biological roles resulting in tumors. Investigations related to all the types of breast lymphomas propose the presence of a mutation in this gene with an overall fraction of 2.62% and 1.2% presence in triple-negative cancer. Nevertheless, it is unknown if *SETD2* mutations are present in Luminal A, Luminal B, or Her+. Various reports mention a link between patient prognosis and *SETD2* expression, suggesting a higher prognosis in case of a higher expression.
- *MDM2* is another gene that was linked with MBC. Its amplification has been reported in approximately 13% of the cases. Apart from *MDM2* and *SETD2*, other aberrant genetic factors are also, seemingly, implicated in the p53 pathway inactivation,

including *PBRM1*, *ARID1A*, and *KMT2C* inactivation, and *SMYD2 and PAK1* amplification (Cathy B Moelans 1, Oct 2019).

The amplification *of MDM2 is* predicted for more aggressive tumor behavior and is further related to protein overexpression (Burgess A, 2016). Consequently, in MBC, *MDM2* is supposed to be a curative target. *MDM2* elevations were linked to protein overexpression and anticipated enhanced violent tumor activity. The increased incidence of *MDM2* overexpression in certain cancers (ER-positive FBC and prostate) and the observations hinting potential of MDM2 inhibitors for facilitating treatment have enhanced interest in investigations involving this group of medications in conjunction with endocrine therapies.

- Four genes *viz*. *E2F7*, *ASH1L*, *PAK1,* and *TGFB2* were found to prophesy poor OS in MBC. The amplification of *PAK1* was observed at about the same rate as ER+. The *PAK1* overexpression is linked with meager outcomes in luminal FBC. FRAX1036, in conjunction with docetaxel, endorsed the role of *PAK1* as a possible target in BC (Ong CC, 2015). *PAK1* is also involved in resistance to tamoxifen (Holm C, 2006). *ASH1L*, an encoder of histone methyltransferase (HMT), demonstrated a comparable frequency of amplification in MBC as ER-positive female breast cancer. Therefore, ASH1L inhibitors can be employed as a drug target (Liu L, 2015); efforts are underway in this regard (Rogawski DS, 2015).
- *E2F7*, also called E2F transcription factor 7, demonstrates more frequent and high amplification in MBC versus ER-positive FBC, that is, 13 against 1.4%, respectively. *E2F7* is a part of numerous biological phenomena, including DNA repair, polyploidization, and angiogenesis. Its excessive expression in breast cancer cells contributes to tamoxifen resistance (Chu J, 2015). The fourth gene in the list, *TGFB2,* is responsible for encoding a secreted ligand (transforming growth factor-beta superfamily). TGFB2 mRNA amounts also forecast the response to tamoxifen in BC (Buck MB, 2008). Therefore, a variety of approaches have been established to disrupt TGF-beta signaling (Colak S, 2017). For instance, antibodies targeting TGFB2 distort the tamoxifen resistance of cancers. In total, 19% of MBC's most commonly amplified genes are clinically viable, and 26% have medication reactions, indicating several possible targets for treatments.
- Human arylamine N-acetyltransferase 1 (NAT1) occurs in the majority of tissues. It functions as a phase II drug-metabolizing enzyme. NAT1 transfers acetyl groups from acetyl-CoA. The recipients of NAT1 activities are hydrazine and arylamine substrates. (Johansson I, 2012). NAT1 is generally present at the location of cancer that is

typically removed. The *NAT1* encoded proteins work combinatorically to acetylate a wide range of exogenous carcinogens such as hydrazine, arylamine, and heterocyclic amine. The compounds induce breast cancer in animal models and are also related to the etiology of human BC as well as other cancers (Ly, 2013).

The relationship between NAT1 and the risk for breast cancer has been reported. The interactions, though, were observed in pre and postmenopausal females. Yet, overall findings do not offer convincing evidence of the function of NAT1 in BC, despite the fact that NAT1 has often been cited as one of the consistently upregulated proteins in breast cancer tissues (Sousa B., 2013).

Cytosine methylation of DNA's regulatory systems is commonly treated as an epigenetic tool related to the transcriptional inactivation of a number of genes. Hypomethylation, contrarily, is thought to aid in the triggering of transcriptions (Deb S, 2016). In previous experiments, methylation profiling of cancer cells, as well as individual gene analysis, showed that hypomethylation of some genes at the gene promoters occurs regularly in a variety of cancerous tissues. The hypomethylation of some genes also coincides with higher levels of transcription (Merino, 2018). So far, no research has explained the *NAT1* methylation in human genes.

According to current studies, NAT1 is involved in the activation and deactivation of certain environmental substances, including heterocyclic amines as well as aromatic amines, which are typically present in cigarettes and meat (Johansson, 2015). Breast cancer risk may also be altered by genetic variations in *NAT1* attributable to susceptibility to aromatic amine and heterocyclic elements. The existence of a connection between *NAT1* and BC has been discovered in modern epidemiological trials. In mammals, DNA methylation has been recognized as a compelling phenomenon of controlling gene expression and transcriptional alteration (Humphries, 2017). The expression of regulatory genes and oncogenes has also been observed in relation to DNA hypomethylation in cancerous tissues. Moreover, a connection between P-cadherin expression and CDH3 promoter hypomethylation in breast cancer also subsists, which has been linked to invasiveness and histological grade (Turashvili, 2018). In this backdrop, the knowledge presented about *NAT1* and cancer cell growth can be used to create a successful gene hypomethylation protocol for treating MBC.

- There are 21 exons in the *PIK3CA* gene (twenty of them are coding exons). The gene encodes a 1068 amino-acid-residual cytoplasmic protein. The *PIK3CA* gene forms a catalytic subunit of the class I PI 3-kinases (PI3K), referred to as p110alpha protein. PI

3-Kinase, also called phosphoinositide 3-kinase, or PI3K, regulates degranulation, proliferation, cell survival, and migration. *PIK3CA* inducing mutations exhibit substantial incidence (40.1% coding mutations in METABRIC) in women's breast cancer (Pereira et al., 2016). These alterations are linked with high age at diagnosis and low tumor grade and stage. Furthermore, *HER2* negativity, hormone receptor positivity, and lymph node negativity are also associated with *PIK3CA* mutations. Additionally, *PIK3CA* mutations have been related to considerably longer-term metastasis-free survival; this has particularly been observed in *HER2*-positive and PR-positive subgroups (Cizkova et al., 2012)(Nahta and Esteva, 2006). Most of the mutations are found in three hotspots, *viz*. *E542*, *H1047*, and *E545*, rendering them important therapeutic targets. *PIK3CA* mutations have less occurrence (20%) in MBC versus ER-positive/HER2-negative FBC. Still, these represent the most mutated genes in MBC. Nearly all *PIK3CA* mutations in male breast cancer influence the hotspots (Piscuoglio et al., 2016).

Conclusions

1. To the best of our knowledge, this is the first study that explored the silent breast cancer incidence among men. We noticed that MBC is a rare disease, and its natural reservoir is extremely low, just like its incidence. Nevertheless, the few cases that exist need to be treated appropriately.
2. The screening of the general population for MBC is unnecessary; however, it should be targeted for men at elevated risk for breast cancer. (Yiming Gao, 2019)
3. Several novel targets/pathways have been identified to date, but their clinical significance/application has yet to be demonstrated.
4. There is a need for consensus, and for that, clinical trials should be a priority. Fortunately, male breast cancer dedicated guidelines have started to appear (Hassett MJ, 2020). Even though we have started to decode, we are still “lost in translation!” (Johansson & al, 2014).

5.2 Female breast Cancer

A forensic autopsy is a postmortem examination performed in order to address medicolegal issues (Menezes & Monteir, 2020). Historically, autopsies have served questions inherent to medical care (diagnostic-related groups, quality assurance, and patient care), medical science and investigation (research, education, transplantation, and prostheses), society (public health, statistics, and forensics), and the family (counseling and understanding the life cycle) (Buja LM, 2019)

Aside from the medicolegal or forensic autopsies, a new term has emerged: research autopsies, which are performed primarily for the purpose of collecting one or more normal or diseased tissues to support basic or translational research. (Iacobuzio-Donahue, 2019) According to Iacobuzio, research autopsies are an underused approach to investigate the fundamental questions in cancer biology and hold tremendous potential in precision medicine.

In the present study, the objective was to define the reservoir of breast cancer in serial, systematic, and research-oriented autopsies (systematic specimen complete and thorough excision of axillary breast content) of individuals that were not supposed to die and for whom assisting physicians could not find a cause of death (excluding in-hospital deaths even more biased by age ranges). The collected tissues were processed (procedure described in the previous chapter) in a systematic way rather than through systematic histological examination. The systematic imaging (mammography and ecography) of both genders' breast glands is what sets our approach apart. In other words, the present study was designed to simulate an “extended screening exam” performed by breast disease dedicated professionals in the serial analysis of individuals.

An obvious point could be, why not collecting samples and verify the presence of tissue alterations pre/malignant. The answer is that being aware of the overdiagnosis issue (Figure 33), the author wanted to suppress it. The latest published systematic review/meta-analysis on autopsy detected breast cancer points out that incidental breast cancer and its precursors are common in women not known to have breast disease during life and that the large pool of undetected *cancer* in-situ and *atypical hyperplasia* in these autopsy studies suggest caution for screening programs (Elizabeth T. Thomas, 2017)

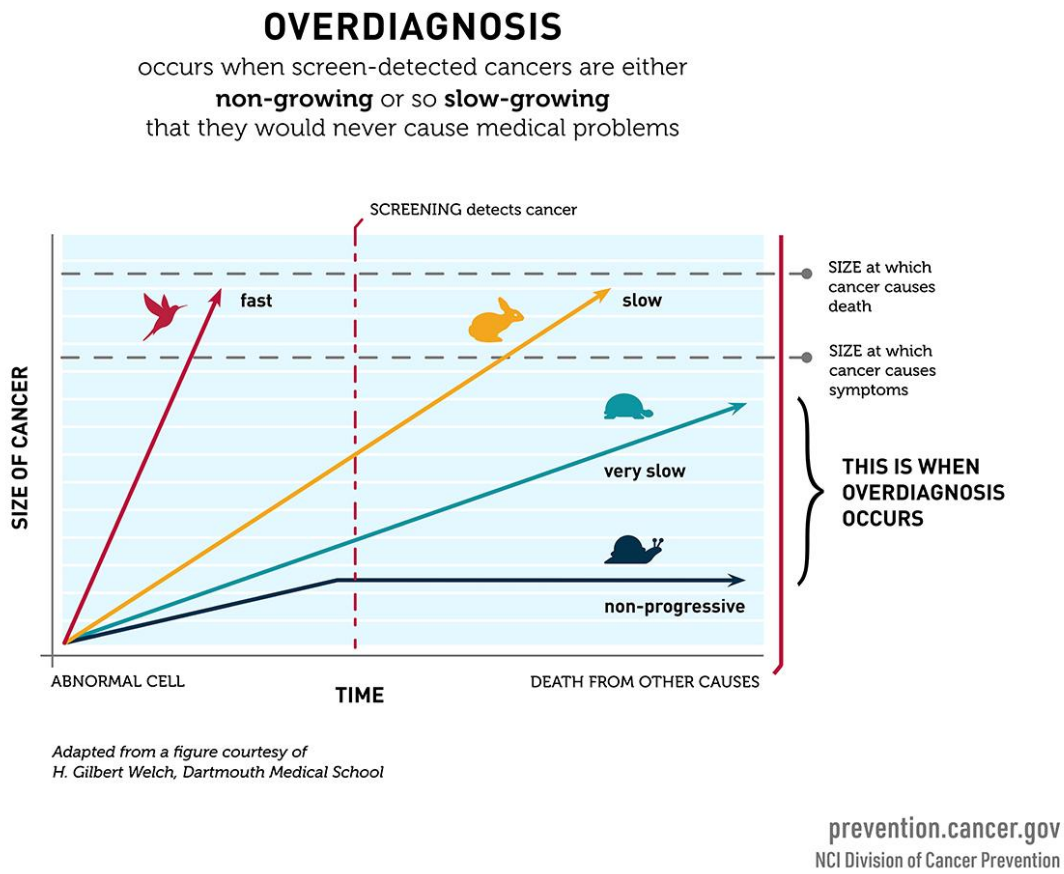


Figure 33. Overdiagnosis schematic definition (The National Cancer Institute., n.d.)

This study evidenciated that the overall incidental cancer and precursor prevalence was as follows: Invasive: 0.8%, In-situ: 8.9% (adjusted), Atypical hyperplasia: 9.8% (adjusted), for a total of 19.5%. In conclusion, autopsy samples, studied by histology, present a small reservoir (almost 1%) of invasive versus a large reservoir of in-situ e premalignant lesions (almost 18%). Hence, the incidental disease exists, but it is not detected by the screening methods, even if they are extended and include ultrasound scanning of the breast tissue.

It is critical to remember that the findings in both approaches (histology and imaging),

- concern individuals who were unaware of having breast pre/malignant alterations
- died for reasons that were not expected.

To summarize, as demonstrated by the null hypothesis, imaging techniques used for breast cancer screening do not overdiagnose the disease.

5.2.1 European Union Reality

The figures regarding the timeliness of breast-screening programs and standardized death rate (per 100,000 inhabitants) for Europe are presented in Tables 21 and 22, respectively. The European Parliament (EP) stated in its resolution (A5-0159/2003) in 2003 that *'…Every*

woman should have access to high-quality screening treatment, and any disparities in access should be minimized….' and promoted the provision of breast cancer screening for all women aged 50-69 years every two years. One of the European parliament's objectives was to reduce mortality from breast cancer by 25% and the disparity rate by 5% in European Union countries by 2008. By 2008, this rate was 23.9%. Thus, there was a decrease of only ~6.2% during 2003-2008 in the EU-27.

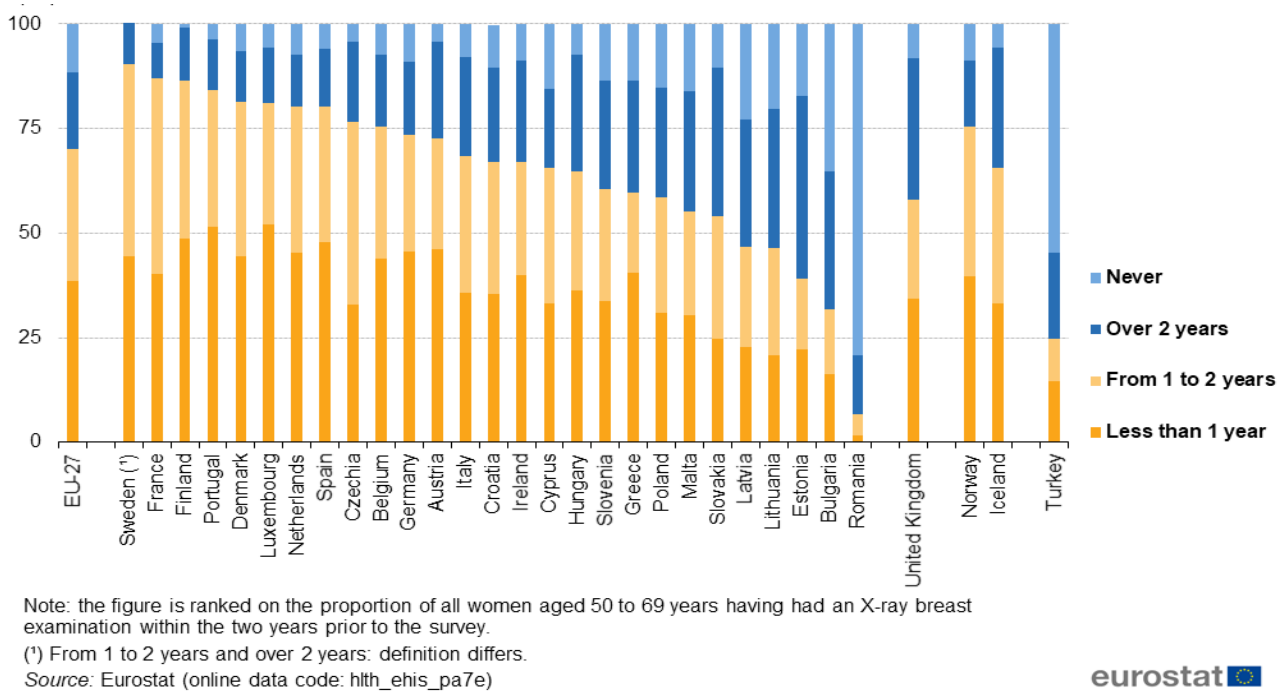
Country	Implementation of screening programmes	Age covered
Austria[1]	1974	40+
Belgium	2001	50-69
Bulgaria	2012	45-69
Czech Republic[2]	2002	45-69
Cyprus	2007	50-69
Denmark	2007	50-69
Estonia[3]	2002	50-69
France[4]	2003	50-74
Germany	2005	50-69
Greece	-	40+
Hungary[5]	2001-2002	45-64
Italy	2005	50-69
Latvia	2009	50-69
Malta	2009	50-60
Poland[6]	2006	50-69
Slovenia[7]	2008	50-69
Spain	1990	45-69
Slovak Republic[8]	-	40+
Romania[9]	-	50-69
Sweden[10]	1986	50-69
Turkey	1999	50-69
United Kingdom[11]	1988	50-64

Table 21. Timeliness of breast-screening programs with age covered in studied countries (after EHIS survey 2010; Source: Eurostat Website)

Country	Malignant neoplasm	Malignant neoplasm of breast
EU-27	129.4	23.1
Belgium	:	:
Bulgaria	117.8	21.3
Czech Republic	148.4	20
Denmark	168.2	28.9
Germany	128.8	24
Estonia	135.7	22.1
Ireland	149.1	28.1
Greece	108.9	21.1
Spain	101.2	17.6
France	116.1	23.6
Italy	122.2	23
Cyprus	99	21.5
Latvia	143.3	25.2
Lithuania	132.5	24.2
Luxembourg	133.1	24.5
Hungary	178.2	28.1
Malta	122.4	34.4
Netherlands	151.3	26.8
Austria	125.5	22.8
Poland	150	20.3
Portugal	110.8	20.2
Romania	129.5	22.6
Slovenia	145.5	25.5
Slovakia	143.7	21.3
Finland	110.8	19.4
Sweden	129.5	19.1
United Kingdom	148.4	25.4

Table 22. Standardized death rate (per 100,000 inhabitants) in Europe in 2009 (Source: Eurostat website)

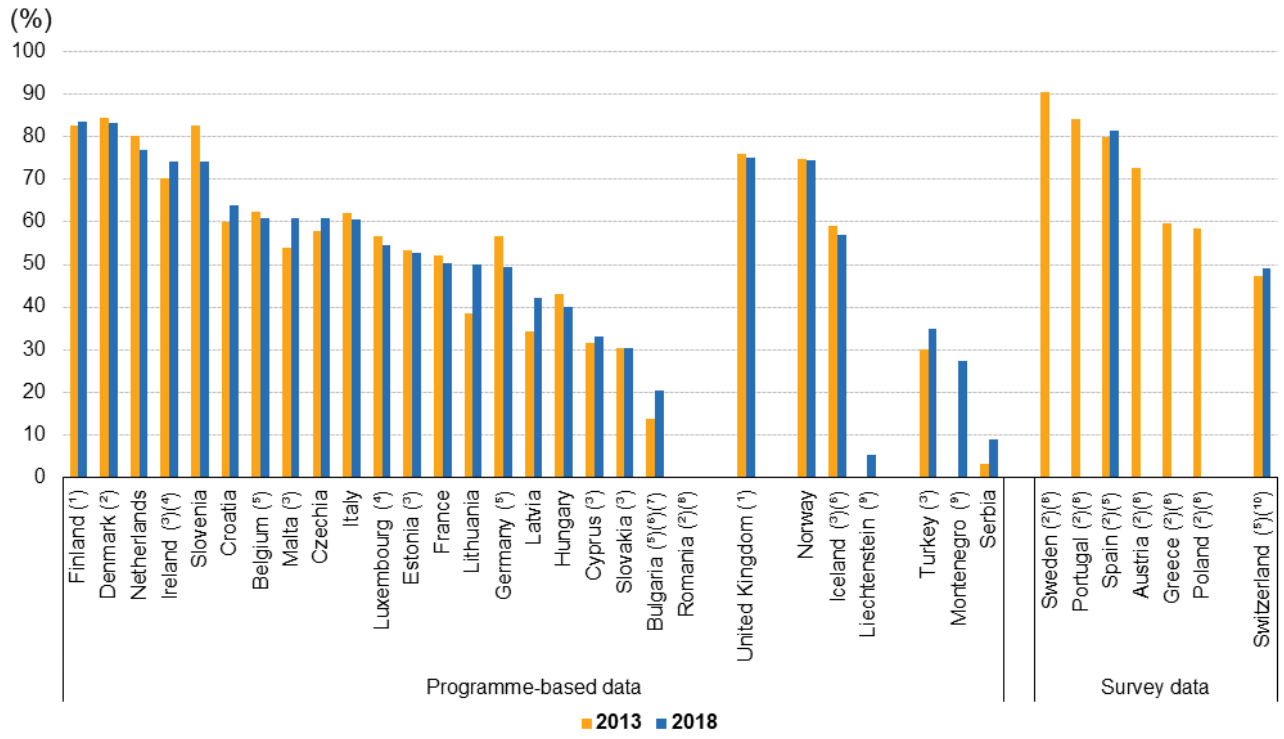
The European health interview survey (EHIS), conducted between 2013 and 2015, shows an analysis of the female population aged 50-69 years in terms of the time since their most mammographic breast examination. In Finland, Sweden, Portugal, Czechia, Austria, and France, the percentage of women who never underwent such an exam was below 5.0%, while in nine other member states, it was within the range of 5.0-10.0% (Figure 34). On the other hand, more than one-fifth of women in Lithuania and Latvia, 35.3 % of women in Bulgaria, and 79.0 % of women in Romania in this age group had never had such an examination.



Note: the figure is ranked on the proportion of all women aged 50 to 69 years having had an X-ray breast examination within the two years prior to the survey.
(1) From 1 to 2 years and over 2 years: definition differs.
Source: Eurostat (online data code: hlth_ehis_pa7e)

eurostat

Figure 34. Self-reported screening (2014) indicating the proportion of women aged 50-69 years having had an X-ray breast examination within the specified time periods. The y-axis presents the percentage for respective countries.



Note: the rate shown is the proportion of women aged 50 to 69 years who have received a mammography within the previous two years (or according to the specific screening frequency recommended in each country). For programme-based data this is shown as a proportion of women eligible for an organised screening programme and for survey data this is shown as a proportion of women answering survey questions on mammography.

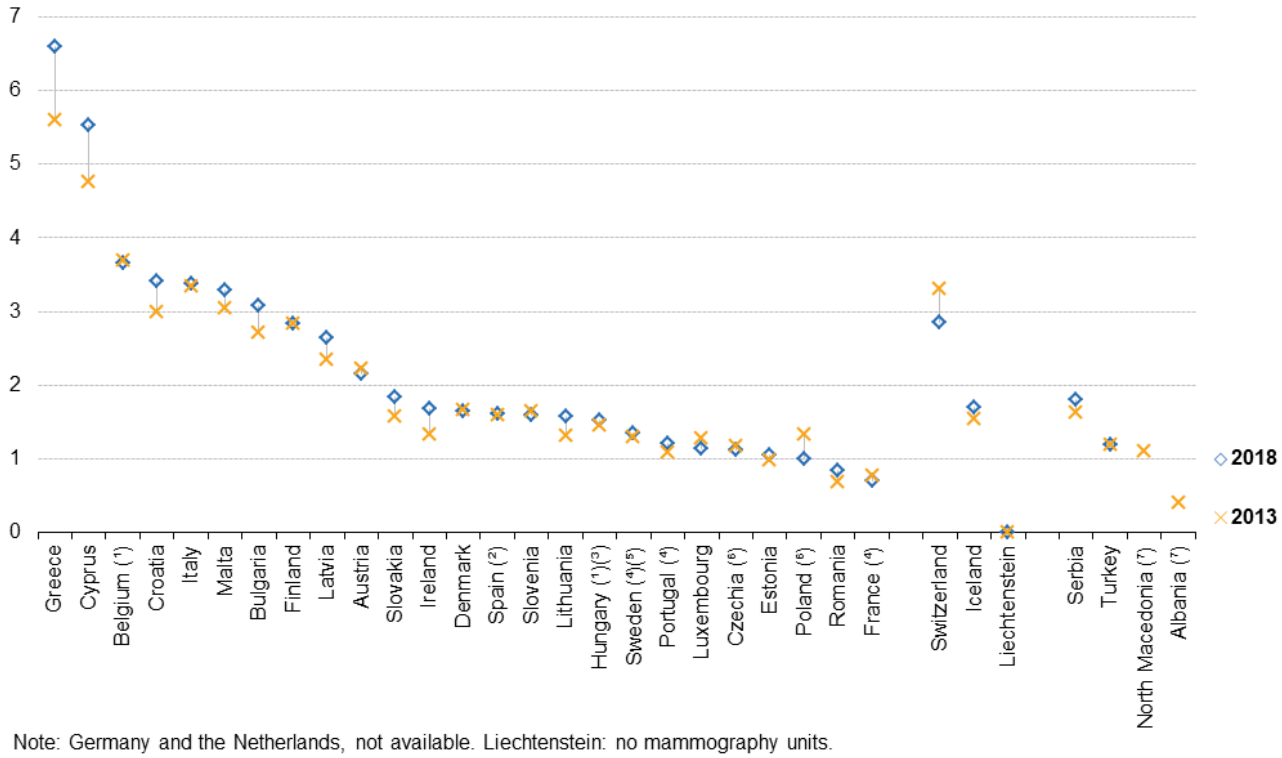
(1) 2018: estimate.
(2) 2014 instead of 2013.
(3) Age group covered differs.
(4) 2018: provisional.
(5) 2017 instead of 2018.
(6) Break in series.
(7) 2015 instead of 2013.
(8) 2018: not available.
(9) 2013: not available.
(10) 2012 instead of 2013.

Source: Eurostat (online data code: hlth_ps_scre)

eurostat

Figure 35. Breast cancer screening (percent) of women aged between 50-69 years during 2013-2018. The y-axis presents the percentage for respective countries.

The data in Figure 35 show the proportion of women aged 50-69 years who had received mammography. Data are currently available for 2018 (sometimes 2017). Among these, screening rates were below 50.0% in six countries, with Bulgaria having a low screening rate of 20.6% (2017 data). Moreover, France, Luxembourg, and Italy also had relatively low screening rates (at most 60.5%). Finland, Denmark, and Spain (survey data: 2017) reported screening rates higher than 80 %, as did Sweden and Portugal (both older survey data), while at least three-quarters of women aged 50-69 years were screened for breast cancer in the Netherlands.



Note: Germany and the Netherlands, not available. Liechtenstein: no mammography units.
(1) 2017 instead of 2018.
(2) 2018: provisional.
(3) 2017: estimate.
(4) Hospitals only.
(5) 2015 instead of 2013.
(6) Break in series.
(7) 2018: not available.
Source: Eurostat (online data code: hlth_rs_equip)

Figure 36. Mammography units per 100,000 inhabitants. The y-axis denotes the number of mammography units for respective European countries. Data for 2013-2018

As we can observe in Figure 36, screening unit availability is also quite variable, though in general, there has been an increment between 2013 and 2018, with the exceptions of Luxembourg, Czechia, Poland, and France. A recently published study (Paweł Koczkodaj, 2020) presents breast cancer mortality trends among women aged 45 years and older in the 28 EU countries (Table 23).

	Number of deaths	Share of all deaths			Standardised death rates				
		Total	Males	Females	Total	Males	Females	Persons aged < 65 years	Persons aged ≥ 65 years
	(number)	(%)			(per 100 000 inhabitants)				
EU-27 (1)	85 336	1.9	0.0	3.7	18.8	0.6	32.7	7.1	67.2
Belgium	2 219	2.0	0.0	4.0	19.8	0.5	34.8	6.9	73.2
Bulgaria	1 243	1.1	0.0	2.3	17.0	0.7	29.4	7.3	57.3
Czechia	1 642	1.5	0.0	3.0	17.1	0.4	28.7	5.2	66.0
Denmark	1 118	2.1	0.0	4.2	20.8	0.3	37.2	6.2	81.2
Germany	18 614	2.0	0.0	3.9	20.4	0.5	35.8	6.9	76.4
Estonia	266	1.7	0.0	3.2	20.4	0.7	31.8	6.7	77.0
Ireland	727	2.4	0.0	4.8	20.8	0.3	37.8	7.6	75.3
Greece	2 185	1.8	0.0	3.5	18.0	0.4	32.2	6.5	65.5
Spain	6 566	1.6	0.0	3.1	13.4	0.4	23.7	5.7	45.5
France (1)	12 968	2.2	0.1	4.3	19.1	0.9	33.1	7.5	67.2
Croatia	862	1.6	0.0	3.1	20.6	0.4	34.9	7.6	74.2
Italy	12 944	2.0	0.0	3.8	18.3	0.5	32.1	7.1	64.6
Cyprus (2)	127	2.1	0.1	4.4	18.5	0.6	34.0	6.8	66.5
Latvia	429	1.5	0.0	2.8	22.1	0.2	34.0	7.7	81.7
Lithuania	489	1.2	0.0	2.4	16.8	0.1	26.8	6.9	57.9
Luxembourg	108	2.7	0.0	5.2	22.7	0.3	40.3	7.1	87.2
Hungary	2 138	1.6	0.0	3.1	22.7	0.4	37.4	8.5	81.6
Malta	64	1.8	:	3.6	15.5	:	28.1	5.9	55.4
Netherlands	3 137	2.1	0.0	4.0	19.5	0.4	34.9	7.6	68.3
Austria	1 593	1.9	0.1	3.7	18.5	0.7	31.7	6.2	69.0
Poland	6 748	1.7	0.0	3.4	20.1	0.6	33.4	7.4	72.4
Portugal	1 794	1.6	0.1	3.2	16.1	0.7	27.5	7.2	53.1
Romania	3 559	1.4	0.0	2.8	19.3	0.9	33.2	8.3	64.8
Slovenia	437	2.1	0.0	4.2	21.4	0.2	36.1	6.2	84.4
Slovakia	1 078	2.0	0.1	4.0	24.9	1.1	40.7	8.0	94.8
Finland	913	1.7	0.0	3.4	16.1	0.2	28.7	6.1	57.4
Sweden	1 427	1.6	0.0	3.0	14.5	0.3	26.4	5.1	53.1
United Kingdom	11 496	1.9	0.0	3.7	18.7	0.3	33.6	7.0	66.7
Iceland	42	1.9	0.1	3.7	16.4	0.6	30.1	4.8	64.0
Liechtenstein	4	1.6	:	3.3	11.4	:	21.8	2.7	47.2
Norway	595	1.5	0.0	2.8	12.9	0.4	23.3	4.6	46.9
Switzerland	1 364	2.0	0.0	3.9	16.7	0.4	29.8	5.2	64.3
Serbia	1 797	1.7	0.1	3.4	25.4	1.0	44.5	10.5	87.2
Turkey	4 029	1.0	0.0	2.1	8.8	0.4	15.9	4.4	27.1

(1) 2016.
(2) Males: 2016.
Source: Eurostat (online data codes: hlth_cd_aro and hlth_cd_asdr2)

eurostat

Table 23. Breast cancer mortality trends among women at the age of 45 years and older (45+) in the 28 EU countries (2017)

	Million EUR	EUR per inhabitant	PPS per inhabitant	% of GDP
EU-27 (1)	1 286 220	2 887	:	9.9
Belgium	45 405	3 992	3 553	10.3
Bulgaria	4 183	591	1 311	8.1
Czechia	13 864	1 309	2 096	7.2
Denmark	29 598	5 134	3 695	10.1
Germany	368 597	4 459	4 300	11.3
Estonia	1 518	1 153	1 559	6.4
Ireland	21 130	4 395	3 405	7.2
Greece	14 492	1 348	1 623	8.0
Spain	103 489	2 221	2 371	8.9
France	259 638	3 883	3 626	11.3
Croatia	3 326	805	1 277	6.8
Italy	152 705	2 523	2 483	8.8
Cyprus	1 313	1 528	1 674	6.7
Latvia	1 610	829	1 213	6.0
Lithuania	2 724	963	1 605	6.5
Luxembourg	3 031	5 083	3 633	5.5
Hungary	8 535	872	1 468	6.9
Malta	1 053	2 250	2 746	9.3
Netherlands	74 448	4 346	3 791	10.1
Austria	38 457	4 371	3 875	10.4
Poland (2)	27 756	731	1 440	6.5
Portugal	17 456	1 695	2 028	9.0
Romania	9 672	494	1 029	5.2
Slovenia	3 520	1 704	2 060	8.2
Slovakia	5 721	1 052	1 609	6.7
Finland	20 614	3 742	3 034	9.2
Sweden	52 364	5 206	3 871	11.0
United Kingdom	225 187	3 409	2 899	9.6
Iceland (2)	1 522	4 539	2 946	8.3
Liechtenstein	337	8 886	:	5.9
Norway	37 010	7 014	4 459	10.5
Switzerland	74 250	8 785	5 255	12.4

(1) Including 2016 data for Poland.
(2) 2016.
Source: Eurostat (online data codes: hlth_sha11_hf, demo_gind and nama_10_gdp)

eurostat

Table 24. Public health expenditure in 2017 (EU 27; Source: Eurostat website)

Finally, analyzing EU data by public health investment yields interesting results (Table 24). Based on the data presented in Table 25, EU countries can be divided into three major groups according to their investment in public health ratio (low health investment countries: LHIC; intermediate health investment countries: IHIC**,** and High health investment countries: HHIC) relative to their GDP.

Country	**5-6.9%GDP**	**Country**	**7,2-9,9 GDP**	**Country**	**10,1-12,4% GDP**
Romania	5,2	Czechia	7,2	Denmark	10,1
Luxembourg	5,5	Ireland	7,2	Netherlands	10,1
Latvia	6	Greece	8	Belgium	10,3
Estonia	6,4	Bulgaria	8.1	Austria	10,4
Lithuania	6,5	Slovenia	8,2	Sweden	11
Poland	6,5	Italy	8,8	Germany	11,3
Cyprus	6,7	Spain	8,9	France	11,3
Slovakia	6,7	Portugal	9	Switzerland	12,4
Croacia	6,8	Finland	9,2		
Hungary	6,9	Malta	9,3		

Table 25. EU countries data by the public health investment

Mortality and incidence for breast cancer distribution over time, according to public health investment groups are presented in Figures 37-44.

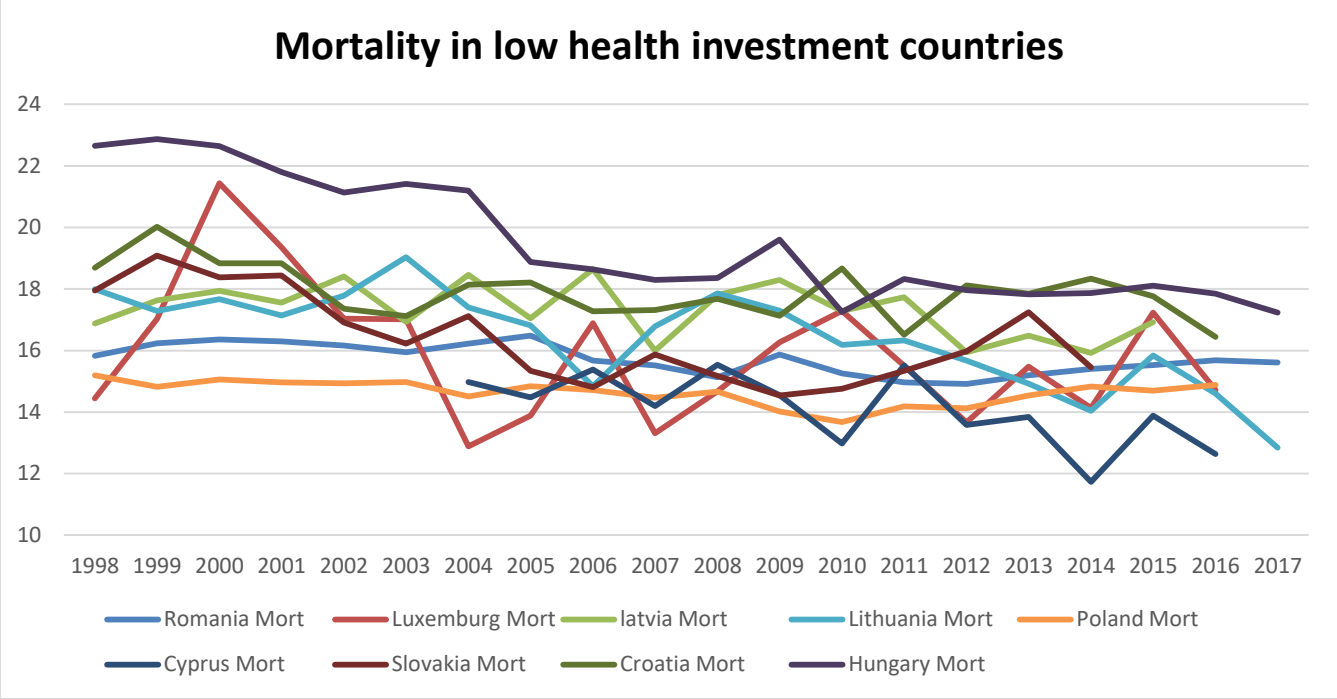


Figure 37. Breast cancer mortality in low health investment countries. The y-axis denotes mortality (number) for LHIC European countries with respect to years on the x-axis.

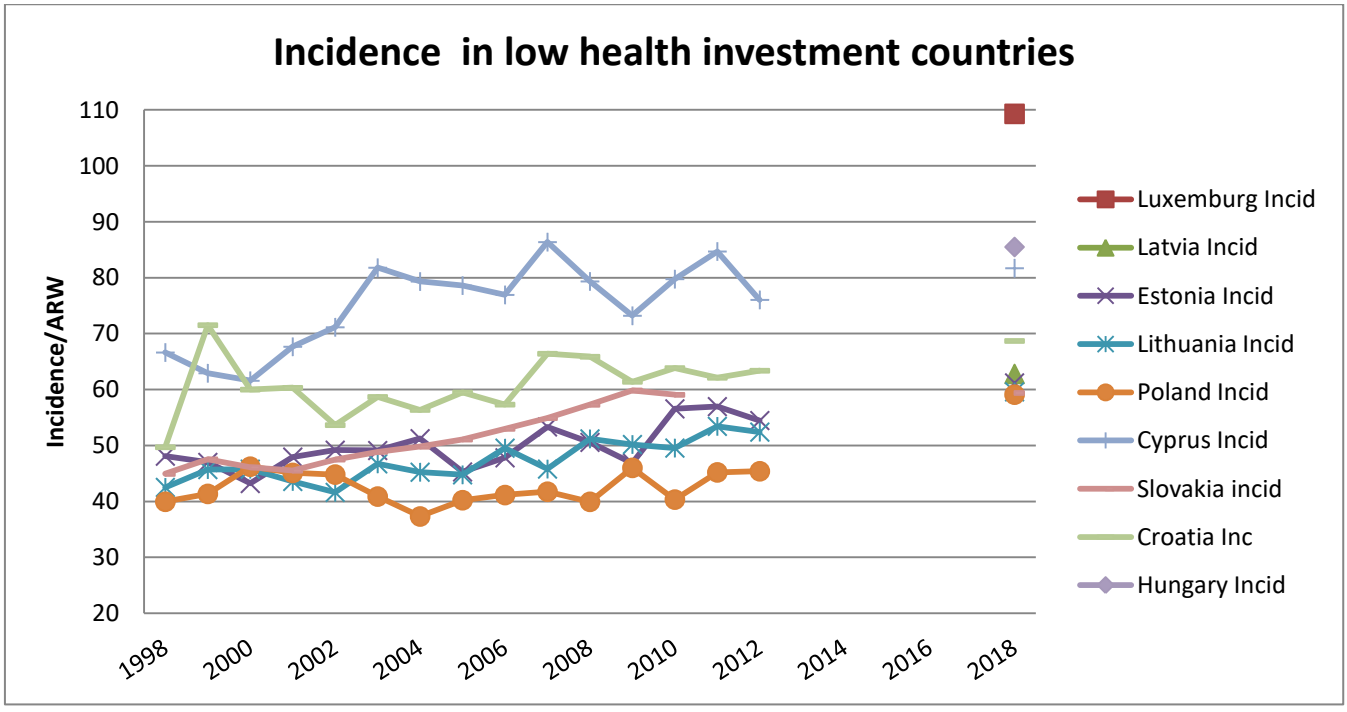


Figure 38. Breast cancer incidence in low health investment countries. The y-axis denotes incidence (number) for LHIC European countries with respect to years on the x-axis.

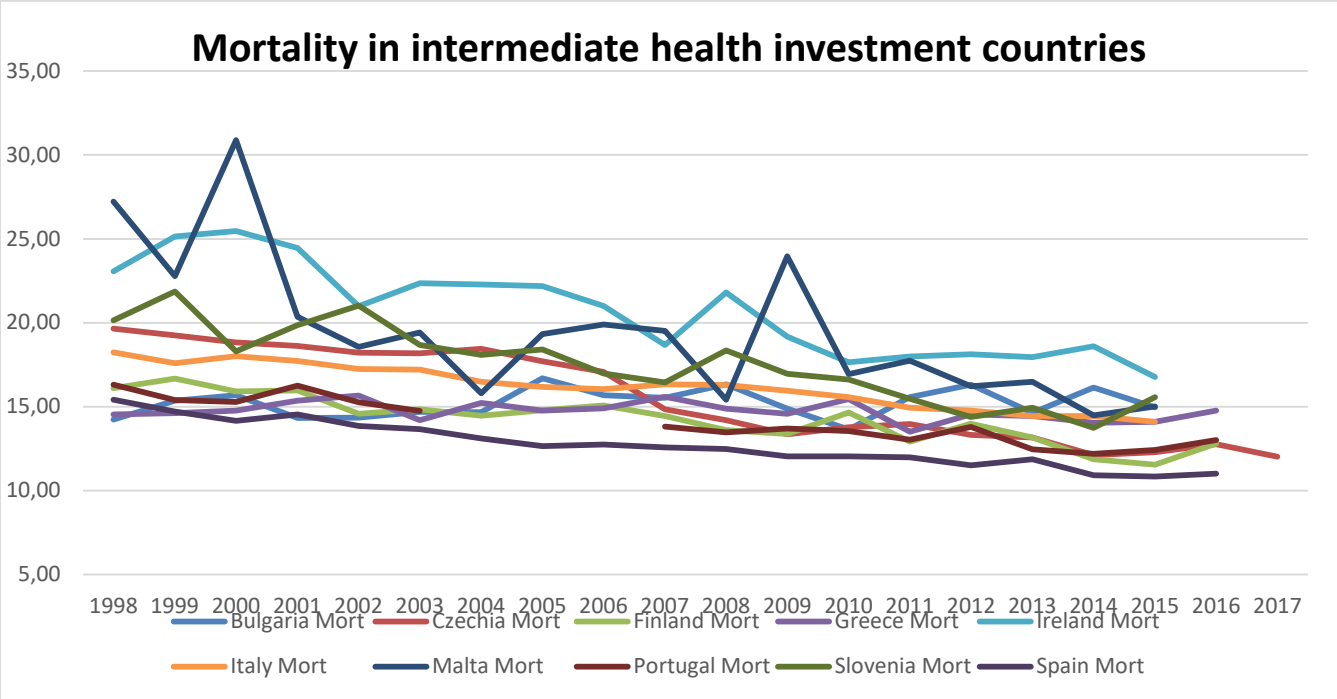


Figure 39. Breast cancer mortality in intermediate health investment countries. The y-axis denotes mortality (number) for IHIC European countries with respect to years on the x-axis.

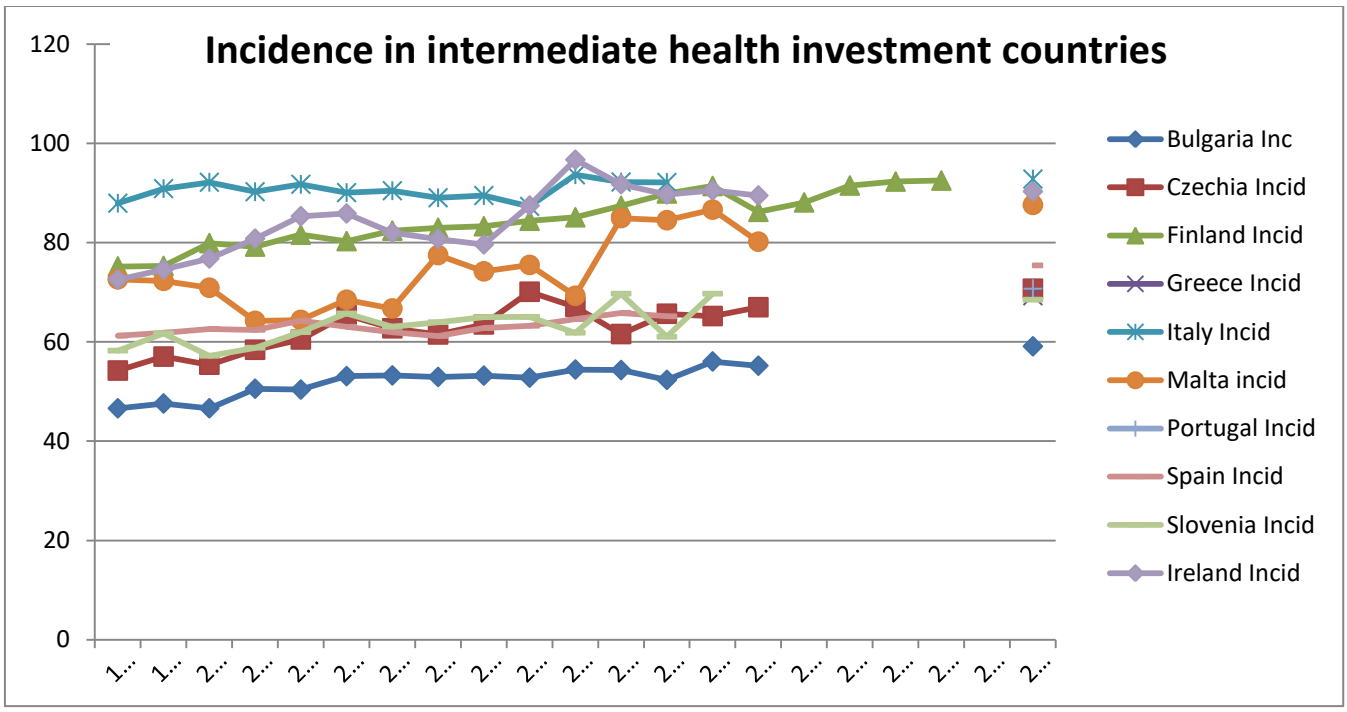


Figure 40. Breast cancer incidence in intermediate health investment countries. The y-axis denotes incidence (number) for IHIC European countries with respect to years on the x-axis.

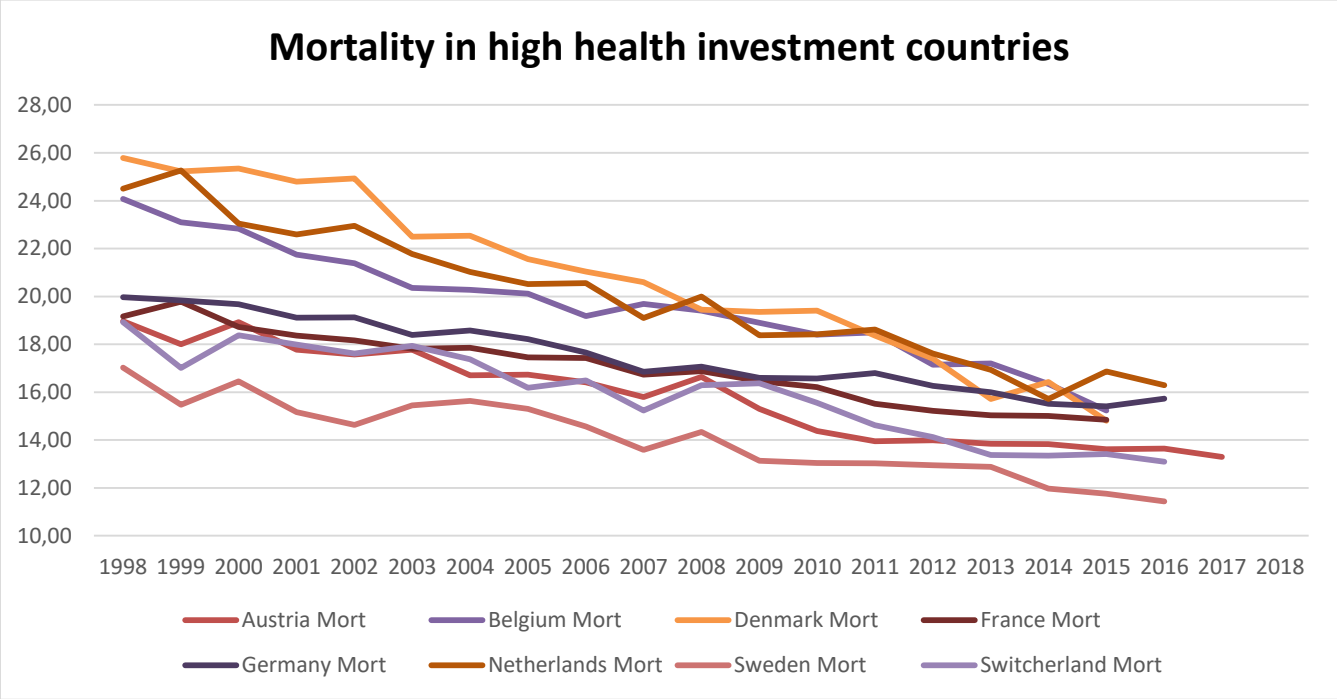


Figure 41. Breast cancer mortality in high health investment countries. The y-axis denotes mortality (number) for HHIC European countries with respect to years on the x-axis.

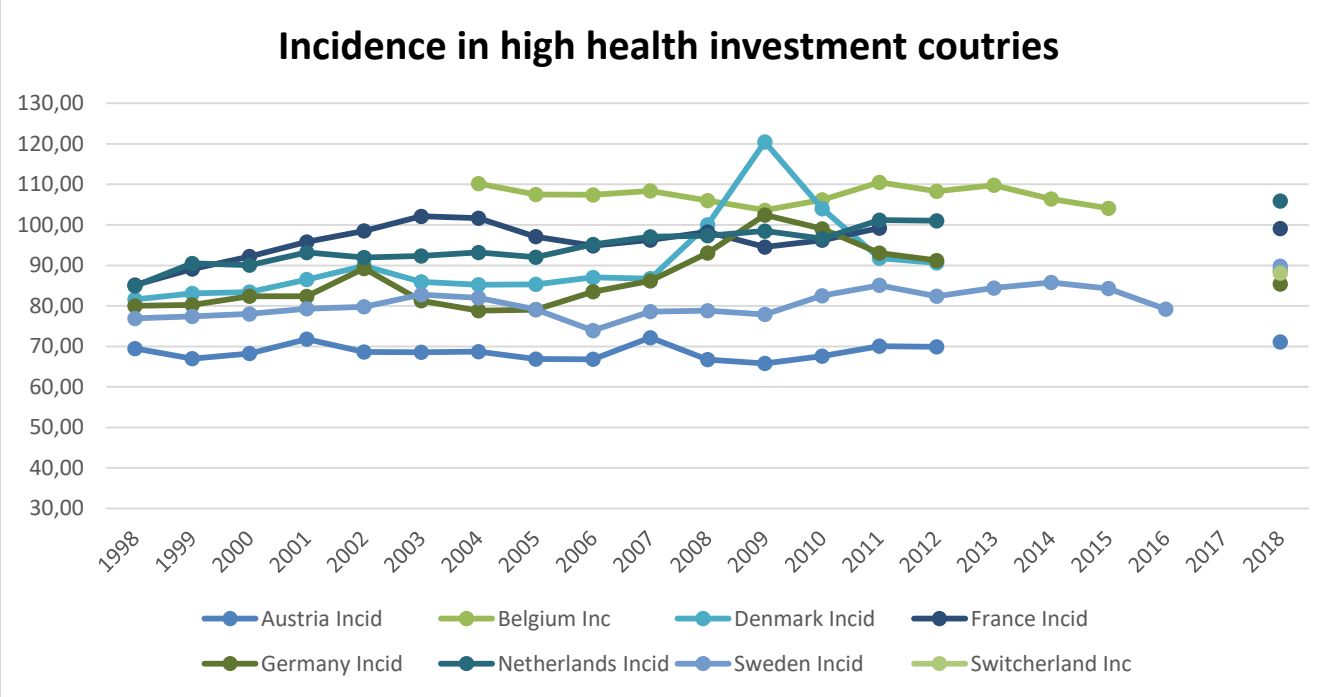


Figure 42. Breast cancer incidence in high health investment countries. The y-axis denotes incidence (number) for HHIC European countries with respect to years on the x-axis.

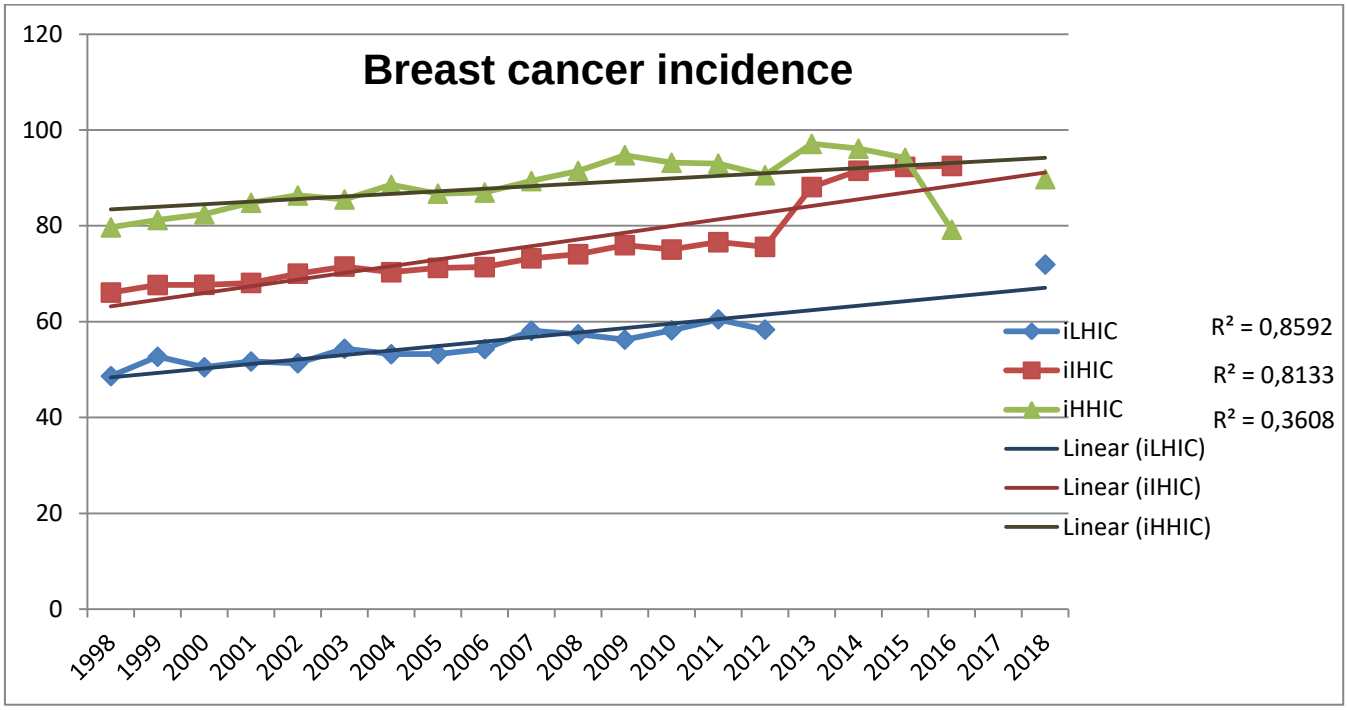


Figure 43. Breast cancer comparative incidence among high, intermediate, and low health investment countries groups. The y-axis denotes incidence (number) for three groups of European countries with respect to years on the x-axis.

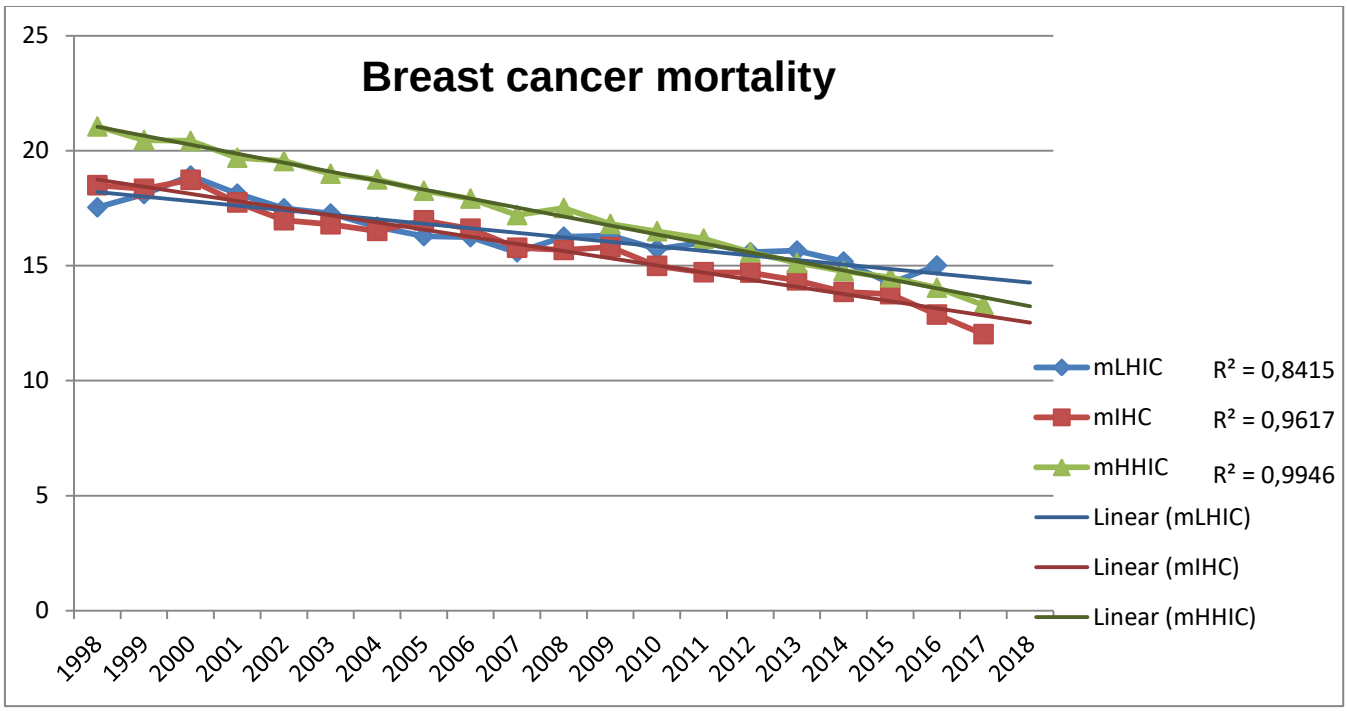


Figure 44. Breast cancer mortality among high, intermediate, and low health investment countries groups. The y-axis denotes mortality (number) for three groups of European countries with respect to years on the x-axis.

Comparing incidences among the three groups using ANOVA analysis, we found that the groups are statistically different, with a p-value of 0.00002 (significant at p <0.01; Figure 45). Moreover, we observed a statistical difference between incidences (p-value 0.0093) and mortalities (p-value 0.0093) using the same analysis on the 2018 projections for breast cancer incidence and mortality for the three groups (p-value 0.00645).

In the HHIC group, a relatively higher decrease in the mortality rate was observed (R^2 of 0.99 compared with 0.84 in LHIC), while the incidence rate increased the least (R^2 of 0.36 vs. 0.85 in LHIC; Figure 46).

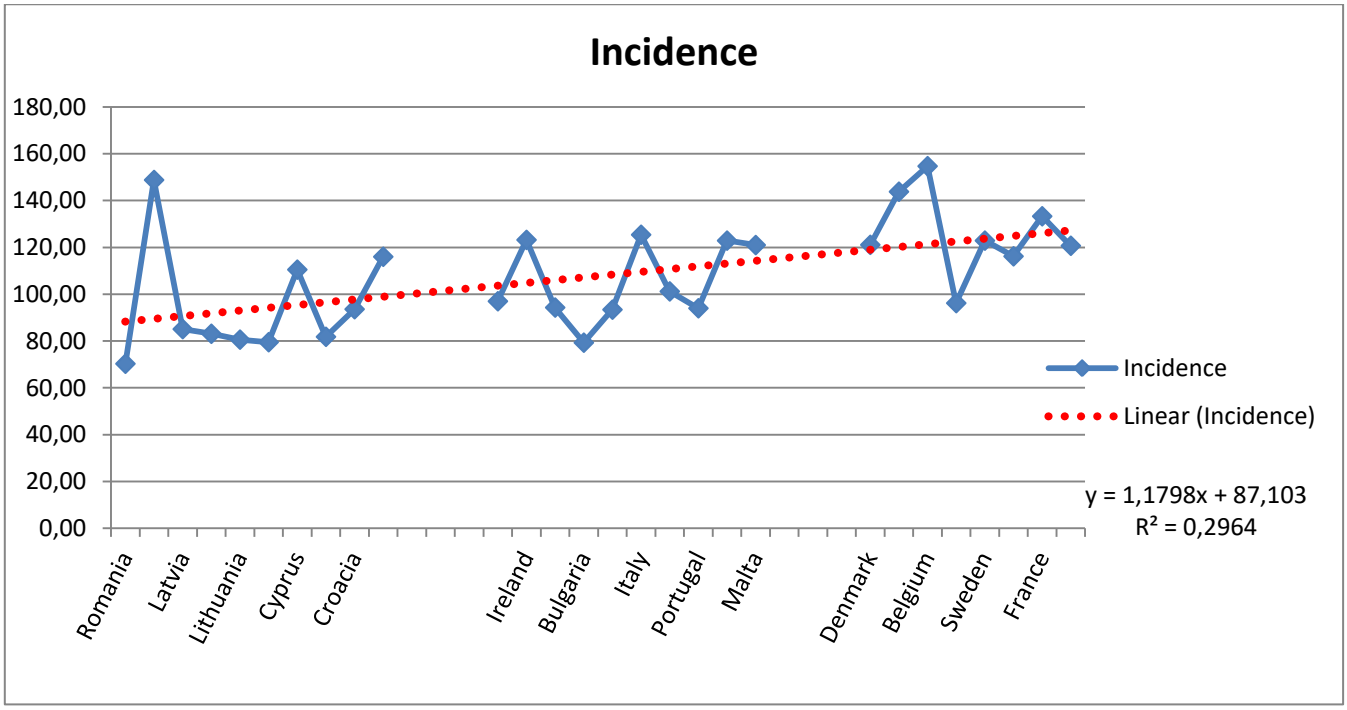


Figure 45. Breast cancer incidence linear evolution trend among three groups across Europe. The y-axis denotes incidence (number) for respective European countries on the x-axis.

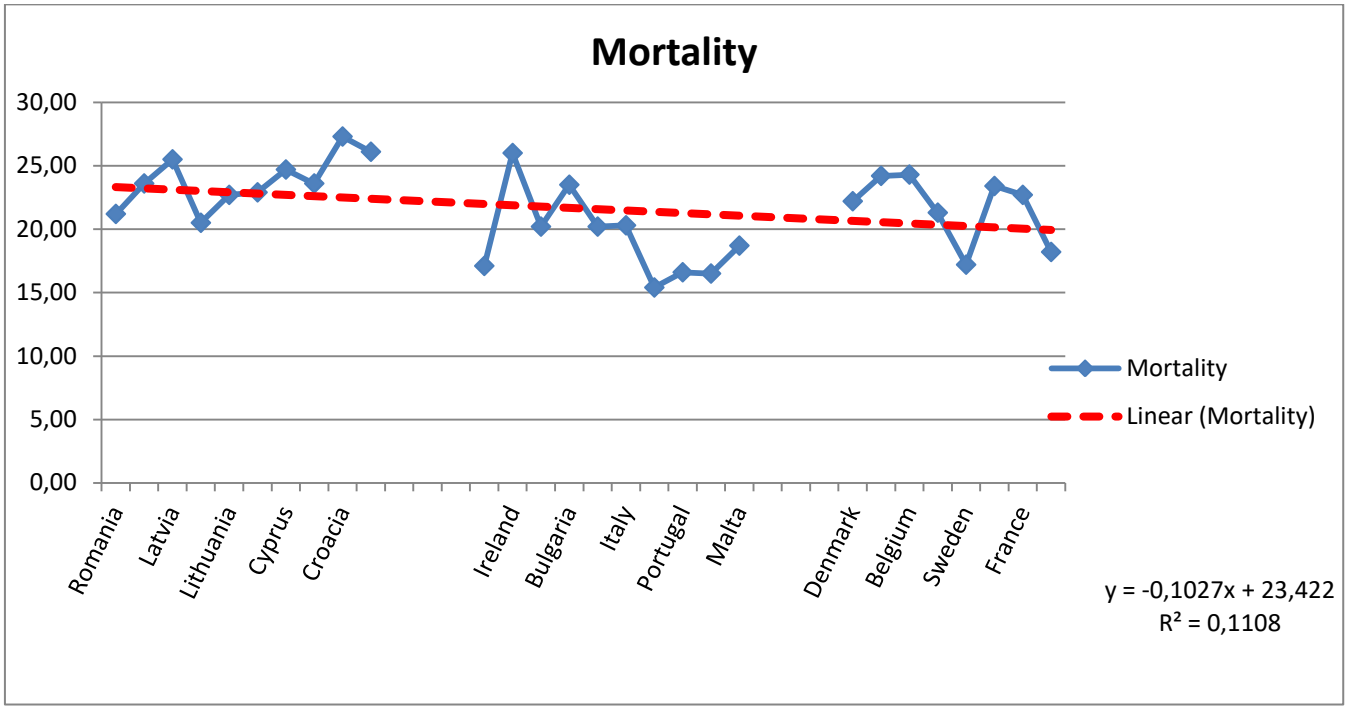


Figure 46. Breast cancer mortality linear evolution trend among three groups across Europe. The y-axis denotes mortality (number) for respective European countries on the x-axis.

Table 26, 27, and 28 show the results of one-way ANOVA, which was used to see if there was a significant difference among the three groups (LHIC, IHIC, and HHIC) in terms of mortality (breast cancer deaths per year) and incidence (new cases of breast cancer per year). The countries for which the data for incidence was not found, namely, Romania, Latvia, Hungary, Greece, Luxemburg, and Switzerland, were excluded from the analysis. The descriptive statistics such as the mean (average) of the mortality and incidence for the three groups of countries are given below in Table 26.

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
Mortality (deaths due to breast cancer per year)	HHIC	153	17.8555	5.35863	.43322	16.9996	18.7114	11.44	70.70
	IHIC	128	16.5451	3.49469	.30889	15.9338	17.1563	10.83	30.88
	LHIC	107	16.0089	1.83969	.17785	15.6563	16.3615	11.73	21.93
	Total	388	16.9139	4.10305	.20830	16.5044	17.3235	10.83	70.70
Incidence (new cases of breast cancer per year)	HHIC	129	85.6995	14.53618	1.27984	83.1672	88.2319	54.22	120.49
	IHIC	111	73.9474	13.96007	1.32503	71.3215	76.5733	46.61	96.69
	LHIC	94	55.1324	12.03364	1.24118	52.6677	57.5972	37.32	86.37
	Total	334	73.1912	18.40915	1.00730	71.2097	75.1726	37.32	120.49

Table 26. Descriptives regarding mortality and incidence of breast cancer for high, intermediate, and low health investment countries

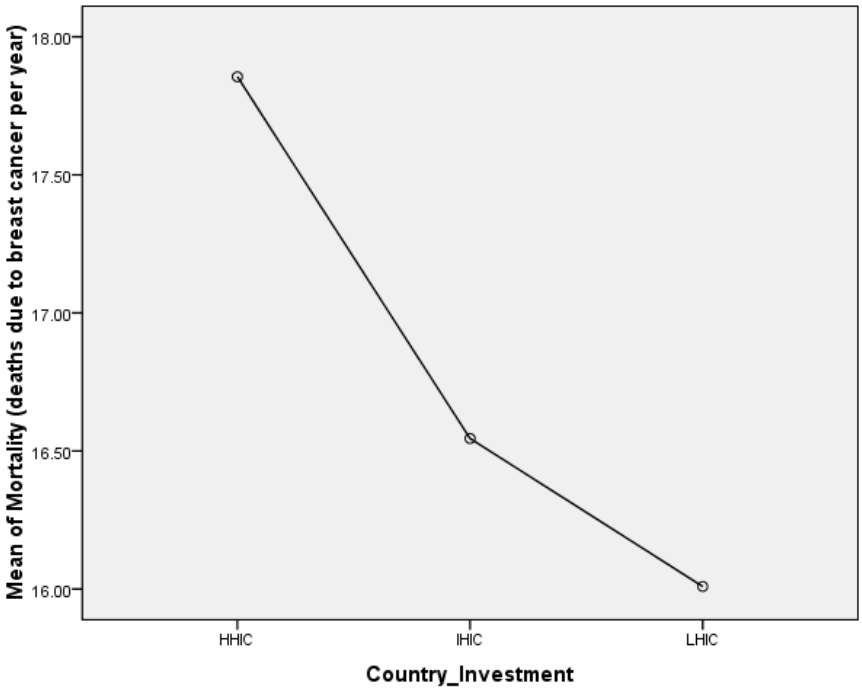
Table 27 shows that Levene's Test of Variance Homogeneity was significant for both variables as the significance value was less than.05. Thus, the variances within each group differ significantly from each other. Moreover, the sig. values of ANOVA were less than .05 for mortality and incidence (.001 and .000, respectively), indicating that there is a significant difference among the three groups of countries for these parameters (Table 28).

	Levene Statistic	df1	df2	Sig.
Mortality (deaths due to breast cancer per year)	6.075	2	385	.003
Incidence (new cases of breast cancer per year)	3.598	2	331	.028

Table 27. Test of homogeneity of variances for mortality and incidence of breast cancer for high, intermediate, and low health investment countries

		Sum of Squares	df	Mean Square	F	Sig.
Mortality (deaths due to breast cancer per year)	Between Groups	240.700	2	120.350	7.385	.001
	Within Groups	6274.457	385	16.297		
	Total	6515.157	387			
Incidence (new cases of breast cancer per year)	Between Groups	50901.756	2	25450.878	135.983	.000
	Within Groups	61950.833	331	187.163		
	Total	112852.589	333			

Table 28. One way analysis of variance for mortality and incidence of breast cancer for high, intermediate, and low health investment countries



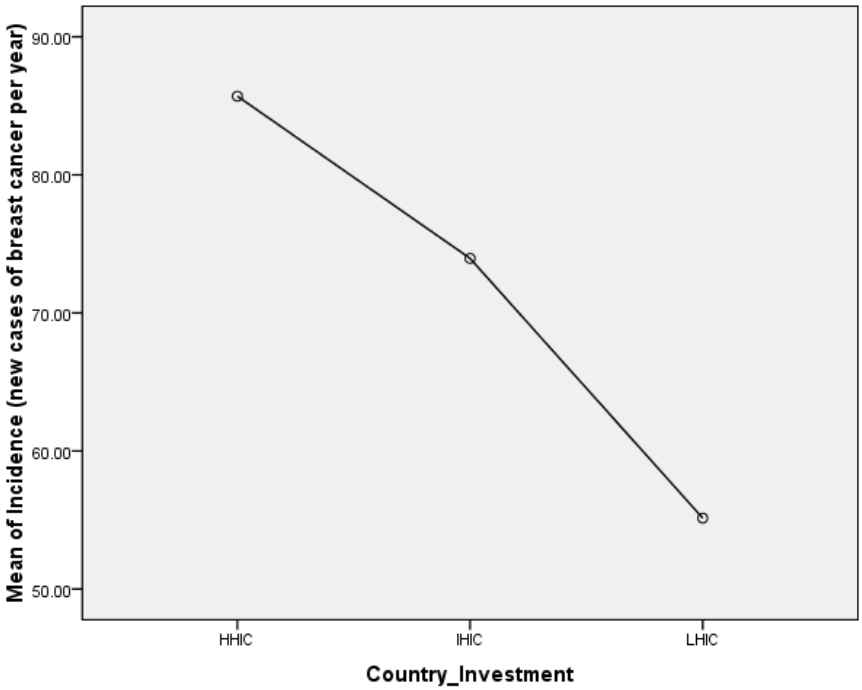


Figure 47. Mean difference in incidence and mortality among high, intermediate, and low health investment countries.

In the above scheme (Figure 47), the mean difference in incidence and mortality among the three groups can be seen, and even though distinct, there is a statistically significant difference in incidences (higher in high health-investment countries) and mortality (also higher in high investment countries).

The variations in breast cancer incidence across European countries can be attributed, at least in part, to differences in over-organized and opportunistic screening activities in various countries, the prevalence and distribution of the major risk factors, and possible biases in methods of calculation (Ferlay J, 2018). The reduction in breast cancer mortality rates in most European (greater decreases in Northern and Western European countries relative to Central and Eastern Europe) probably is a result of the combined effects of earlier detection and a range of improvements in treatment. Another possible factor, in addition to the countries' geopolitical allocation, could be the level of investment in public health systems, allowing for greater equality of access to prevention and treatment strategies.

Since 1986, the European Community's (EC) Committee of Cancer Experts has recommended that systematic population-based screening be implemented for cancers for which such a strategy has been shown to reduce mortality. Later on, the Council of Europe recommended population-based organized mammography screening for breast cancer for women aged 50–69 years and required that screening programs should comply with the European guidelines. (Perry N, 2006.)

EU countries should make an effort to uniformize screening strategies, public awareness, as well access to treatments, at the same time that custom needs of distinct regions are taken into account (Urania Dafnia, Breast Care 2019;14:344–352)

In the latest resolution of the EP 13/02/2019, after continuous resolutions and recommendations almost since EU´s foundation, it is obvious that:

1. Whereas the Charter of Fundamental Rights of the European Union recognizes the right for persons to access preventive health care and the right to benefit from medical treatment;
2. Whereas cancer and other related comorbidities hit both women and men, but with the types of cancer-specific to each sex and approaches to diagnostics and prevention differing for women and men, there is a need for a targeted policy;
3. Whereas the main forms of cancer affecting women are breast, uterine and cervical cancers; whereas breast cancer is the most common cancer that has fatal consequences among the female population, not only within the EU (16 %), but also globally;
4. Whereas data show that women who work night shifts face a 30 % greater risk of developing breast cancer;
5. Whereas data show that up to half of all cancer deaths could be prevented[(14)] if the cancer is detected on time and adequately treated;
6. Whereas the survival rate of patients affected by breast cancer can reach 80 % in cases of early diagnosis and timely treatment;

7. Whereas women affected by cancer also often have to confront serious and frequently underestimated psychological problems, especially in cases where a mastectomy or a hysterectomy is performed;

8. Whereas cancer can have negative fertility and physical consequences for women, such as pain, lymphedema, etc.;

9. Whereas cancer negatively affects women's personal, social and professional lives and deals a heavy blow to their self-esteem and self-acceptance;

10. Whereas even today, the EU continues to be characterized by many significant disparities both within and between the member states: in private and public settings, in rural and urban areas, in regions and cities, and even in hospitals in the same city, when it comes to the quality of the treatment provided; whereas member states have vastly different health systems and varying standards; whereas there is a serious gap in incidence and mortality between Central and Eastern Europe and the European average; whereas responsibility for the organization of healthcare systems and provisions for cancer diagnosis and treatment rests with the individual Member States; whereas cooperation and exchange of best practices at EU level is of great added value;

1. Welcomes the progress made with the early detection rate, which has boosted survival rates among breast cancer patients, and points out that all Member States should aim to improve treatments of other types of cancer, such as ovarian or cervical cancer, and related comorbidities

2. Points out that breast cancer is the most common fatal cancer among women in the EU

3. Invites the Commission and the member states to continue to accord the fight against cancer priority status in health policy by developing and putting in place a comprehensive EU strategy and evidence-based, cost-effective policies against cancer and related comorbidities

4. Stresses that while responsibility for organizing healthcare systems and the provision of long-term healthcare rests with the individual Member States, cooperation at the European level, together with the efficient use of EU funds, can contribute to the development of an effective EU strategy against cancer

5. Calls on the Commission to step up its efforts to improve EU-wide coordination within the field of women's cancer research which is very fragmented and diverse across the EU

6. Invites the Commission and the member states to establish awareness campaigns on gender-specific cancers that disproportionally affect women and on how to prevent cancer, providing information about the modifiable lifestyle factors for prevention, such as changes in diet, alcohol consumption, and exercise; stresses that these should also encourage women to take part in cancer screening programs for breast

7. Invites the member states to collaborate on cancer prevention by fully implementing the European Code against Cancer

8. Notes that one-third of the population still lacks high-quality cancer registration, mostly in regions with the poorest resources and health status;

9. Reiterates that data collection on cancer-screening activities should be linked with Eurostat's European Health Interview Survey (EHIS) and National Health Interview Surveys to obtain more precise information on attendance and intervals in spontaneous and organized screening settings;
10. Welcomes the Commission's support in developing the European Quality Assurance Scheme for Breast Cancer Services; asserts that this scheme should provide guidance on rehabilitation, survivorship, and palliative care, with a particular focus on the needs of women cancer patients and survivors in vulnerable situations;
11. Invites the member states to improve access to timely screening through more effective funding and greater resources and to initiate awareness-raising campaigns encouraging all groups at risk to take advantage of early medical check-ups (Anon., s.d.)

In the latest update of the European Commission Initiative on Breast Cancer (28/05/2020):

" Mammography screening is recommended for women between the ages of 45 and 74 and strongly recommended for women between the ages of 50 and 69. " and "Although in 2003 the Council of the EU recommended the implementation of organized screening programs, in practice in Europe ***organized*** *or* ***non-organized screening*** *co-existed and there are some uncertainties regarding their effectiveness."*

That is 17 years after the first recommendation; according to the Europa Donna survey report (Europa Donna, 2020) published in September 2020, one can still observe that:

- Just sixty-two percent reported that breast screening in their country is performed through state-of-the-art technology such as digital mammography or digital breast tomosynthesis
- Only 59% of countries that responded in the case of high mammographic breast density in an otherwise asymptomatic woman additional tests are generally carried out through digital mammography or DBT.
- Just fifty-five percent of respondents indicated that their country has Specialist Breast Units (SBUs), but several stated either that they are not certified or, as one put it, "far from all meet the EUSOMA standard."
- Just 66% reported that SBUs in their country have multidisciplinary teams, though some do not have a data manager or a specially trained breast care nurse.
- Just 34% indicated that there is a certification/accreditation system for SBUs in their country, and 41% said that there is an authority in charge of monitoring the quality of SBUs in their country.
- Just 65% of European women living with MBC have access to SBUs.

- Just 54% said that their country had passed legislation protecting or implementing breast cancer survivors' right to return to work;
- Just 42% of countries have passed legislation protecting or implementing survivors' right to access insurance
- Just only 12% of countries polled have passed "right to be forgotten" legislation for cancer survivors.

A recent systematic review (Nadine Zielonke 1, 2020 Mar) pointed out that organized screening reduced breast cancer mortality in all European regions where screening was implemented and monitored (lacking sufficient information for Eastern Europe). Most researchers agree that combining screening and treatment reduces BC mortality, though some argue that the reduction in BC mortality observed in Europe since the 1990s is primarily due to changes in cancer. (Nadine Zielonke 1, 2020 Mar).

The MyPeBS (DELALOGE, 2018) trial results are expected to highlight future directions toward standard screening versus personalized risk-stratified screening. MyPeBS is an international randomized, open-label, multicentric study assessing the effectiveness of a risk-based breast cancer screening strategy compared to standard screening (according to the current national guidelines in each participating country) for detecting stage 2 or higher breast cancers. The investigators plan to enroll 85,000 participants from five different countries (three EU countries, UK, and Israel). It is critical that this study succeeds in reducing the overall burden of breast cancer by allowing earlier detection of breast cancer in women at a higher risk (cases in which an earlier diagnosis is associated with a better prognosis, fewer treatments needs, less morbidity from the therapies, and lower costs), and on the other hand, reduces the amount of over-diagnosed breast cancers (and thus overtreatment) by extending the screening interval in women with low risk.

It will be interesting to see which direction breast screening takes by 2021.

5.2.2 Imaging tecniques

5.2.2.1 Automated whole breast ultrasound (ABUS)

Ultrasound is a popular and effective strategy for identifying breast cancer (J. Eisenbrey, 2016). The shortcomings of the Human Kept Ultrasonography Device (HHUS) prompted the creation of ABUS. There is no requirement for highly trained personnel to operate the ABUS system. This approach delivers high-quality, reliable, and reproducible images (Geisel J, 2018). In this system, interpretation and capturing are dealt with separately. According to

certain reports, ABUS has the same or better lesion detection capability as HHUS, while it requires less staff training and is relatively automated (Gilbert FJ, 2018).

- While studies have suggested its utility as a supplementary screening method for females with denser breasts, the possible therapeutic use of ABUS in the coming 5 - 10 years is not clear (Brem RF, 2015).
- Research shows that combining ABUS and FFDM with optical mammography results in slightly higher cancer diagnosis rates among women with denser breasts. (Corsetti V, 2008).
- Since no safety concerns have been found and the testing procedure is far less intrusive than other modalities, such as automated mammography, ABUS is expected to be highly acceptable to females (Geisel J, 2018)
- The technology has not been put into any screening program or rendered regarding national care recommendations for asymptomatic women. Certain reservations concerning its use remain unanswered, for instance, providing effective and responsive exams by relevant experts and increasing recall rates (Geisel J, 2018).
- There is no proof that ABUS prevents BC-related deaths by detecting the disease timely (Ohuchi N, 2016).

5.2.2.2 Contrast enhanced mammography

Contrast-enhanced mammography (CEM) is a highly advanced methodology that enhances digital mammography precision by using iodinated contrast before mammography to visualize improving neovascularity, which indicates the location of cancer. CEM allows the assessment of morphologic characteristics of breast tumors while still representing the presence of a tumor.

- Clinical trials are ongoing to evaluate the screening efficiency of CEM. The clinical research has shown that the approach does have a good potential (Ghaderi KF, 2019) (Sung JS, 2019).
- There is currently no indication regarding when the clinical potential of this technique will be exploited for BC screening; nevertheless, the prospective trials indicate a greater specificity, sensitivity, and prediction potential for CEM as compared with conventional mammography (Stuart Beresford, 2018).
- There is no adequate evidence whether the early detection by CEM would reduce the number of deaths related to BC.

- By now, CEM has not been integrated into any BC screening programs. Moreover, no national position statements on its usage have been issued for asymptomatic women's BC screening.

5.2.2.3 Digital breast tomosynthesis

Digital breast tomosynthesis (DBT) is a modern digital mammography technique. It produces quasi–3-dimensional representations of the breast tissues with enhanced specificity as well as sensitivity (Zackrisson S, 2018). Initially, DBT was employed as a supplemental approach with mammography, but it is now being exploited as a replacement.

- The combinatorial use of FFDM + DBT and DBT + s2DM offers better cancer diagnosis. Moreover, DBT is more perceptive than FFDM alone. However, it has been noticed that reading technique also influences the magnitude of amelioration (Hodgson R, 2016)
- DBT, when used as a complement to FFDM, has been shown to decrease recall rates and false-positive outcomes as opposed to FFDM alone. Nevertheless, various studies have noticed some differences, which may be due to the already poor recall rates in certain screening programs (Daniela Bernardi, 2016).
- Although DBT increases BC diagnosis and reduces recall rates versus FFDM alone, there is a lack of sufficient evidence regarding sole usage of DBT (Per Skaane, Feb 19 2019).
- DBT certainly improves cancer detection; however, there is inadequate evidence that DBT can reduce the death rate by early detection of BC (Nehmat Houssami, 2019).

5.2.2.4 Ductoscopy

Mammary ductoscopy is a new technique that allows direct imaging of the ductal arrangement. The technique employs a nipple cânula to analyze epithelial cells and other breast milk ducts' internal characteristics (Tang SS, 2011). This technique uses flexible or rigid scopes having a range of diameter from 0.7 to 1.2mm. The scopes provide a magnification of up to 60 times, thus ensuring high-definition images (Tang SS, 2011).

- The current studies have made use of this technology only for ductoscopy of symptomatic individuals. Its potential for screening symptomless BC is not clear yet (Ye Han, 2017)
- Currently, it is not clear if ductoscopy will be helpful as a diagnostic technique in the future. It is also not obvious whether the approach will be acceptable as a screening modality to women.

- For now, scientific evidence is inadequate to establish if ductoscopy will limit breast cancer mortality by identifying the disease early.

5.2.2.5 Magnetic resonance imaging

Magnetic resonance imaging (MRI) was initially introduced in the 1980s by Heywang (S H Heywang, Mar-Apr 1986) and Kaiser and Zeitler (W A Kaiser 1, 1989). Variations of the technique were later introduced to enhance efficiency and sensitivity. For instance, the permeability of blood vessels is assessed using contrast material–enhanced MRI, which employs an intravenous contrast agent (gadolinium chelate) to shorten the local T1 duration. This variation provides higher signals on T1-weighted photographs (Ritse M. Mann, 2019). Neoangiogenesis induces the development of leaky vessels, which allows faster contrast agent extravasation. In spite of various advancements in breast MRI, this theory remains the foundation of MRI protocols. Nonetheless, in the current era, the majority of the MRI protocols are multiparametric (Ritse M. Mann, 2019).

- In certain cases, MRI provides a direct clinical advantage as a complement to mammography, especially for women at high risk for breast cancer (Marta Román, 2019). In patients with an elevated risk of BC, MRI is less specific but more sensitive than mammography in detecting insignificant tumors. It is a non-invasive imaging strategy that creates incredibly accurate and precise photographs that are otherwise difficult to image through other techniques. Another advantage is the fact that MRI does not subject tissue to ionizing radiation, while mammography does. Moreover, the chemical agents in MRI are less prone to trigger an allergic response than iodine-based agents that other imaging modalities exploit.
- In spite of several advantages mentioned above, the use of MRI faces limitations for general population screening. The technique has a high rate of false positives, leading to over-diagnosis and thus increasing the associated costs (K.ShettyMD, 2011). False positives cause the unwarranted consumption of limited resources and clinical facilities. Furthermore, mammography detects certain tumors more effectively than MRI, for instance, DCIS.
- MRI has high costs. Additionally, although MRI is painless, the patient has to stay still, which is a challenge for claustrophobic people. Another reported demerit relates to the accretion of gadolinium as it has been suggested that it can accumulate in individuals who undertake several contrast-enhanced MRIs.

- The statements of the American Cancer Society and the European Society of Breast Cancer Specialists are available regarding the usage of MRI in BC screening. Cott Chubiz et al. (Cott Chubiz JE, 2013) suggested alternating screening through mammography and MRI every six months after 30 years of age. Nevertheless, no national breast screening program has integrated MRI.

5.2.2.6 Microwave imaging

Microwave imaging deduces dielectric properties (permittivity and conductivity) or contrast within a specified volume, referred to as the imaging domain, using electromagnetic radiation. The electromagnetic radiations with frequencies ranging from 0.3 to 9.0 GHz are used. The electromagnetic radiations illuminate the imaging volume by passing through the imaging domain. Radiations are dispersed by dielectric contrasts, following which data is captured to create the image. Numerous variations of the system are available, some of which also offer 3D images (Brian M. Moloney, 2020)

- The application of microwave imaging in asymptomatic women's BC identification is only in its initial stages. The emphasis of the current studies is on providing efficient microwave imaging devices with adequate sensitivity and detectability or clinical usage. Like other techniques, improvements are being introduced in this strategy as well. Research has relatively progressed in the usage of ultrawideband frequency systems. Moreover, Galway University Hospital (CRFG) introduced the Wavelia system with a low-power two components electromagnetic wave system. This system conducts a non-invasive and non-compressive breast assessment. Its first subsystem is called the optical breast contour detection (OBCD) subsystem that gathers data to further enhance the precision of the corresponding microwave breast imaging subsystem. The second subsystem conducts a longitudinal scan of the pendulous breast and captures sequential coronal segments (Fasoula, et al., 2019).
- There is currently no estimate of when microwave imaging's maximum therapeutic promise for breast cancer diagnosis would be realized. However, various trials indicate that this system can be utilized in the field.

5.2.2.7 Molecular breast imaging

The molecular breast imaging (MBI) technique is an advancement of scintimammography, a previous nuclear imaging technique that utilized a conventional gamma camera instead of a breast-specific one. Because of the use of a conventional gamma camera, scintimammography presented snags in detecting tumors smaller than 1cm (Newel1, 2015).

The MBI offers relatively high-quality photographs. Moreover, it employs smaller doses of radiation and is thus a potential BC screening technique (BE Adrada, 2016).

- The efficacy of MBI for screening purposes has been reported in some retrospective trials; nevertheless, large-scale studies should be conducted to illustrate whether this technique could be a potential option for early cancer detection in symptomless females.
- At this point, it is not clear when MBI's therapeutic promises for BC diagnosis would be realized. Current studies have found excellent sensitivity and modest specificity thresholds. When MBI is used in combination with mammography, cancer diagnosis rates increase.
- New MBI systems show good detection and use low radiation doses (~2.4 mSv). The expense of supplementing screening through MBI is greater per test versus mammography alone, but when MBI is combined with mammography, the expense per cancer identified is lower.
- While these findings could underrate MBI for females with dense breasts due to categorization problems, there is increasing support regarding MBI's effectiveness in the early BC identification for females with dense breasts in comparison to mammographic screening.

5.2.2.8 Spectroscopy

Vibrational spectroscopy techniques have gained much attention due to their ability to deliver diagnostic details and predict tumors' biochemical progress non-invasively. One of such approaches called Raman spectroscopy detects the inelastic scattering of photons in the near-IR, visible, or near-UV range as electromagnetic energy is applied. Since this change is peculiar to each molecule, the Raman continuum may be used as a fingerprint (Daniela Lazaro-Pacheco, 2019).

- With recent studies focused on evolving and optimizing technologies for clinical usage, the possible application of spectroscopic tools in BC screening of asymptomatic populations is unknown yet.
- According to some clinical trials, optical mammography can find therapeutic applications in high-risk populations. Spectroscopy techniques for BC diagnosis are improving over time.

5.2.2.9 Thermography

Thermography is a technique that measures temperature using infrared radiation. It is a non-invasive, radiation-free, non-intrusive, and safe procedure in comparison to other modalities.

- The usage of thermography as a method for BC screening of asymptomatic patients is currently not supported by substantial scientific evidence. The studies conducted in this context mainly involve a limited number of samples. Moreover, the findings are incredibly variable.
- Thermography and EIT (electrical impedance tomography) are not novel methods for BC screening, and they were not considered equivalent until the last decade. However, the developments in computation and thermal camera efficiency contributed to the emergence of machine learning and CAD systems that could help physicians analyze bio-medical results, and thus, these techniques emerged as potential approaches for BC screening (J. Zuluaga-Gomez, 2019).

5.2.2.10 Tomography

5.2.2.10.1 Computer tomography

Breast CT systems for early BC diagnosis are in the initial phases yet. Currently, only observational findings are found in the literature.

- Breast CT detects breast tumors almost as good as or even better than mammography, but it is less successful at imaging microcalcifications. As a result, the use of breast CT as a predominant BC screening method in symptomless individuals may remain limited.
- The complete therapeutic promise of breast CT for timely diagnosis of BC in symptomless women is yet to be understood. It is not clear when this technique will be clinically employed for screening purposes.
- Breast CT screening technologies have improved in recent years, reaching radiation exposure ranges similar to traditional mammography. Moreover, the expense is not expected to be a deterrent to using breast CT for BC diagnosis.
- Despite the lack of primary research, one review suggested that breast CT may be effective in BC screening, particularly in women with dense breasts.
- Breast CT tends to be slightly more convenient compared with mammography as it does not involve breast compression.
- There is no indication at the moment as if breast CT scans will help prevent BC deaths by early diagnosis.

5.2.2.10.2 Cone-beam breast CT

The investigations into the usage of CBBCT are currently in the early stages. Clinical experiments utilizing asymptomatic samples are not being conducted at present.

- Presently, it is not clear when CBBCT's clinical application for breast cancer screening would be realized. Having said that, the findings of studies utilizing symptomatic samples are encouraging.
- According to current studies, there is no statistical difference in radiation exposure between CBBCT and FFDM scans. The cost of CBBCT was not mentioned in any of the studies that were found.
- No report was found regarding the use of CBBCT scan in non-symptomatic females with dense breasts, but findings from symptomatic samples indicate that CE-CBBCT can offer greater sensitivity for such patients versus FFDM.
- Patient comfort is reported to be higher in the case of CBBCT as compared with mammography.

5.2.2.10.3 Positron emission tomography

The research regarding the use of Positron Emission Tomography (PET) for early BC diagnosis in symptomless women has advanced to prospective clinical investigations; nevertheless, more studies are needed to assess the safety and efficacy of this technique.

- There is no definite timeframe for when PET's clinical potential will be realized for screening purposes; however, the literature indicates that PET's capacity to identify small tumors may be limited.
- The use of a high amount of radiation and relatively higher costs are two major limitations of the PET system that may hinder its adoption for routine screening of asymptomatic individuals.
- Data was not found regarding PET's sensitivity and precision for symptomless people with dense breasts or females having undergone breast surgery/augmentation.
- There is also a lack of evidence about the acceptability of PET. For FFDM, such information is available.
- According to the findings of a screening program in Japan, FDG-PET showed 84% sensitivity in identifying BC, which was not substantially different from mammography rates. Moreover, FDG-PET scans encounter concerns about radiation dosage and expense, which limit their incorporation in screening programs.
- There is also a lack of national position statements about the usage of PET to identify BC in non-symptomatic females.
- At present, available data is insufficient to determine if PET imaging may mitigate BC deaths by identifying tumors in symptomless females.

5.2.3 Biomarkers

5.2.3.1 Blood tests

- Circulating tumor DNA (ctDNA) is a form of circulating cell-free DNA that is associated with several cancers, including BC. Since ctDNA is formed as a consequence of cell death, it may often occur due to other health issues such as pregnancy, myocardial infarction, or severe infections (Cree et al., 2017). Consequently, elevated amounts of ctDNA are not cancer-specific and can decrease specificity when exploited in asymptomatic women's BC screening. Currently, researchers are working to classify ctDNA markers that are unique to BC. Methylation in a panel of tumor-suppressor genes is detected in screening blood tests dependent on ctDNA. Since no single gene is methylated in any BC specimen, a panel of genes is needed (Kloten et al., 2013). There is presently no theoretical agreement about which genes can be used in the testing panel. A vast majority of the research in this field is currently focused on identifying genes that have appropriate degrees of specificity and sensitivity.
- Circulating tumor cells (CTCs) derive from the primary tumor site and circulate in the peripheral blood system. In order to use the characteristic features of CTCs for diagnostic purposes, attempts were carried out to develop blood tests that could detect CTCs; however, so far, no single characteristic of CTCs has been identified that could be used to distinguish them (Mostert et al., 2009) accurately. Moreover, CTCs occur at low levels in the bloodstream. Another drawback is the fact that different types of tumors give rise to dissimilar CTC attributes. These hitches limit the specificity and sensitivity of CTCs in identifying BC early and preclude the use of CTCs detection approaches for screening purposes. Nevertheless, research is underway at concept testing stages to utilize CTC measurement for BC screening. The aim of the current research is to find the apposite set of CTC markers to ensure enough sensitivity and specificity. Just one research that investigated the use of CTCs in BC screening came to our knowledge. The 2009 study by Mostert et al. also looked into the usage of CTCs in cancer screening in general.
- Another possible blood testing-based approach is the use of circulating microRNAs. BC patients exhibit a raised level of microRNAs (Ng et al., 2013). In the case of cancers, the MicroRNAs expression is modified. MicroRNA levels in plasma and serum are otherwise stable, making them a valuable test predictor for BC screening (Godfrey et al., 2013). Even though their potential for breast cancer screening has not been extensively explored, the research on microRNA usage is still more advanced versus CTC or cfDNA tests. Potential

field trials on the application of microRNA monitoring in asymptomatic women's breast cancer screening have started, with the findings of one research released (Godfrey et al., 2013), while some other studies are also in progress (Giordano, Gallo, Petracci, Chiorino, & Segnan, 2017). In the future, microRNAs monitoring may emerge as a valuable tool for population screening for breast cancer.

- Overall, blood testing for asymptomatic women's breast cancer screening is currently in its early stages. Most of the literature in this context relates to the identification of potential biomarkers that could offer adequate sensitivity and accuracy to justify their application. Work on microRNAs is comparatively advanced regarding screening purposes; however, there is a need for more research. Currently, it is difficult to predict when blood testing will clinically be used for BC diagnosis. Nevertheless, initial findings from retrospective trials are encouraging, and technology is steadily ameliorating.

5.2.3.2 Saliva testing

Saliva testing has also been recognized as a potential strategy to detect asymptomatic breast cancer in women. Saliva testing has numerous benefits, including the fact that it is easy, cost-effective, and non-invasive. Moreover, it does not require specialized experience (Liu & Duan, 2012; Pfaffe, Cooper-White, Beyerlein, Kostner, & Punyadeera, 2011). Furthermore, since saliva is continuously produced, it may offer an accurate description of state and health at the time of collection (Streckfus, Brown, & Bull, 2010). By now, no sufficiently reliable test is available for regular or specific saliva-based clinical screening (Sugimoto, Wong, Hirayama, Soga, & Tomita, 2010). Nevertheless, studies are underway to exploit the diagnostic potential of this approach. Research is being conducted to refine saliva testing to a level that its maximum therapeutic value could be realized. Currently, work on saliva testing for BC screening of symptomless females is in the initial stages for finding potential biomarkers that could specifically detect BC cancer with adequate sensitivity.

5.2.3.3 Breathe biopsy

Exhaled air contains thousands of volatile components and, therefore, is a rich resource to get an insight into the human body's biological status. Breath biopsy (BB) is an entirely non-invasive procedure that analyzes breath samples for early disease detection and determines treatment response. This approach detects the presence of a particular biomarker (volatile compound) by analyzing breath samples. For identifying biomarkers through mass spectroscopy (MS), different approaches, including gas chromatography, field asymmetric ion mobility spectrometry (FAIMS), and heat desorption, are employed. Medical breath biopsy has

significantly advanced over time due to recent developments (Abderrahman B, 2019). The accurate, early, and cost-effective detection are the major aims of breath biopsy. An instrument developed on this concept, called the ReCIVA sampler, is a non-invasive device that asserts to capture an exhaled breath and its volatile organic compounds in one minute.

5.2.3.4 X-ray diffraction of hair

It is a non-invasive approach that employs synchrotron small-angle X-ray scattering of hair for cancer diagnosis. In females with BC, a variation in X-ray diffraction of hair has been reported. The changes in α-keratin of the patients' hair can be used to differentiate them from the regular pattern of individuals (Mistry DAH, 2012). Patients with BC showed that an "extra section" might potentially bind to α-keratin (Corino GL, 2009). It is also conceivable that eliminating some unwanted content from the hair fiber may restore its X-beam diffraction pattern. For X-ray diffraction analysis, a single hair fiber is delicately expelled and stacked into a holder that can accommodate up to 10 single hair filaments. Expansion springs are used in the sample holders to grasp the fiber to ensure proper orientation for analysis. The X-ray diffraction analysis is a potential technique for accurate and early detection of breast cancer.

6 Conclusions

6.1 Male Breast Cancer

1. To the best of our knowledge, this is the first study that explored the silent breast cancer incidence among men. We noticed that MBC is a rare disease, and its natural reservoir is extremely low, just like its incidence. Nevertheless, the few cases that exist need to be treated appropriately.
2. The screening of the general population for MBC is unnecessary; however, it should be targeted for men at elevated risk for breast cancer. (Yiming Gao, 2019)
3. Several novel targets/pathways have been identified to date, but their clinical significance/application has yet to be demonstrated.
4. There is a need for consensus, and for that, clinical trials should be a priority. Fortunately, male breast cancer dedicated guidelines have started to appear (Hassett MJ, 2020). Even though we have started to decode, we are still “lost in translation!” (Johansson & al, 2014).

6.2 Female breast cancer

Breast population-based screening is intended to detect breast cancer at an early stage to enable lower mortality rates. (Peintinger, 2019) Three separate meta-analyses demonstrated a statistically significant (18%–20%) reduction in mortality among the women who were invited to screen (M G Marmot, 2013). An overall estimate of various studies is that the mean reduction in mortality across all models is 15%, with the greatest reduction (39.6%) realized in the model initiating annual screening at age 40 (Jeanne S. Mandelblatt, 2016).

Most societies making recommendations about breast cancer screening consider overdiagnosis as a substantial disadvantage. Overdiagnosis refers to the potential for overdetection of disease in asymptomatic women who are screened, which ultimately leads to overtreatment; in other words, diagnosing and treating breast cancer that would otherwise not threaten a woman’s health or longevity. (Laura B. Shepardson, 2020). Overdiagnosis primarily

refers to diagnoses of ductal carcinoma in situ (DCIS), as there is little evidence that overdiagnosis occurs in cases of invasive breast carcinoma (M G Marmot, 2013).

The risk of recall for additional imaging of an otherwise normal or benign finding is the second disadvantage of screening mammography. These screening results, also known as “false positives,” lead to additional diagnostic imaging and benign breast biopsies, which may incur additional costs to the patient. Following a single screening mammogram, estimated recall rates for women of any age range from 9.6 percent to 11.6 percent (Cindy S. Lee, et al., 2017).

Various autopsy studies attempted to define the natural reservoir of the disease to highlight the contribution of screening in the overdiagnosis issue. The latest meta-analysis of autopsy-based studies (Elizabeth T. Thomas, 2017) evidenciated that the overall incidental cancer and precursor prevalence was: Invasive 0.8%, In-situ 8.9% (adjusted), and Atypical hyperplasia 9.8% (adjusted) for a total of 19.5%. In conclusion, histological examination of autopsy samples reveals a small reservoir (almost 1%) of invasive versus a large reservoir of in-situ premalignant lesions (almost 18%). Malignant and premalignant lesions in reduction mammoplasty specimens are expected to be between 1.5 and 14 percent in patients with no history of breast cancer (Iskender Sinan Genco, 2020).

The current study did not support the above conclusions. The incidental disease exists, but it is not detected by the current screening methods (mammography) used in the present study, even if they are extended and include ultrasound scanning of the breast tissue.

A recently published review by (Murillo, 2019) on breast cancer screening, pointed out that mammography screening for women aged 50 to 69 years results in a decrease in breast cancer mortality, but not all- cancer and all-cause mortality. It also has negative consequences, such as overdiagnosis. The conclusions of the reviews on the benefits and harms of mammography were not consistent for the other age groups. Moreover, no clear determinants of benefits and harms of mammography screening were identified.

According to Monticciolo (Debra L. Monticciolo, 2020) a 40% reduction in breast cancer death can be achieved with annual screening starting at age 40. Later initiation of or less frequent screening will result in less mortality benefit. Women younger than 50 and over 74 years are at risk of losing coverage for screening and could suffer worse outcomes without early detection.

In the European Union, breast cancer contributed to 12.4% of the total number of cases (522,513 new cases) among females of all ages and caused 137,707 deaths. (Ferlay J, 2018). Significant differences have been developed in screening protocols and organization (double reading of the test, mammographic classification for recall, histology classification criteria, number of readings per radiologist, number of screening tests per year, reliability of reported data) (Armaroli, et al., 2020) Despite the fact that mortality, incidence, and adhesion rates remain highly variable, it appears that the public health investment budget has a significant impact on this issue. As observed in previous publications (F. Ades, 2013), screening-increased incidence leads to a breast cancer mortality rate reduction, a fact that has also been observed in the current work under the analysis of the three distinct groups over the level of public health investment. While a 'real increase' in cancer incidence would lead to increased mortality, a 'screening increase' incidence would result in decreased mortality because of disease diagnosis at an early stage. The data presented here also indicate that the second scenario is probably true in the EU-27.

Resuming:

1. In the light of the findings, it can not be concluded that the imaging detected silent breast cancer prevalence is higher than the actual incidence of the disease, contrary to the author's initial hypothesis.
2. Benign breast alterations are common, accounting for 43.6% of the corpses collected, while low suspicion alterations were discovered in 1.84% of breast samples.
3. The objective exam, which included inspection and palpation, missed 37.5% of the biopsied breast changes. This finding indicated that an objective exam presenting a significant number of false-negative results could not be used as a screening method.
4. Breast screening programs, data reporting, treatment, and population awareness should be uniformized in the European Union context, and until a more efficient screening method is developed, efforts should be directed towards widespread implementation of properly done manual mammography of each woman above 40 y.o. all over across EU.
5. There is no ideal breast screening modality, but it seems that consensus focuses on imaging techniques, with digital mammography being the most commonly proposed one.

7 Limitations

The present research is subject to several limitations. First of all, the sampling number question is allocated. Since it was hypothesized that the prevalence of silent breast cancer is unknown and the actual disease incidence is low, finding a case of silent male breast cancer would be quite unusual. This limitation becomes strength in the case of the female gender because contrary to what is believed, imaging sampling does not evidenciate more malignancies than that are actually detected.

Another limitation of this study is that medical data from the analyzed corpses could not be collected, leaving out potentially harmful or protective factors that would have been very interesting to investigate. The third and perhaps the most obvious limitation of this study is that specimens were not examined through systematic histology. This “limitation” stems from the study's somewhat unique design that aimed to identify imaging-detected silent breast cancer, which breast screening has been shown to overdiagnose.

Future directions should point to a combined autopsy study, which would include a large number of glands and compare imaging findings to the histology analyses. Such a study can, in the end, provide an unblemished answer to the allocated question: "In what grade does breast cancer screening over detect the disease?"

Bibliography

(NCCN), 2.2019. *Guidelines: Prostate Cancer Early Detection. Version 2.2019..* s.l.:s.n.

(NCCN), 2020. *Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic. Version 1.2020.* s.l.:s.n.

A. Gucalp, S. T. S. I. e. a., 2013. Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic Breast Cancer. *Clin. Cancer Res,* Volume 19, pp. 5505-5512.

Abderrahman B, 2019. Exhaled breath biopsy: a new cancer detection paradigm.. *Future oncol 15:1679–1682,* Volume 15, p. 1679–1682.

ACR, s.d. *acr.org.* [Online] Available at: https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Bi-Rads

Adank, M. v. M. S. G. J. e. a., 2011. PALB2 analysis in BRCA2-like families. *Breast Cancer Res Treat,* Volume 127, pp. 357-362.

AJ., A. Y., 2017 Aug. Male Breast Cancer: Epidemiology and Risk Factors. *Semin Oncol. ,* Volume 44(4), pp. 267-272.

Andleeb, A. e. a., 2016. Male Breast Cancer: A 10-Year Experience of a Tertiary Care Center in North India. *Clinical Cancer Investigation Journal,* Volume 5, pp. 521-526.

André S, P. A. L. C. a., 2007. Male and female breast cancer–differences in DNA ploidy, p21 and p53 expression reinforce the possibility of distinct pathways of oncogenesis. *Pathobiology,* Volume 74, pp. 323-327.

Anon., s.d. *https://www.europarl.europa.eu/doceo/document/TA-8-2019-0112_EN.html.* [Online].

Antoniou. A, e. a., 2003. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 cancer mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet,* Volume 72, pp. 1117-1130.

Armaroli, P. et al., 2020. PERFORMANCE INDICATORS IN BREAST CANCER SCREENING IN THE EUROPEAN UNION: A COMPARISON ACROSS COUNTRIES OF SCREEN POSITIVITY AND DETECTION RATES. *International Journal of Cancer.*

Aşchie M, B. G. M. A., 2013. Clinico-pathological and molecular subtypes of male breast carcinoma according to immunohistochemistry. *Rom J Morphol Embryol,* Volume 54 , pp. 749-755.

B.D. Lehmann, J. B. X. C. e. a., 2011. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J. Clin. Invest,* Volume 121 , p. 2750–2767.

Baker, S. e. a., 1990. Suppression of human colorectal carcinoma cell growth by wild- type p53.. *Science,* Volume 249 (4971), pp. 912-915.

Balasundaram, M. e. a., 2017. Clinical Study of Molecular Hormonal Receptor Level Status among Carcinoma of Breast in Karaikal Populatio. *International Archives of Integrated Medicine,* Volume 4, pp. 151-156.

Bartow SA, P. D. B. W. K. C. T. S., 1987. Prevalence of benign, atypical, and malignant breast lesions in populations at different risk for breast cancer. A forensic autopsy study. *Cancer,* Volume 60, pp. 2751-2760.

Basham, V. e. a., 2002. BRCA1 and BRCA2 mutations in a population-based study of male breast. *Breast Cancer Res,* p. 4: R2..

BE Adrada, T. M. G. R., 2016. Molecular Breast Imaging: Role as a Screening Modality. *Current Breast Cancer Reports.*

Benson, J. e. a., 2009. Early breast cancer. *Lancet,* Volume 373(9673), pp. 1463-79..

Berg, K. &. L. .., 2004. *Essentials of Research Methods in Health, Physical Education, Exercise Science and Recreation..* 2nd ed. s.l.:Lippincott Williams & Wilkis..

Bhathal PS, B. R. L. G. R. I., 1985. Frequency of benign and malignant breast lesions in 207 consecutive autopsies in Australian women.. *Br J Cancer,* Volume 51, pp. 271-278.

Bieche I, P. B. T. S. a., 2001. Quantitation of androgen receptor gene expression in sporadic breast tumors by real-time RT-PCR: evidence that MYC is an AR-regulated gene. *Carcinogenesis ,* Volume 22(9), p. 1521–1526 .

Bieche, I. a. R. L., 1995. Genetic alterations in breast cancer. Genes Chromosomes. *Cancer,* Volume 14(4), pp. 227-251.

Blanco, A. d. l. H. M. B. J. e. a., 2012. Detection of a large rearrangement in PALB2 in Spanish breast cancer families with male breast cancer. *Breast CancerRes Treat,* Volume 132, pp. 307-315.

Bloom KJ, G. H. G. P. e. a., 2001. Status of HER-2 in male and female breast carcinoma. *Am J Surg ,* Volume 182, pp. 389-392.

Blows FM, D. K. S. M. a., 2010. Sub-typing of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: a collaborative analysis of data for 10,159 Cases from 12 Studies. *PLoS Med ,* Volume 7, p. e1000279.

Brem RF, T. L. D. S. e. a., 2015. Assessing improvement in detection of breast cancer with three-dimensional automated breast US in women with dense breast tissue: the SomoInsight Study. *Radiology,* Volume 274(3), pp. 663-73.

Brian M. Moloney, D. O. ,. A. E. a. M. J. K., 2020. Breast Cancer Detection—A Synopsis of Conventional Modalities and the Potential Role of Microwave Imaging. *Diagnostics ,* Volume 10(2), p. 103.

Brinton LA, K. T. K. L. e. a., 2015. Prediagnostic sex steroid hormones in relation to male breast cancer risk. *J Clin Oncol ,* Volume 33, pp. 2041-2050.

Brinton, L. C. J. G. G. e. a., 2010. Etiologic factors for male breast cancer in the U.S Veterans Affairs medical care system database. *Breast Cancer Res Treat,* Volume 119, pp. 185-192.
Brinton, L. C. M. M. V. e. a., 2014. Anthropometric and hormonal risk factors for male breast cancer: male breast cancer pooling project results. *J Natl Cancer Inst,* Volume 106, p. djt465.
Brinton, L. e. a., 2008. Prospective evaluation of risk factors for male breast cancer. *J Natl Cancer,* Volume 100, pp. 1477-1481.
Brinton, L. K. T. K. L. e. a., 2015. Prediagnostic sex steroid hormones in relation to male breast cancer risk. *J Clin Oncol,* Volume 33, pp. 2041-2050.
Buck MB, C. J. M. T. E. M. &. K. C., 2008. TGFbeta2 and TbetaRII are valid molecular biomarkers for the antiproliferative effects of tamoxifen and tamoxifen metabolites in breast cancer cells. *Breast Cancer Research and Treatment ,* Volume 107, p. 15–24.
Buja LM, B. R. K. G. B. S. H. R., 2019. The Importance of the Autopsy in Medicine: Perspectives of Pathology Colleagues. *Acad Pathol. 2019,* Volume 6.
Burgess A, C. K. H. S. T. D. H. Y. &. L. E., 2016. Clinical overview of MDM2/X-targeted therapies.. *Frontiers in Oncology,* Volume 6.7.
Cancerfonden, S., 2013. *Cancer i siffror 1–64.,* s.l.: s.n.
Cardoso, F. e. a., 2018. Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. *Annals of Oncology,* Volume VOLUME 29, ISSUE 2, P405-417, FEBRUARY 01, 2018, pp. 405-417.
Casadei, S. N. B. W. T. e. a., 2011. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. *Cancer Res,* Volume 71, pp. 2222-2229.
Cathy B Moelans 1, J. d. L. 2. ,. P. v. d. G. 1. ,. 3. ,. P. P. 2. ,. N. J. M. B. 2. ,. 4. ,. M. H. 2. ,. N. D. t. H. 1. ,. M. M. L. 1. ,. R. K. 5. ,. C. C. v. d. P. 6. ,. W. W. J. d. L. 1. ,. E. B., Oct 2019. The molecular genetic make-up of male breast cancer. *Endocrine-Related Cancer,* p. 779–794.
Cathy B Moelans, P. v. d. G. P. J. v. D., 2018. Male breast cancer. *Atlas Genet Cytogenet Oncol Haematol,* Volume 22/4, pp. 170-181.
Chang, A. E. e. a., 2006. *Oncology: An Evidence-Based Approach.* s.l.:NY: Springer New YorK.
Cheang, M. e. a., 2009. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer.. *J Natl Cancer Inst,* Volume 101(10), pp. 736-50.
Chen X, L. X. Z. L. e. a., 2013. Poorer survival of male breast cancer compared with female breast cancer patients may be due to biological differences. *Jpn J Clin Oncol,* Volume 43, pp. 954-963.
Chikaraddi, S. B. e. a., 2012. "Male Breast Cancer in Indian Patients: Is It the Same?. *Indian Journal of Cancer,* Volume 49, pp. 272-276.
Choi, M.-Y. e. a., 2016. Characterization of Korean male breast cancer using an online nationwide breast-cancer database: matched-pair analysis of patients with female breast cancer. *Medicine ,* Volume 95, p. 16.
Chu J, Z. Y. L. Y. S. L. L. X. W. Y. H. P. S. F. G. C. S. E. e. a., 2015. E2F7 overexpression leads to tamoxifen resistance in breast cancer cells by competing with E2F1 at miR-15a/16 promoter. *Oncotarget,* Volume 6, p. 31944–31957.
Cindy S. Lee, M., Debapriya Sengupta, M. M. & Bhargavan-Chatfield, M., 2017. Association of Patient Age With Outcomes of Current-Era, Large-Scale Screening Mammography. *JAMA Oncol.,* Volume 3(8), pp. 1134-1136..
Ciocca V, B. A. G. Z. e. a., 2006.. Cytokeratin profiles of male breast cancers. *Histopathology ,* Volume 49, pp. 365-370.
Cochran, W. G., 1977. *Sampling Techniques..* 3rd ed. NY: John Wiley & Sons.
Cohen, L. M. L. &. M. K., 2007. *Research methods in education..* s.l.:Taylor & Francis Group.
Colak S, &. T. D., 2017. Targeting TGF-beta signaling in cancer. *Trends in Cancer,* Volume r 3, p. 56–71.
Corino GL, F. P. L. M. A. M. H. J. M. D. P. K. Y. P., 2009. Characterization of a test for invasive breast cancer using X-ray diffraction of hair-results of a clinical trial.. *Breast Cancer (Auckl),* Volume 3, p. 83–90.
Corsetti V, H. N. F. A. e. a., 2008. Breast screening with ultrasound in women with mammography-negative dense breasts: evidence on incremental cancer detection and false positives, and associated cost. *Eur J Cancer,* Volume 44(4), pp. 539-44..
Costa, J., s.d. [Online] Available at: https://www.britannica.com/science/cancer-disease
Cott Chubiz JE, L. J. G. M. K. C. L. K. H. E. M. P. R. P. G. G., 2013 . Cost-effectiveness of alternating magnetic resonance imaging and digital mammography screening in BRCA1 and BRCA2 gene mutation carriers. *Cancer. ,* Volume 119(6), pp. 1266-76..
Cybulski, C. et al., . 2004. CHEK2 is a multiorgan cancer susceptibility gene. Am. J. Hum. Genet. 2004, 75, 1131–1135.. *Am. J. Hum. Genet. ,* Volume 75, p. 1131–1135..
D.R. Cochrane, S. B. B. J. e. a., 2014. Role of the androgen receptor in breast cancer and preclinical analysis of enzalutamide. *Breast Cancer Res,* p. R7.
Daniela Bernardi, M., 2016. Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study. *Tha Lancet Oncology,* Volume 17, pp. 1105-1113.

Daniela Lazaro-Pacheco, A. M. S. S. R. &. I., 2019. Raman spectroscopy of breast cancer. *Applied Spectroscopy Reviews.*
Dawson PJ, P. T. W. S., 1992. Immunocytochemical characterization of male breast cancer. *Mod Pathol ,* Volume 5, pp. 621-625.
Dawson, C., 2009. *"Introduction to research methods: A practical guide for anyone undertaking a research project"..* 4th ed. s.l.: Oxford: How To Books Limite.
Deb S, L. S. O. L. e. a., 2016. The cancer genetics and pathology of male breast cancer.. *Histopathology,* Volume 68, pp. 110-118.
Debra L. Monticciolo, M., 2020. Current Guidelines and Gaps in Breast Cancer Screening. *J Am Coll Radio.*
Deb, S. e. a., 2012. Genotypic and phenotypic analysis of familial male breast cancer shows under representation of the HER2 and basal subtypes in BRCA associated carcinomas. *BMC Cancer,* Volume 12, p. 510.
Deb, S. e. a., 2014. Mutational Profiling of Familial Male Breast Cancers Reveals Similarities with Luminal A Female Breast Cancer with Rare TP53 Mutations.. *British Journal of Cancer,* Volume 111, pp. 2351-2360.
Dehghan, F. e. a., 2015. Estrogen receptor (ER)-α, β and progesterone receptor (PR mediates changes in relaxin receptor (RXFP1 and RXFP2) expression and passive range of motion of rats' knee. *Environmental toxicology and pharmacology ,* Volume 40.3, pp. 785-791.
DELALOGE, S., 2018. *https://clinicaltrials.gov/ct2/show/NCT03672331?term=mypebs&rank=1.* [Online].
Demers PA, T. D. R. K. e. a., 1991. Occupational exposure to electromagnetic fields and breast cancer in men. *Am J Epidemiol ,* Volume 134, pp. 340-347.
Devilee, P. a. C. C., 1994. Somatic genetic changes in human breast cancer.. *Biochim Biophys Acta,* Volume 1198(2-3), pp. 113-130.
Di Monaco M, B. E. L. L. e. a., 1995. Inhibitory effect of hydroxyflutamide plus tamoxifen on oestradiol-induced growth of MCF-7 breast cancer cells. *J. Cancer Res. Clin. Oncol. ,* Volume 121(12), p. 710–714 .
Ding, Y. e. a., 2011. Mutations in BRCA2 and PALB2 in male breast cancer cases from the United States.. *Breast Cancer Res Treat,* Volume 126, pp. 771-778.
Downward, J., 2003. Targeting RAS signalling pathways in cancer therapy.. *Nat Rev Cancer,* Volume 3(1), pp. 11-22.
Dunnwald LK, R. M. L. C., 2007. Hormone receptor status tumor characteristics, and prognosis: a prospective cohort of breast cancer patients.. *Breast Cancer Res,* Volume 9, p. R6.
Dwivedi, S. e. a., 2017. Scientometric Profile of Global Male Breast Cancer Research. *Current Science,* Volume 112, pp. 1814-1821.
Edge, S. a. C. C., 2010. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM.. *Ann Surg Oncol,* Volume 17(6), pp. 1471-4..
Eggemann, H. e. a., 2018. Survival Benefit of Tamoxifen and Aromatase Inhibitor in Male and Female Breast Cancer. *Journal of Cancer Research & Clinical Oncology,* Volume 144, pp. 337-341.
Elizabeth T. Thomas, 1. C. D. M. P. G. G. W. A. B. a. K. J. L. B., 2017. Prevalence of incidental breast cancer and precursor lesions in autopsy studies: a systematic review and meta-analysis. *BMC Cancer,* Volume 17, p. 808.
Elston, C., 1984. The assessment of histological differentiation in breast cancer.. *Aust N Z J Surg,* Volume 54(1), pp. 11-5..
Elston, C. a. I. E., 1991. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long- term follow-up.. *Histopathology ,* Volume 19, pp. 403-410.
Erkko, H. X. B. N. J. e. a., 2007. A recurrent mutation in PALB2 in Finnish cancer families. *Nature,* Volume 446, pp. 316-319.
Eroles P, B. A. P.-F. J. e. a., 2012. Molecular biology in breast cancer: intrinsic subtypes and signaling pathways. *Cancer Treat Rev ,* Volume 38, p. 698–707.
Europa Donna, 2020. *Survey Report the Current Stateof Breast Services in Europe,* s.l.: s.n.
F. Ades, C. S. E. d. A. R. S. R. P. F. P. &. M. P., 2013. Discrepancies in cancer incidence and mortality and its relationship to health expenditure in the 27 European Union member states. *Annals of Oncology,* Volume 24, pp. 2897-2902.
F. Cardoso, S. P.-S. E. S. G. C. M. A. F. A. C., 2020 sept. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Annals of Oncology,* Volume (20), pp. 42460-3.
F. Cardoso, S. P.-S. E. S. G. C. M. A. F. A. C., 2020. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Annals of Oncology,* (20)(sept), pp. 42460-3.
Fackenthal, J. M. D. R. A. e. a., 2001. Male breast cancer in Cowden syndrome patients with germline PTEN mutations. *J Med Genet,* Volume 38, pp. 159-164.
Fasoula, A. et al., 2019. *Super-Resolution Radar Imaging for Breast Cancer Detection with Microwaves: The Integrated Information Selection Criteria..* Berlin Germany, s.n.
Fei Wang, M. P., Xiang Shu, Ingrid Meszoely, M. & al, e., 2019. Overall Mortality After Diagnosis of Breast Cancer in Men vs Women. *JAMA Oncol.,* Volume 5(11), pp. 1589-1596.
Fentiman.I, 1., 2017. Prognosis. In: *Male Breast Cancer.* s.l.:Springer International, p. 145.
Fentiman, I., 2017. *Male Breast Cancer.* s.l.:Springer International.
Fentiman, I. S. e. a., 2006. Male Breast Cancer. *Lancet,* Volume 367, pp. 595-604.

Ferlay J, e. a., 2013. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012.. *Eur J Cance,* Volume 49, pp. 1374-1403.
Ferlay J, e. a., 2018. , Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers. *European Journal of Cancer .*
Ferlay J, E. M. L. F. C. M. M. L. P. M. Z. A. S. I. B., 2018. Global Cancer Observatory: Cancer Today. *Int Agency Res Cancer*.
Ferlay, J. e. a., 2015. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer,* pp. E359-386.
Fidler, I., 1989. . Fidler, I.J., Origin and biology of cancer metastasis.. *Cytometry,* Volume 10(6), p. 673.
Finver, S. e. a., 1988. Sequence analysis of the MYC oncogene involved in the t(8;14)(q24;q11) chromosome translocation in a human leukemia T-cell line indicates that putative regulatory regions are not altered.. *Proc Natl Acad Sci.*
Fisher, B. e. a., 2002. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer.. *N Engl J Med,* Volume 347(16), pp. 1233-41.
Fostira, F. et al., 2018. Germline deleterious mutations in genes other than BRCA2 are infrequent in male breast cancer.. *Breast Cancer Res. Treat. ,* Volume 169, p. 105–113.
Freeman, M., Gopman, J. & Salzberg, C., 2018. The evolution of mastectomy surgical technique: from mutilation to medicine.. *Gland Surg.,* Volume 7(3), pp. 308-315.
Friedenson, B., 2007. The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers.. *BMC Cancer,* Volume 7, p. 152.
Friedman, L., 1997. Mutation analysis of BRCA1 and BRCA2 in a male breast cancer population. *Am J Hum Genet 1997,* Volume 60, pp. 313-319.
Garcia-Saenz Ariadna, e. a., Apr. 2018. Evaluating the Association between Artificial Light-At-Night Exposure and Breast and Prostate Cancer Risk in Spain (MCC-Spain Study). *Environmental Health Perspectives,* Volume 126, pp. 1-11..
Gargiulo P, P. M. M. M. e. a., 2016. Long-term survival and BRCA status in male breast cancer: a retrospective single-center analysis. *BMC Cancer,* Volume 16, p. 375.
Ge Y, e. a., 2009. Immunohistochemical characterization of subtypes of male breast. *Breast Cancer Research,* p. 11:R28.
Geisel J, R. M. H. R., 2018. The Role of Ultrasound in Breast Cancer Screening: The Case for and Against Ultrasound.. *Semin Ultrasound CT MR,* Volume 39, pp. 25-34..
Ghaderi KF, P. J. P. H. L. P. M. T., 2019. Contrast-enhanced Mammography: Current Applications and Future Directions.. *RadioGraphics,* Volume 39, pp. 1907-20.
Gianfrancesco, M. A. e. a., 2017. Causal effect of genetic variants associated with body mass index on multiple sclerosis susceptibility. *American journal of epidemiology ,* Volume 185.3, pp. 162-171.
Gilbert FJ, S. A., 2018. Personalised screening: is this the way forward?. *Clin Radiol. ,* Volume 73(4), pp. 327-333..
Giordano SH, 2008. Male breast cancer: it's time for evidence instead of extrapolation [editorial].. *Onkologie,* Volume 31, pp. 505-506.
Giordano. SH, e. a., 2004. Breast carcinoma in men: a population-based study. *Cancer,* Volume 101, pp. 51-57.
Giordano, S., 2018. Breast Cancer in Men. *The new england journal of medicine,* Volume 378, pp. 2311-20.
Gogra. A, e. a., 2015. Male Breast Cancer: A Single Institute Experience. *Indian Journal of Cancer.,* Volume 52, pp. 526-529.
Goldhirsch A, W. W. C. A. e. a., 2011. Panel members : Strategies for subtypes–dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol 22,* Volume 22, pp. 1736-1747.
Gomberawalla, A. e. a., 2018. Breast Conservation for Male Breast Cancer: Case Report of Intraoperative Radiation. *Breast Journa,* pp. 74-77.
Goss PE, R. C. P. M. e. a., 1999. Male breast carcinoma: a review of 229 patients who presented to the Princess Margaret Hospital during 40 years: 1955-1996. *Cancer 1999,* Volume 85, pp. 629-639.
Greif JM, P. C. K. V. e. a., 2012. Gender differences in breast cancer: analysis of 13,000 breast cancers in men from the national cancer database. *Ann Surg Oncol,* Volume 19, p. 3199–3204.
Group, B. D. W., 2001. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework.. *Clin Pharmacol Therapeutics,* Volume 69, pp. 89-95.
Gucalp A, I. S. I. S. e. a., 2012. Targeting the androgen receptor in women with AR+ ER-/PR- metastatic breast cancer TBCRC011.. *J. Clin. Oncol.,* Volume 15, p. 1006 .
Guénel, P. C. D. S. S. e. a., 2004. Alcohol drinking may increase risk of breast cancer in men: a European population-based case-control study. *Cancer Causes Control,* Volume 15, pp. 571-580.
Günhan-Bilgen I, B. H. U. E. a., 2002. Male breast disease: clinical,mammographic, and ultrasonographic features. Eur J Radiol 2002; 43: 246-55.. *Eur J Radiol 2002,* Volume 43, pp. 246-255.
Hakimi A.A., O. I. R. B. S. N. C. Y.-B. G. M. L. H. T. S. V. M. T. S. e. a., 2013. Adverse outcomes in clear cell renal cell carcinoma with mutations of 3p21 epigenetic regulators BAP1 and SETD2: A report by MSKCC and the KIRC TCGA research network. *Clin. Cancer ResClin. ,* Volume 19, p. 3259–3267.

Hanahan, D. a. R. W., 2011. Hallmarks of cancer: the next generation.. *Cell,* Volume 144(5), pp. 646-74..
Harbeck, B. M. ·. T. C. ·. W. R. ·. G. M. ·., 2019. St. Gallen/Vienna 2019: A Brief Summary of the Consensus Discussion on the Optimal Primary Breast Cancer Treatment. *Breast Care,* Volume 14, pp. 103-110.
Harvey Lodish, A. B. S. L. Z. P. M. D. B. a. J. D., 2000. *Molecular Cell Biology.* 4th ed. s.l.:s.n.
Hassett MJ, S. M. B. E. C. F. K. K. K. D. P. J. R. C. R. A. R. K. S. J. V. P. C. Y. R. G. S., 2020. Management of Male Breast Cancer: ASCO Guideline. *J Clin Oncol. ,* Volume 38(16), pp. 1849-1863..
Heim, S. a. F. M., 2015.. *Cancer cytogenetics: chromosomal and molecular genetic aberrations of tumor cells..* s.l.:John Wiley & Sons.
Heitz, F. e. a., 2009. Triple-negative and HER2-overexpressing breast cancers exhibit an elevated risk and an earlier occurrence of cerebral metastases.. *Eur J Cancer,* Volume 45(16), pp. 2792-8..
Hodgson R, H.-K. S. H. S. E. M. S. J. A. M. G. J., 2016 . Systematic review of 3D mammography for breast cancer screening.. *Breast,* Volume 27, pp. 52-61..
Holm C, R. S. J. K. S. O. K. R. &. L. G., 2006. Association between Pak1 expression and subcellular localization and tamoxifen resistance in breast cancer patients.. *Journal of the National Cancer Institute,* Volume 98 , p. 671–680.
Honma, N. e. a., 2015. Differences in clinical importance of Bcl-2 in breast cancer according to hormone receptors status or adjuvant endocrine therapy. *BMC Cancer,* Volume 15.1, p. 698.
Hortobagyi GN, C. J. D. C. e. a. B. I. A. M. E. S. G. F. e. a. e., 2017. Hortobagyi GN, Connolly JL, D'Orsi CJ et al. Breast. In: Amin MB, Edge S, Greene F et al, eds; American Joint Committee on Cancer. . In: *AJCC cancer staging manual.* New York: Springer, p. 589–636.
Howlader, N. e. a., 2018. *Surveillance, Epidemiology, and End Results Program. SEER cancer statistics review (CSR) 1975–2014,* National Cancer Institute. Bethesda: s.n.
Hsing, A. M. J. C. P. e. a., 1998. Risk factors for male breast cancer (United States). *Cancer Causes Control,* Volume 9, pp. 269-275.
Hultborn, R. H. C. K. I. e. a., 1997. Prevalence of Klinefelter's syndrome in male breast cancer patients. *Anticancer Res,* Volume 17, pp. 4293-4297.
Humphries, M. J. V. S. V. e. a., 2015. Obesity and male breast cancer: provocative parallels?. *BMC Medicine,* Volume 13, p. 134.
Humphries, M. P. e. a., 2017. *Characterisation of male breast cancer: a descriptive biomarker study from a large patient series.,* s.l.: Scientific reports 7.
Iacobuzio-Donahue, C. M. C. B. P. e. a., 2019. Cancer biology as revealed by the research autopsy.. *Nat Rev Cancer,* Volume 19, p. 686–697.
I, F., 2017. *Make Breast Cancer.* s.l.:Springer International.
Iskender Sinan Genco, J. S. C. B. B. T., 2020. The Rate of Incidental Atypical and Malignant Breast Lesions in Reduction Mammoplasty Specimens. *Histopathology.*
J H Farrow, F. E. A., 1942. EFFECT OF ORCHIDECTOMY ON SKELETAL METASTASES FROM CANCER OF THE MALE BREAST. *Science,* Volume 95(2478), p. 654.
J. Eisenbrey, J. D. F. F., 2016. Recent technological advancements in breast ultrasound. *ULTRASONICS,* Volume 70 , pp. 183-190.
J. Zuluaga-Gomez, N. Z. Z. A. M. C. D. &. C. V., 2019. A survey of breast cancer screening techniques: thermography and electrical impedance tomography. *Journal of Medical Engineering & Technology,* Volume 43:5, pp. 305-322.
Jatoi, I., 2006. *Atlas of Breast Surgery.* s.l.:Springer.
Jeanne S. Mandelblatt, M. M. N. K. S. P. C. B. S. M. M., 2016. Collaborative Modeling of the Benefits and Harms Associated With Different U.S. Breast Cancer Screening Strategies. *Annals of Internal Medicine.*
Johansson I, N. C. B. P. e. a., 2012. Gene expression profiling of primary male breast cancers reveals two unique subgroups and identifies N-acetyltransferase-1 (NAT1) as a novel prognostic biomarker. *Breast Cancer Res ,* Volume 14, p. R31.
Johansson I, R. M. H. I., 2013. The landscape of candidate driver genes differs between male and female breast cancer. *PLoS One ,* Volume 8(10), p. e78299.
Johansson, I. & al, e., 2014. Molecular profiling of male breast cancer – Lost in translation?. *The International Journal of Biochemistry & Cell Biology,* Volume Volume 53, pp. 526-535.
Johansson, I. e. a., 2015. Genome methylation patterns in male breast cancer–Identification of an epitype with hypermethylation of polycomb target genes. *Molecular Oncology,* Volume 9.8, pp. 1565-1579.
Jones RL, S. J. A. R. e. a., 2010. Relationship between oestrogen receptor status and proliferation in predicting response and long-term outcome to neoadjuvant chemotherapy for breast cancer. *Breast Cancer Res Treat ,* Volume 119, pp. 315-323.
K.ShettyMD, I. T.-P. M., 2011. Magnetic Resonance Imaging and Breast Ultrasonography as an Adjunct to Mammographic Screening in High-Risk Patients. In: *Seminars in Ultrasound, CT and MRI.* s.l.:s.n.
Kalekou H, K. I. M. S. e. a., 2005. Comparative study of CD34, alpha-SMA and h-caldesmon expression in the stroma of gynaecomastia and malebreast carcinoma. *Histopathology ,* Volume 47, pp. 74-81.
Kaneda, A. a. Y.-i. T., 2017. *DNA and Histone Methylation as Cancer Targets.* s.l.:Springer International Publishing.

Kanhai RC, H. J. v. D. P. B. E. e. a., 2000. Short-term and long-term histologic effects of castration and estrogen treatment on breast tissue of 14 male-to-female transsexuals in comparison with two chemically castrated men. *Am J Surg Pathol,* Volume 24, pp. 74-80.
KanthanR, F. I. R. T. e. a., 2010. Expression of cell cycle proteins in male breast carcinoma. *World J Surg Oncol,* Volume 8, p. 10.
Karangadan, S. e. a., 2016. "Immunohistochemically Characterization of Molecular Classification of Breast Carcinoma and Its Relation with Ki-67.. *Clinical Cancer Investigation Journa,* Volume 5, pp. 430-436.
Khalkhali-Ellis Z, C. A. K. D. e. a., 2004. Regulating the tumor suppressor gene maspin in breast cancer cells: a potential mechanism for the anticancer properties of tamoxifen. *Clin. Cancer Res.,* Volume 10(2), p. 449–454 (.
Kidwai N, G. Y. S. X. e. a., 2004. Expression of androgen receptor and prostate-specific antigen in male breast carcinoma. *Breast Cancer Res,* Volume 6, pp. R18-23.
Kiluk, J. V. e. a., 2011. Male Breast Cancer: Management and Follow-Up Recommendations.. *Breast Journal,* Volume 17, pp. 503-509.
Kornegoor R, V.-M. A. B. H. e. a., 2011. Molecular subtyping of male breast cancer by immunohistochemistry. *Mod Pathol ,* Volume 25, p. 1–7.
Kornegoor, R. e. a., 2012. Immunophenotyping of Male Breast Cancer. *Histopathology,* Volume 61, pp. 1145-1155.
Kwiatkowska, E. e. a., 2003. BRCA2 mutations and androgen receptor expression as independent predictors of outcome of male breast cancer. *Clin Cancer Res,* Volume 9, pp. 4452-4459.
Kwiatkowski, F. e. a., 2015. BRCA Mutations Increase Fertility in Families at Hereditary Breast/Ovarian Cancer Risk. *Plos ONE,* Volume 10, pp. 1-12.
Kyritsis, A. P. e. a., 2016. s Cancer-specific risk in multiple sclerosis patients. *Critical reviews in oncology/hematology,* Volume 98, pp. 29-34.
Labrie F, L.-T. V. L. C. e. a., 2003. Endocrine and intracrine sources of androgens in women: inhibition of breast cancer and other roles of androgens and their precursor dehydroepiandrosterone. *Endocr. Rev. 24(2), 152–182 (2003),* Volume 24(2), p. 152–182 .
Lacle MM, v. D. P. G. R. e. a., 2015. Expression of connective tissue growth factor in male breast cancer: clinicopathologic correlations and prognostic value.. *PLoS ONE ,* Volume 10, p. e0118957.
Lacle, M. M. e. a., 2013. Prognostic value of mitotic index and Bcl2 expression in male breast cancer. *PloS one,* Volume 8.4, p. e60138.
Laura B. Shepardson, M. L. D. M., 2020. Current controversies in breast cancer screening. *Seminars in Oncology,* Volume 47, pp. 177-181.
Le Tourneau, C. e. a., 2015. Molecularly targeted therapy based on tumor molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open- label, proof-of-concept, randomized, controlled phase 2 trial. *The lancet oncology ,* Volume 16.13 , pp. 1324-1334..
Lebrun, C. e. a., 2008. Cancer risk and impact of disease-modifying treatments in patients with multiple sclerosis. *Multiple Sclerosis Journal,* Volume 14.3, pp. 399-405.
Lee, U. J. a. J. S. J., 2009. Incidence of Prostate Cancer in Male Breast Cancer Patients: A Risk Factor for Prostate Cancer Screening.. *Prostate Cancer & Prostatic Diseases,* Volume 12, pp. 52-56.
Leverson, J. D. e. a., 2015. Exploiting selective BCL-2 family inhibitors to dissect cell survival dependencies and define improved strategies for cancer therapy. *Science translational medicine,* Volume 7, p. 279.
Lincoln, Y. S. &. G. E. G., 1985. *Naturalistic inquiry..* Newbury Park, CA: Sage.
Lippman, e. a., 1976. The effect of glucocorticoids and progesterone on hormone-responsive human breast cancer in long-term tissue culture. *Cancer Research ,* Volume 36(12), pp. 4602-9.
Little, M. P. a. D. M. M., 2017. Male Breast Cancer Incidence and Mortality Risk in the Japanese Atomic Bomb Survivors - Differences in Excess Relative and Absolute Risk from Female Breast Cancer.. *Environmental Health Perspectives,* Volume 125, pp. 223-229.
Liu L, K. S. L. H. H. A. &. Y. Z., 2015. Genetic alterations of histone lysine methyltransferases and their significance in breast cancer. *Oncotarget ,* Volume 6 , p. 2466–2482.
Lodish H, B. Z. S. e. a., 2000.. *Molecular Cell Biology.* 4th ed. s.l.:s.n.
Lucía Carril-Ajuria, 1. M. S. J. M. R.-R. C. R.-A. a. G. d. V., 2020. Prognostic and Predictive Value of PBRM1 in Clear Cell Renal Cell Carcinoma. *Cancers ,* Volume 1, p. 16.
Ludwig, J. a. J. W., 2005. Biomarkers in cancer staging, prognosis and treatment selection.. *Nat Rev Cancer,* Volume 5(11), pp. 845-56.
Ly, D. e. a., 2013. An international comparison of male and female breast cancer incidence rates. *International journal of cancer,* Volume 132.8, pp. 1918-1926.
M G Marmot, D. G. A. D. A. C. J. A. D. S. G. T. &. M. W., 2013. The benefits and harms of breast cancer screening: an independent review. *British Journal of Cancer ,* Volume 108, p. 2205–2240.
M. Callari, V. C. L. D. C. V. M. P. M. S. V. e. a., 2011. Gene expression analysis reveals a different transcriptomic landscape in female and male breast cancer. *Breast Cancer Res. Treat,* Volume 127 , p. 601–610.
Macedo LF, G. Z. T. S. e. a., 2006. Role of androgens on MCF-7 breast cancer cell growth and on the inhibitory effect of letrozole. *Cancer Res.,* Volume 66(15), p. 7775–7782 .

Macher-Goeppinger S., K. M. T. K. S. S. W. J. H. T. P. S. D. S. H. M. K. J., 2015. PBRM1 (BAF180) protein is functionally regulated by p53-induced protein degradation in renal cell carcinomas.. *J Pathol. 2,* Volume 237, p. 460–471.
Magny, S. J., Shikhman, R. & Keppke., A. L., 2020. Breast Imaging Reporting and Data System. *StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing*.
Mainiero MB, L. A. B. L. a., 2015. ACR appropriateness criteria evaluation of the symptomatic male breast. *J Am Coll Radiol 2015,* Volume 12, pp. 678-682.
Malhotra, G. e. a., 2010. Histological, molecular and functional subtypes of breast cancers.. *Cancer Biol The,* Volume 10(10), pp. 955-960.
Manikandan, J. e. a., 2008. Oncomirs: the potential role of non-coding microRNAs in understanding cancer. *Bioinformation 2.8,* p. 330.
Mann, N. e. a., 2017. Neurofibromatosis Type 1 and Male Breast Cancer: Emerging Risk Factor. *Journal of Surgical Case Reports,* Volume 2017, pp. 1-3.
Marabelli, M., Cheng, S.-C. & Parmigiani, G., 2016. Marabelli, M.; Cheng, S.-C.; Parmigiani, G. Penetrance of ATM Gene Mutations in Breast Cancer: A Meta-Analysis of Different Measures of Risk. Genet. Epidemiol. 2016, 40, 425–431. *Genet. Epidemio,* Volume 40, p. 425–431.
Marrie, R. A. e. a., 2015. A systematic review of the incidence and prevalence of cancer in multiple sclerosis. *Multiple Sclerosis Journal,* Volume 21.3, pp. 294-304.
Marta Román, M. S. D. P. L. C., 2019. Personalized breast cancer screening strategies: A systematic review and quality assessment. *PLOS ONE.*
Martínez-Bouzas, C. e. a., 2007. CHEK2 1100delC is present in familial breast cancer cases of the BasqueCountry. *Breast Cancer Res Treat,* Volume 103, pp. 111-113.
Masci G, C. M. C. F. e. a., 2015. Clinicopathological and immunohistochemical characteristics in male breast cancer: a retrospective case series. *Oncologist ,* Volume 20, pp. 586-592.
Matsen, C. a. L. N., 2013 . Breast cancer: a review for the general surgeon.. *JAMA Surg. ,* Volume 148(10) , pp. 971-9. .
Mavaddat, N. et al., 2013. Mavaddat, N.; Peock, S.; Frost, D.; Ellis, S.; Platte, R.; Fineberg, E.; Evans, D.G.; Izatt, L.; Eeles, R.A.; Adlard, J.; et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: Results from prospective analysis of EMBRACE.. *J. Natl. Cancer Inst. ,* Volume 105, p. 812–822. .
McNamara, e. a., 2013. Androgen receptor in triple negative breast cancer. *J Steroid Biochem Mol Biol,* Volume 133, pp. 66-76.
Medras, M. F. A. J. P. e. a., 2006. Breast cancer and long-term hormonal treatment of male hypogonadism. *Breast Cancer Res Treat,* Volume 96, pp. 263-265.
Meijer, M. e. a., 2018. Finasteride Treatment and Male Breast Cancer: A Register-Based Cohort Study in Four Nordic Countries. *Cancer Medicine,* Volume 7, pp. 254-260.
Meijers-Heijboer, H. e. a., 2002. Low-penetrance susceptibility to breast cancer due to CHEK2(*)1100delC in noncarriers of BRCA1 or BRCA2 mutations. *Nat Genet,* Volume 31, pp. 55-59.
Menezes, R. G. & Monteir, F. N., 2020. *https://www.ncbi.nlm.nih.gov/books/NBK539901/.* [Online].
Merino, M. J. e. a., 2018. The Unknown microRNA Expression of Male Breast Cancer. Similarities and Differences with Female Ductal Carcinoma. Their Role as Tumor Biomarker. *Journal of Cancer,* Volume 9.3, pp. 450-459.
Miao H, V. H. C. K. e. a., 2011. Incidence and outcome of male breast cancer: an international population-based study. *J Clin Oncol ,* Volume 29, pp. 4381-4386.
Mishra, A. a. M. V., 2010. Cancer biomarkers: are we ready for the prime time?. *Cancers,* Volume 2(1), pp. 190-208..
Mistry DAH, H. J. F. P., 2012. Identification of breast cancer-associated lipids in scalp hair.. *Breast Cancer ,* Volume 6, p. 113–123.
MJ, W., 1963. Gynecomastia: its incidence recognition and host characterization in 447 autopsy cases. *Am J Med,* Volume 34, pp. 103-112.
Moghadasi, S. e. a., 2018. Performance of BRCA1/2 Mutation Prediction Models in Male Breast Cancer Patients. *Clinical Genetics,* Volume 93, pp. 52-59.
Mourão Netto M, L. A. N. S. e. a., 2001. Expression of c-ERBB-2, p53 and c-myc proteins in male breast carcinoma: Comparison with traditional prognostic factors and survival. *Braz J Med Biol Res,* Volume 34, pp. 887-894.
Muir D, K. R. K. S., 2003. Male versus female breast cancers. A population-based comparative immunohistochemical analysis. *Arch Pathol Lab Med,* Volume 127, pp. 36-41.
Murakami A., W. L. K. S. S. P. R. W. T. A. N. R. S. K. J. B. R. M. e. a., 2017. Context-dependent role for chromatin remodeling component PBRM1/BAF180 in clear cell renal cell carcinoma. *Oncogenesis. ,* p. 6:e287.
Murillo, O. M. N. Z. F. M. J. (. S. N. G. R. H. A. R., 2019. Systematic reviews as a 'lens of evidence': Determinants of benefits and harms of breast cancer screening. *Cancer Therapy and Prevention .*
Mwakigonja, A. R. e. a., 2017. Characterization of Hormonal Receptors and Human Epidermal Growth Factor Receptor-2 in Tissues of Women with Breast Cancer at Muhimbili National Hospital, Dar Es Salaam, Tanzania. *Infectious Agents & Cancer,* Volume 12, pp. 1-12.

Nadine Zielonke 1, A. G. 2. E. E. L. J. 2. A. A. 3. N. S. 4. A. P. 4. P. V. 5. H. J. d. K. 2. N. T. v. R. 2. E. A. M. H. 2. E.-T. c., 2020 Mar. Evidence for reducing cancer-specific mortality due to screening for breast cancer in Europe: A systematic review. *Eur J Cancer,* Volume 127, pp. 191-206.
NCCN, 2017. *Clinical Practice Guidelines in Oncology,* s.l.: s.n.
NCCN, C. P. G. i. O., 2017. *NCCN guidelines for genetic/familial high-risk assessment: breast and ovarian,* s.l.: s.n.
Nehmat Houssami, D. L. M. C. V. P. D. T. G. M. J. E. P., 2019. Pilot trial of digital breast tomosynthesis (3D mammography) for population-based screening in BreastScreen Victoria. *MJA,* Volume 11, pp. 357-362.
Nelson, D. e. a., 2004. Hypoxia and defective apoptosis drive genomic instability and tumorigenesis. *Genes Dev,* pp. 2095-2107.
Neuhausen, S. e. a., 2004. Role of CHEK2*1100delC in unselected series of non-BRCA1/2 male breast cancers. *Int J Cancer,* Volume 108, pp. 477-478.
Newel1, A. H. a. M. S., 2015. Alternative Screening for Women With Dense Breasts: Breast-Specific Gamma Imaging (Molecular Breast Imaging). *American Journal of Roentgenology,* Volume 204, pp. 252-256.
Ni YB, M. S. S. M. e. a., 2014. Columnar cell-like changes in the male breast. *J. Clin. Pathol,* Volume 67, pp. 45-48.
Ni, e. a., 2013. Amplitude modulation of androgen signaling by c-MYC. *Genes Dev.,* Volume 27, pp. 734-748.
Nielsen M, T. J. P. S. D. U. A. J., 1987. Breast cancer and atypia among young and middle-aged women: A study of 110 medicolegal autopsies. *Br J Cancer. ,* Volume 56, pp. 814-819.
Nilsson C, H. M. B. L. e. a., 2011. Similarities and differences in the characteristics and primary treatment of breast cancer breastcancer in men and women – a population based study (Sweden). *Acta Oncol,* Volume 50, p. 1083–1088.
Nilsson C, J. I. A. C. e. a., 2013. Molecular subtyping of male breast cancer using alternative definitions and its prognostic impact. *Acta Oncol,* Volume 52, pp. 102-109.
Nykiel, R., 2007. *Handbook of Marketing Research Methodologies for Hospitality and Tourism..* NY: Harworth Hospitality & Tourism Press..
O'Malley, C. e. a., 2005. Incidence of male breast cancer in California 1988-2000: racial/ethnic variation in 1759 men. *Breast Cancer Res Treat,* Volume 93, pp. 145-150.
Ohuchi N, S. A. S. T. e. a., 2016. Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial.. *Lancet,* Volume 387, pp. 341-8..
Ong CC, G. S. P. C. S. M. C. C. Z. W. J. A. S. L. S. M. D. S. e. a., 2015. Small molecule inhibition of group I p21-activated kinases in breast cancer induces apoptosis and potentiates the activity of microtubule stabilizing agents. *Breast Cancer Research,* Volume 59, p. 17.
Onitilo, A. e. a., 2009. Breast cancer subtypes based on ER/PR and Her2 expression: comparison of clinicopathologic features and survival.. *Clin Med Res,* Volume 7(1-2), pp. 4-13.
Orr, N. C. R. J. M. e. a., 2011. Genetic variants at chromosomes 2q35, 5p12, 6q25.1, 10q26.13, and 16q12.1 influence the risk of breast cancer in men. *PLoS Genet,* p. 7(9): e1002290.
Orr, N. L. A. C. R. e. a., 2012. Genome-wide association study identifies a common variant in RAD51B associated with male breast cancer risk. *Nat Genet,* Volume 44, pp. 1182-1184.
Ottini. L, e. a., 2003. BRCA1 and BRCA2 mutation status and tumor characteristics in male breast cancer a population-based study in Italy. *Cancer Res,* Volume 63, pp. 342-347.
Park, e. a., 2011. Androgen receptor expression is significantly associated with better outcomes in estrogen receptor-positive breast cancers. *Ann Oncol,* Volume 22(8), pp. 1755-62.
Parker, J. e. a., 2009. Supervised risk predictor of breast cancer based on intrinsic subtypes.. *J Clin Oncol,* Volume 27(8), pp. 1160-7.
Paweł Koczkodaj, U. S. J. G. a. M. M., 2020. Breast cancer mortality trends in Europe among women in perimenopausal and postmenopausal age (45+). *Arch Med Sci. ,* Volume 16, p. 146–156..
Peintinger, F., 2019. National Breast Screening Programs across Europe.. *Breast Care,* Volume 14, pp. 354-358.
Per Skaane, A. I. B. L. T. N. S. S. B. H. Ø. R. G. D. G. S. H., Feb 19 2019. Digital Mammography versus Digital Mammography Plus Tomosynthesis in Breast Cancer Screening: The Oslo Tomosynthesis Screening Trial. *Radiology.*
Pereira B, C. S. R. O. e. a., 2016. The somatic mutation profiles of 2,433 breast cancers refines their genomic and transcriptomic landscapes. *Nat Commun.,* Volume 7, p. 11479.
Perou CM, S. T. E. M. e. a., 2000. Molecular portraits of human breast tumours. *Nature ,* Volume 406, pp. 747-752.
Perou, A. P. &. C. M., august 2009. Mammary development meets cancer genomics. *nature medicine,* Volume 15(8), p. 843.
Perry N, B. M. d. W. C. T. S. H. R. v. K. L., 2006. . European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis. Luxembourg: Office for Official Publications of the European Communities; 2006.. *Luxembourg: Office for Official Publications of the European Communities.*
Pich A, M. E. C. L., 1994. Proliferative activity is a significant prognostic factor in male breast carcinoma. *Am J Pathol,* Volume 145, pp. 481-489.
Pich A, M. E. C. L., 1998. BCL2 expression in male breast carcinoma. *Virchows Arch ,* Volume 433, pp. 229-235.
Pich A, M. E. C. L., 2000. Oncogenes and male breast carcinoma: c-ERBB-2 and p53 coexpression predicts a poor survival. *J Clin Oncol,* Volume 18, pp. 2948-2956.

Pich et al., 1999.
Piscuoglio S, N. C. M. M. e. a., 2016. The genomic landscape of male breast cancers. *Clin Cancer Res ,* Volume 22, pp. 4045-56.
Prat, A. P. J. K. O. e. a., 2010. Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer. *Breast Cancer Res,* p. r 68.
Rabbee, Z. a. S. G., 2016. Young Men's Understandings of Male Breast Cancer: "Pink Ribbons" and "War Wounds.. *International Journal of Men's Health,* Volume 15, pp. 210-217.
Radhakrishna, S., 2015. *Breast Diseases: Imaging and Clinical Management..* 133: s.n.
Ragonese, P. e. a., 2017. Association between multiple sclerosis, cancer risk, and immunosuppressant treatment: a cohort study. *BMC Neurology,* Volume 17.1, p. 155.
Rahman, N. e. a., 2007. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nat Genet 2007; 39: 165-7.. *gene. Nat Genet,* Volume 39, pp. 165-167.
Rayson D, E. C. S. V. a., 1998. Molecular markers in male breast carcinoma. *Cancer ,* Volume 83, pp. 1947-1955.
Reis, L. O. e. a., 2011. Male Breast Cance. *Aging Male,* Volume 14, pp. 99-109.
Ritse M. Mann, N. C. L. M., 2019. Breast MRI: State of the Art. *rsna radiology.*
Rizzolo, P. et al., 2019. Insight into genetic susceptibility to male breast cancer by multigene panel testing: Results from a multicenter study in Italy.. *Int. J. Cancer ,* Volume 145, p. 390–400.
Roed Nielsen, H. e. a., 2016. Increased Risk of Male Cancer and Identification of a Potential Prostate Cancer Cluster Region in BRCA2. *Acta Oncologica,* Volume 55, pp. 38-44.
Rogawski DS, N. J. C. H. M. I. G. J. &. C. T., 2015. Two loops undergoing concerted dynamics regulate the activity of the ASH1L histone methyltransferase. *Biochemistry ,* Volume 54 , p. 5401–5413.
Rogers S, D. C. F. S., 1993. Expression of cathepsin D and estrogen receptor in male breast carcinoma. *Hum Pathol ,* Volume 24, pp. 148-151.
Ron E, I. T. P. D. e. a., 2005. Male breast cancer incidence among atomic bomb survivors. *J Natl Cancer Inst ,* Volume 97, pp. 603-605.
Roshanisefat, H. e. a., 2015. All-cause mortality following a cancer diagnosis amongst multiple sclerosis patients: a Swedish population-based cohort study. *European journal of neurology,* Volume 22.7, pp. 1074-1080.
Rudlowski C, F. N. F. A. e. a., 2004. HER2/neu Gene amplification and protein expression in primary male breast cancer. *Breast Cancer Res Treat ,* Volume 84, pp. 215-223.
Rui Chen, W.-q. Z. C. F. X. Y. a. M. J., 2020. Histone methyltransferase SETD2: a potential tumor suppressor in solid cancers. *J Cancer,* Volume 11(11), p. 3349–3356..
Rusciano, D. a. M. B., 1992. Why do cancer cells metastasize into particular organs?. *Bioessays,* Volume 14(3), pp. 185-194.
S H Heywang, D. H. H. S. I. K. W. E. R. B. J. L., Mar-Apr 1986. MR imaging of the breast using gadolinium-DTPA. *J Comput Assist Tomogr,* Volume 10(2), pp. 199-204..
Sacks, N. a. M. B., 1993. Primary management of carcinoma of the breast. *Lancet,* Volume 342(8884), pp. 1402-8..
Sawaimul, K. e. a., 2015. Occult Male Breast Cancer with Axillary Metastasis: A Rare Case Report. *Journal of the Scientific Society,* Volume 42, pp. 109-111.
Schildhaus HU, S. L. M.-B. S. e. a., 2013. Therapeutic strategies in male breast cancer: clinical implications of chromosome 17 gene alterations and molecular subtypes. *Breast ,* Volume 22, pp. 1066-1071.
Schippinger, e. a., 2006. Evaluation of the prognostic significance of androgen receptor expression in metastatic breast cancer. *Archiv für Pathologische Anatomie und Physiologie und für Klinische Medicin,* Volume 449, pp. 24-30.
Schmitt, P. F., 2016. *BREAST CANCER CLASSIFICATION:TRADITIONAL PATHOLOGY AND MOLECULAR SUBTYPES,* Lisbon : ESMO proctorship program.
Senkus, E. e. a., 2013. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.. *Ann Oncol,* Volume 24 Suppl 6, pp. vi7-23..
Seong, M.-K. e. a., 2015. Bcl-2 is a highly significant prognostic marker of hormone-receptor- positive, human epidermal growth factor receptor-2-negative breast cancer. *Breast cancer research and treatment ,* Volume 150.1, pp. 141-148.
Serra C, V. F. A. L. e. a., 2002. Expression and prognostic significance of lysozyme in male breast cancer. *Breast Cancer Res ,* Volume 4, p. R16.
Serra C, V. F. L. M. a., 2000. Comparative study of two androgen-induced markers (apolipoprotein D and pepsinogen C) in female and male breast carcinoma. *Int J Surg Investig ,* Volume 2, pp. 183-192.
Serra Díaz C, V. F. L. M. a., 1998. Expression and clinical significance of apolipoprotein D in male breast cancer and gynaecomastia. *Br J Surg ,* Volume 86, pp. 1190-1197.
Shaaban, A. e. a., 2012. A comparative biomarker study of 514 matched cases of male and female breast cancer reveals gender-specific biological differences.. *Breast Cancer Research and Treatment,* Volume 133, pp. 949-958.
Shahidsales, S. a. M. F. E., 2017. Male Breast Cancer: A Review of Literature. *Reviews in Clinical Medicine,* Volume 4, pp. 69-72.
Shandiz FH, T. A. S. N. a., 2015. Hormone receptor expression and clinicopathologic features in male and female breast cancer. *Asian Pac J Cancer Prev,* Volume 16, pp. 471-474.

Shao N, X. C. S. Y. Y. R. L. J. S. H. S. Z. T. A. L. Y., 2019. Comparison of the 7th and 8th edition of American Joint Committee on Cancer (AJCC) staging systems for breast cancer patients: a Surveillance, Epidemiology and End Results (SEER) An. *Cancer Manag Res. ,* Volume 11, pp. 1433-1442.
Sharifi, S. e. a., 2014. Roles of the Bcl-2/Bax ratio, caspase-8 and 9 in resistance of breast cancer cells to paclitaxel. *Asian Pac J Cancer Prev,* Volume 15.20, pp. 17-22.
Sharma, R. a. V. K., 2016. Pure Mucinous Carcinoma in Male Breast with Axillary Lymph Node Metastasis. *Clinical Cancer Investigation Journal,* Volume 5, pp. 40-42.
Sidiropoulou Z et al, 2019. *Silent male breast cancer: The natural reservoir of the disease in autopsy specimens..* Mystras 24th Int Congress Advances in Oncology, s.n.
Sidiropoulou Z, e. a., 2017. Prevalence of Silent Breast Cancer in Autopsy Specimens: Study of the Disease Held by Image-Guided Biopsies: Pilot study and Literature Review. *MOLECULAR AND CLINICAL ONCOLOGY,* pp. 193-199.
Sidiropoulou, Z. e. a. E. J. o. S. O. ,. V. 4. ,. I. 9. ,. S. -. S. (. 2. P. P., 2017. *Silent breast cancer: Study of the disease prevalence held by image-guided biopsies on autopsy specimens (Sisyphus study).* S126 - S127 ESSO 2017, European Journal of Surgical Oncology.
Siegel, R. e. a., 2018. Cancer Statistics 2018. *CA Cancer J Clin,* Volume 68, pp. 7-30.
Silvestri, V. e. a., 2016. Male breast cancer in BRCA1 and BRCA2 mutation carriers: pathology data from the Consortium of Investigators of Modifiers of BRCA1/2. *Breast Cancer Research ,* Volume 18.1, p. 15.
Simpson PT, G. T. R.-F. J. e. a., 2005. Columnar cell lesions of the breast: the missing link in breast cancer progression? A morphological and molecular analysis. *Am. J. Surg. Pathol.,* Volume 29, p. 734–746.
Sinobiological, 2020. *https://www.sinobiological.com/resource/cancer-biomarker/definition.* [Online] [Acedido em 2020].
Smerage, J. B. e. a., 2013. Monitoring apoptosis and Bcl-2 on circulating tumor cells in patients with metastatic breast cancer. *Molecular Oncology,* Volume 7.3, pp. 680-692.
Sobin, L., 2003. TNM: evolution and relation to other prognostic factors.. *Semin Surg Oncol,* Volume 21(1), pp. 3-7.
Society, A. C., 2018. *Key statistics for breast cancer in men:cancer facts & figures 2018.* [Online] Available at: https://www.cancer.org/cancer/breast-cancer-in-men/about/key-statistics.html
Soliman, A. A. e. a., 2014. A Retrospective Analysis of Survival and Prognostic Factors of Male Breast Cancer from a Single Center. *BMC Cancer,* Volume 14, pp. 1-5.
Sørensen, H. F. S. O. J. e. a., 1998. Risk of breast cancer in men with liver cirrhosis. *Am J Gastroenterol,* Volume 93, pp. 231-233.
Sorlie T, e. a., 2003. Repeated observation of breast tumour subtypes in independent gene expression sets.. *PNAS,* Volume 100.
Sorlie, T. e. a., 2001. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sc,* Volume 98(19), pp. 10869-74.
Sousa B., e. a., 2013. An update on male breast cancer and future directions for research and treatment. *European Journal of Pharmacology,* Volume 717, pp. 71-83.
Stalsberg H, A. E. O.-A. O., 2015. No difference in the prevalence of benign breast changes between women from Ghana and Norway: An autopsy study.. *Breast Cancer Res Treat. ,* Volume 151, pp. 177-182.
Streng, M. e. a., 2018. A Comparison of Tumor Size Measurements with Palpation, Ultrasound and Mammography in Male Breast Cancer: First Results of the Prospective Register Study.. *Journal of Cancer Research & Clinical Oncology,* Volume 144, pp. 381-387.
Strimbu K, T. J., 2010,Nov. What are biomarkers?. *Curr Opin HIV AIDS.,* Volume 5(6), pp. 436-6.
Stuart Beresford, J. C. A. G. J. H. A. S. E. W., 2018. *HORIZON SCAN: POSSIBLE FUTURES FOR BREAST SCREENING,* s.l.: Allen + Clarke.
Sung JS, L. L. K. D. D. D. C. C. L. C. P. M. A. M. M. C. M. E. J. M., 2019. Performance of Dual-Energy Contrast-enhanced Digital Mammography for Screening Women at Increased Risk of Breast Cancer.. *Radiology ,* Volume 293, pp. 81-8..
Sun, L. e. a., 2014. Increased breast cancer risk for patients with multiple sclerosis: a nationwide population-based cohort study. *European journal of neurology,* Volume 21.2, pp. 238-244.
Swerdlow, A. S. M. H. C. e. a., 2005. Cancer incidence and mortality in men with Klinefelter syndrome: a cohort study. *J Natl Cancer Inst,* Volume 97, pp. 1204-1210.
Syrjäkoski, K. e. a., 2004. CHEK2 1100delC is not a risk factor for male breast cancer population. *Int J Cancer,* Volume 108, pp. 475-476.
T.A. Traina, K. M. D. Y. e. a., 2015. Results from a phase 2 study of enzalutamide (ENZA), an androgen receptor (AR) inhibitor, in advanced AR+ triple-negative breast cancer (TNBC). *J. Clin. Oncol,* Volume 33, p. abstr 1003.
T.E. Hickey, J. R. J. C. W. T., 2012. Minireview: the androgen receptor in breast tissues: growth inhibitor, tumor suppressor, oncogene?. *Mol. Endocrinol,* Volume 26, p. 1252–1267.
Tai, Y., Domchek, S., Parmigiani, G. & Chen, S., 2007. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers.. *J. Natl. Cancer Inst. ,* Volume 99, p. 1811–181.
Tang SS, T. D. I. C. G. G., 2011. Mammary ductoscopy in the current management of breast disease.. *Surgical Endoscopy ,* Volume 25, p. 1712–1722.

Tedaldi et al, 2020. Male Breast Cancer: Results of the Application of Multigene Panel Testing to an Italian Cohort of Patients. *Diagnostics ,* Volume 10(5), p. 269.
Tedaldi, G. et al., 2014. First evidence of a large CHEK2 duplication involved in cancer predisposition in an Italian family with hereditary breast cancer.. *BMC Cancer ,* Volume 14, p. 478.
Temmim L, L. Y. J. M. e. a., 2001. Evaluation of prognostic factors in male breast cancer. *Breast,* Volume 10, pp. 166-175.
Terms., N. D. o. C., s.d. *"Biomarker".* s.l.:National Cancer Institute..
The National Cancer Institute., s.d. *https://prevention.cancer.gov/news-and-events/infographics/what-cancer-overdiagnosis.* [Online].
Thomas, D. J. L. M. A., 1992. Breast cancer in men: risk factors with hormonal implications.. *Am J Epidemiol,* Volume 135, pp. 734-748.
Thomas, D. R. K. J. L. e. a., 1994. Ionizing radiation and breast cancer in men (United States). *Cancer Causes Control,* Volume 5, pp. 9-14.
Thompson D, E. D. B. C. L. C., 2001. Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. *Am J Hum Genet ,* Volume 68, pp. 410-419.
Thorlacius, S. e. a., 1998. Population-based study of risk of breast cancer in carriers of BRCA2 mutation. *Lancet,* Volume 352, pp. 1337-1339.
Tintore, M. e. a., 2015. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. *Brain,* Volume 138.7, pp. 1863-1874.
Tracy-Ann Moo, R. S. C. D. a. M. M., 2018 Jul. Overview of Breast Cancer Therapy. *Moo TA, Sanford R, Dang C, Morrow M. Overview of Breast Cancer Therapy. ,* Volume 13(3), pp. 229-354.
Turashvili, G. e. a., 2018. The 21-gene recurrence score in male breast cancer. *Annals of surgical oncology,* Volume 25.6, pp. 1530-1535.
Urania Dafnia, Z. T. I. A., Breast Care 2019;14:344–352. Breast Cancer Statistics in the European Union: Incidence and Survival across European Countries. *Breast Care 2019,* Volume 14, p. 344–352.
V.S.P.K. Sankara Aditya Jayanthi, A. B. D. U. S., 2019. Grade-specific diagnostic and prognostic biomarkers in breast cancer. *Genomics.*
Vaillant, F. e. a., 2013. Targeting BCL-2 with the BH3 mimetic ABT-199 in estrogen receptor-positive breast cancer. *Cancer cel,* Volume 24.1, pp. 120-129.
Vanderstoep, S. &. J. D., 2009. *Research methods for everyday life: Blending qualitative and quantitative approaches..* San Francisco, CA: Jossey: CA: Jossey.
Varela I., T. P. R. K. H. D. O. C. S. P. D. H. J. D. L. M. T. J. e. a., 2011. Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma.. *Nature.,* Volume 469, p. 539–542.
Veena, R. e. a., 2016. Intracystic papillary carcinoma in the male breast: A diagnostic challenge. *Clinical Cancer Investigation Journal,* Volume 5, pp. 345-348.
Vera-Badillo, e. a., 2013. Androgen receptor expression and outcomes in early breast cancer: a systematic review and meta-analysis. *J Natl Cancer Inst,* Volume 106(1), p. djt319.
Vermeulen, M. A. e. a., 2018. Copy number profiling of oncogenes in ductal carcinoma in situ of the male breast. *Endocrine-related cancer ,* Volume 25.3 , pp. 173-184.
Vivanco, M., 2010. Biomarkers in breast cancer.. *Methods Mol Biol,* Volume 593, pp. 137-56..
W A Kaiser 1, E. Z., 1989. MR imaging of the breast: fast imaging sequences with and without Gd-DTPA. Preliminary observations. *Radiology,* Volume 170(3 Pt 1), pp. 681-6..
Walsh, T. et al., 2006. Walsh, T.; Casadei, S.; Coats, K.H.; Swisher, E.; Stray, S.M.; Higgins, J.; Roach, K.C.; Mandell, J.; Lee, M.K.; Ciernikova, S.; et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer.. *JAMA ,* Volume 295, p. 1379–1388.
Wang Y, I. D. N. B. a., 2008. Estrogen receptor-negative invasive breast cancer: imaging features of tumors with and without human epidermal growth factor receptor type 2 overexpression. *Radiology ,* Volume 246, pp. 367-375.
Wang-Rodriguez J, C. K. G. S. e. a., 2002. Male breast carcinoma:Correlation of ER, PR, Ki-67, Her2-Neu, and p53 with treatment and survival, a Study of 65 cases.. *Mod Pathol,* Volume 15, pp. 853-861.
Wang-Rodriguez, J. e. a., 2012. Male breast carcinoma: correlation of ER, PR, Ki-67, Her2- Neu, and p53 with treatment and survival, a study of 65 cases. *Modern Pathology ,* Volume 15.8, p. 853.
Wang, Y. A. e. a., 2018. Germline Breast Cancer Susceptibility Gene Mutations and Breast Cancer Outcomes. *BMC Cancer,* Volume 18, p. 1.
Wasielewski, M. e. a., 2009. CHEK2 1100delC and male breast cancer in the Netherlands. *Breast Cancer Res Treat,* Volume 116, pp. 397-400.
Weber-Chappuis K, B.-B. S. H. J., 1996. Comparison of prognostic markers detected by immunohistochemistry in male and female breast carcinomas. *Eur J Cancer ,* Volume 2A, pp. 1686-1692.
Weigel, M. a. M. D., 2010. Current and emerging biomarkers in breast cancer:prognosis and prediction.. *Endocr Relat Cancer,* Volume 17(4), pp. R245-62..
Weinberg, R., 1988. Finding the anti-oncogene.. *Sci Am,* Volume 259(3), pp. 44-51.
Welch HG, B. W., 1997. Using autopsy series to estimate the disease ‘reservoir’ for ductal carcinoma in situ of the breast: how much more breast cancer can we find?. *Ann Intern Med. ,* Volume 127, p. 1023–1038..

Wenhui, Z. e. a., 2014. Androgen receptor expression in male breast cancer predicts inferior outcome and poor response to tamoxifen treatment. *European journal of endocrinology,* Volume 171.4 , pp. 527-533.
Willsher PC, L. I. E. I. e. a., 1997. Male breast cancer:pathological and immunohistochemical features. *Anticancer Res,* Volume 17, pp. 2335-2338.
Wooster, R. M. J. E. R. e. a., 1992. A germline mutation in the androgen receptorgene in two brothers with breast cancer and Reifenstein syndrome. *Nat Genet,* Volume 2, pp. 132-134.
Yang, X. et al., 2019. Cancer Risks Associated With Germline PALB2 Pathogenic Variants: An International Study of 524 Families.. *J. Clin. Onc.*
Ye Han, c. a. J. L. S. H. S. J. Y. Z. a. W. Z., 2017. Diagnostic value of endoscopic appearance during ductoscopy in patients with pathological nipple discharge. *BMC Cancer,* Volume ; 17, p. 300..
Yen PP, S. N. B. P. e. a., 2015. Benign and malignant male breast diseases: radiologic and pathologic correlation.. *Can Assoc Radiol J,* Volume 66, pp. 198-207.
Yersal, O. a. S. B., 2014. Biological subtypes of breast cancer: Prognostic and therapeutic implications.. *World J Clin Oncol,* Volume 5(3), pp. 412-424.
Yiming Gao, J. E. G. T. K. Y. J. S. B. L. M. S. L. H., 2019. Breast Cancer Screening in High-Risk Men: A 12-year Longitudinal Observational Study of Male Breast Imaging Utilization and Outcomes. *Radiology.*
Young, I. K. K. A. C. e. a., 1999. A polymorphism in the CYP17 gene is associated with male breast cancer. *Br J Cancer,* Volume 81, pp. 141-143.
Yu X-F, F. W.-L. M. L.-L. e. a., 2013. The prognostic significance of molecular subtype for male breast cancer: a 10-year retrospective study.. *Breast,* Volume 22, p. 824–827..
Zackrisson S, L. K. R. A. e. a., 2018. One-view breast tomosynthesis versus two-view mammography in the Malmö Breast Tomosynthesis Screening Trial (MBTST): a prospective, population-based, diagnostic accuracy study.. *Lancet Oncol.,* Volume 19(11), pp. 1493-150.
Zhao TP, H. G., 1988. A Phase II clinical trial of flutamide in the treatment of advanced breast cancer. *Tumori ,* Volume 74(1), p. 53–56 .

Appendix

The present apendix contains the statistical analysis data output of the SPSS software.

Silent male breast cancer

Frequencies

Statistics

		Race	DeathCause	Palpation	Glands	Ecography	Mamography
N	Valid	74	74	74	74	5	9
	Missing	0	0	0	0	69	65

Frequency Table

Glands

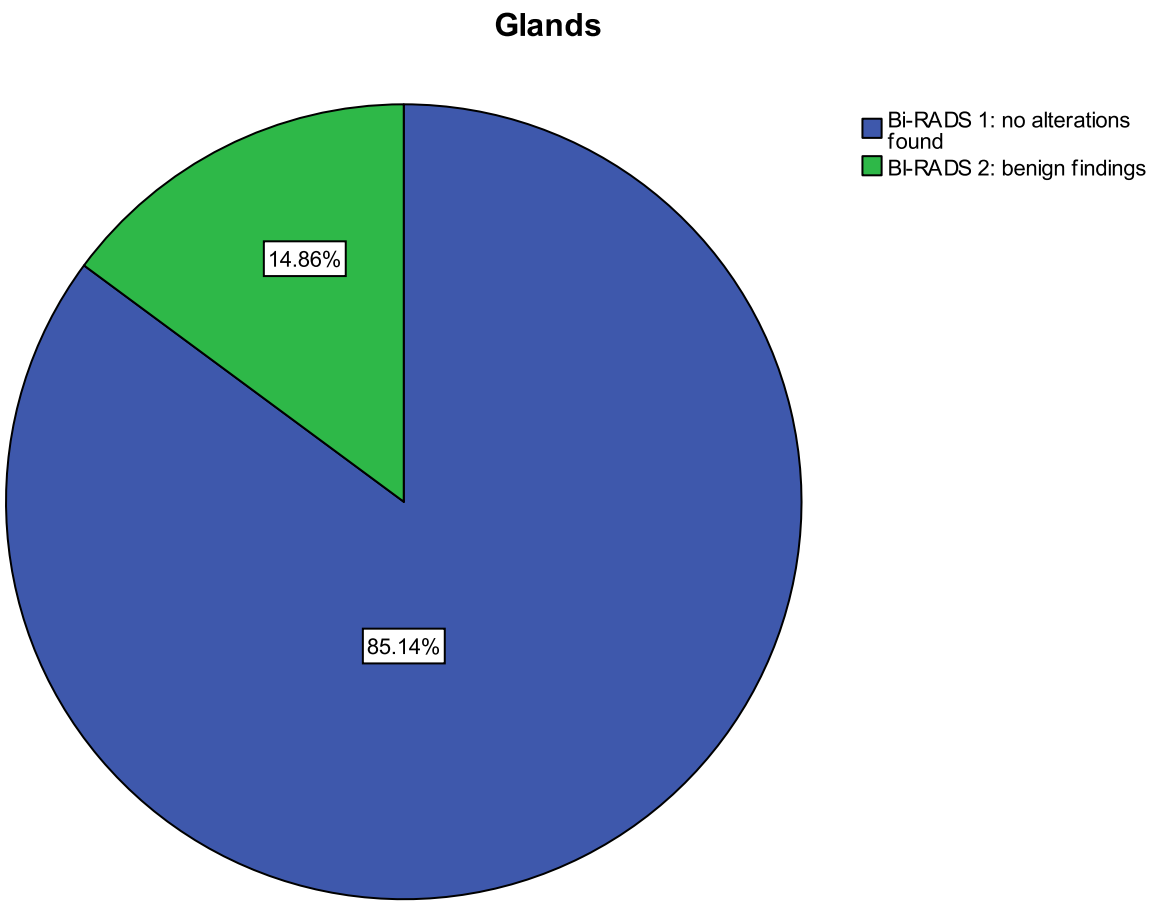
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Bi-RADS 1: no alterations found	63	85.1	85.1	85.1
	BI-RADS 2: benign findings	11	14.9	14.9	100.0
	Total	74	100.0	100.0	

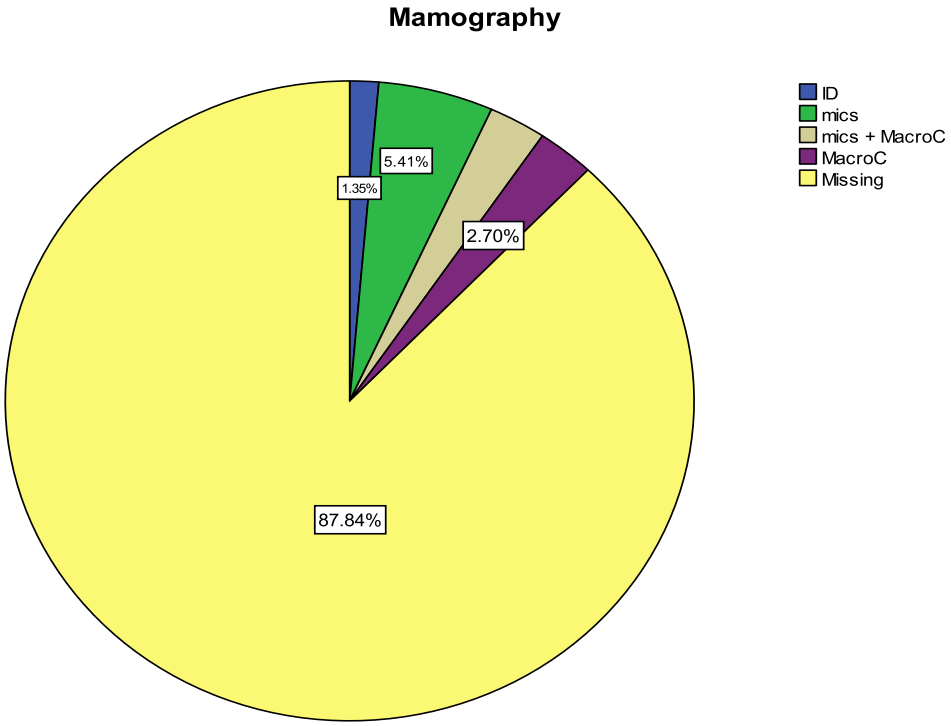
Ecography

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Intramammary lymphnodes	3	4.1	60.0	60.0
	Axilary lypmhnodes	2	2.8	40.0	100.0
	Total	5	6.8	100.0	
Missing	System	69	93.2		
Total		74	100.0		

Mamography

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	ID	1	1.4	11.1	11.1
	mics	4	5.4	44.4	55.6
	mics + MacroC	2	2.7	22.2	77.8
	MacroC	2	2.7	22.2	100.0
	Total	9	12.2	100.0	
Missing	System	65	87.8		
Total		74	100.0		





Point 2

Correlations

Correlations

		Glands (Bi-RADS)	Age	Weight	Height	BMI
Glands (Bi-RADS)	Pearson Correlation	1	-.113	-.202*	.078	-.182*
	Sig. (2-tailed)		.170	.020	.346	.028
	N	148	148	134	148	146
Age	Pearson Correlation	-.113	1	-.223**	-.130	-.302**
	Sig. (2-tailed)	.170		.010	.115	.000
	N	148	148	134	148	146
Weight	Pearson Correlation	-.202*	-.223**	1	.054	.863**
	Sig. (2-tailed)	.020	.010		.538	.000
	N	134	134	134	134	134
Height	Pearson Correlation	.078	-.130	.054	1	-.229**
	Sig. (2-tailed)	.346	.115	.538		.005
	N	148	148	134	148	146
BMI	Pearson Correlation	-.182*	-.302**	.863**	-.229**	1
	Sig. (2-tailed)	.028	.000	.000	.005	
	N	146	146	134	146	146

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

		DeathCause	Mammography	Ecography	Glands (Bi-RADS)
DeathCause	Pearson Correlation	1	.568*	.134	-.142
	Sig. (2-tailed)		.027	.732	.085
	N	148	15	9	148
Mammography	Pearson Correlation	.568*	1	1.000**	-.206
	Sig. (2-tailed)	.027		.000	.462
	N	15	15	3	15
Ecography	Pearson Correlation	.134	1.000**	1	-.550
	Sig. (2-tailed)	.732	.000		.125
	N	9	3	9	9
Glands (Bi-RADS)	Pearson Correlation	-.142	-.206	-.550	1
	Sig. (2-tailed)	.085	.462	.125	
	N	148	15	9	148

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

		Glands (Bi-RADS)	Ecography	Mammography
Glands (Bi-RADS)	Pearson Correlation	1	-.550	-.206
	Sig. (2-tailed)		.125	.462
	N	148	9	15
Ecography	Pearson Correlation	-.550	1	1.000**
	Sig. (2-tailed)	.125		.000
	N	9	9	3
Mammography	Pearson Correlation	-.206	1.000**	1
	Sig. (2-tailed)	.462	.000	
	N	15	3	15

Correlations

		Glands (Bi-RADS)	Ecography	Mammography
Glands (Bi-RADS)	Pearson Correlation	1	-.550	-.206
	Sig. (2-tailed)		.125	.462
	N	148	9	15
Ecography	Pearson Correlation	-.550	1	1.000**
	Sig. (2-tailed)	.125		.000
	N	9	9	3
Mammography	Pearson Correlation	-.206	1.000**	1
	Sig. (2-tailed)	.462	.000	
	N	15	3	15

**. Correlation is significant at the 0.01 level (2-tailed).

Cross Tabs

Glands (Bi-RADS) * Mammography Crosstabulation

			Mammography				
			ID	mics	mics + MacroC	MacroC	Total
Glands (Bi-RADS)	Bi-RADS 1: no alterations found	Count	0	2	3	2	7
		% within Glands (Bi-RADS)	.0%	28.6%	42.9%	28.6%	100.0%
		% of Total	.0%	13.3%	20.0%	13.3%	46.7%
	BI-RADS 2: benign findings	Count	1	3	2	2	8
		% within Glands (Bi-RADS)	12.5%	37.5%	25.0%	25.0%	100.0%
		% of Total	6.7%	20.0%	13.3%	13.3%	53.3%
Total		Count	1	5	5	4	15
		% within Glands (Bi-RADS)	6.7%	33.3%	33.3%	26.7%	100.0%
		% of Total	6.7%	33.3%	33.3%	26.7%	100.0%

Glands (Bi-RADS) * Ecography Crosstabulation

			Ecography		
			Intramammary lymphnodes	Axlilary lypmhnodes	Total
Glands (Bi-RADS)	Bi-RADS 1: no alterations found	Count	1	3	4
		% within Glands (Bi-RADS)	25.0%	75.0%	100.0%
		% of Total	11.1%	33.3%	44.4%
	BI-RADS 2: benign findings	Count	4	1	5
		% within Glands (Bi-RADS)	80.0%	20.0%	100.0%
		% of Total	44.4%	11.1%	55.6%
Total		Count	5	4	9
		% within Glands (Bi-RADS)	55.6%	44.4%	100.0%
		% of Total	55.6%	44.4%	100.0%

Correlations

Correlations

		Glands	Age	Weight	Height	BMI
Glands	Pearson Correlation	1	-.158	-.297*	-.064	-.256*
	Sig. (2-tailed)		.178	.015	.586	.029
	N	74	74	67	74	73
Age	Pearson Correlation	-.158	1	-.223	-.130	-.302**
	Sig. (2-tailed)	.178		.070	.270	.009
	N	74	74	67	74	73
Weight	Pearson Correlation	-.297*	-.223	1	.054	.863**
	Sig. (2-tailed)	.015	.070		.666	.000
	N	67	67	67	67	67
Height	Pearson Correlation	-.064	-.130	.054	1	-.229
	Sig. (2-tailed)	.586	.270	.666		.051
	N	74	74	67	74	73
BMI	Pearson Correlation	-.256*	-.302**	.863**	-.229	1
	Sig. (2-tailed)	.029	.009	.000	.051	
	N	73	73	67	73	73

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

		DeathCause	Mamography	Ecography	Glands
DeathCause	Pearson Correlation	1	.593	.079	-.100
	Sig. (2-tailed)		.092	.900	.395
	N	74	9	5	74
Mamography	Pearson Correlation	.593	1	.866	.[a]
	Sig. (2-tailed)	.092		.333	.000
	N	9	9	3	9
Ecography	Pearson Correlation	.079	.866	1	.[a]
	Sig. (2-tailed)	.900	.333		.000
	N	5	3	5	5
Glands	Pearson Correlation	-.100	.[a]	.[a]	1
	Sig. (2-tailed)	.395	.000	.000	
	N	74	9	5	74

Correlations

		DeathCause	Mamography	Ecography	Glands
DeathCause	Pearson Correlation	1	.593	.079	-.100
	Sig. (2-tailed)		.092	.900	.395
	N	74	9	5	74
Mamography	Pearson Correlation	.593	1	.866	.[a]
	Sig. (2-tailed)	.092		.333	.000
	N	9	9	3	9
Ecography	Pearson Correlation	.079	.866	1	.[a]
	Sig. (2-tailed)	.900	.333		.000
	N	5	3	5	5
Glands	Pearson Correlation	-.100	.[a]	.[a]	1
	Sig. (2-tailed)	.395	.000	.000	
	N	74	9	5	74

a. Cannot be computed because at least one of the variables is constant.

Correlations

Correlations

		Glands	Ecography	Mamography
Glands	Pearson Correlation	1	.[a]	.[a]
	Sig. (2-tailed)		.000	.000
	N	74	5	9
Ecography	Pearson Correlation	.[a]	1	.866
	Sig. (2-tailed)	.000		.333
	N	5	5	3
Mamography	Pearson Correlation	.[a]	.866	1
	Sig. (2-tailed)	.000	.333	
	N	9	3	9

a. Cannot be computed because at least one of the variables is constant.

Cross Tabs

Glands * Mamography Crosstabulation

			Mamography				
			ID	mics	mics + MacroC	MacroC	Total
Glands	Bi-RADS 1: no alterations found	Count	0	2	2	2	6
		% within Glands	.0%	33.3%	33.3%	33.3%	100.0%
		% of Total	.0%	22.2%	22.2%	22.2%	66.7%
	BI-RADS 2: benign findings	Count	1	2	0	0	3
		% within Glands	33.3%	66.7%	.0%	.0%	100.0%
		% of Total	11.1%	22.2%	.0%	.0%	33.3%
Total		Count	1	4	2	2	9
		% within Glands	11.1%	44.4%	22.2%	22.2%	100.0%
		% of Total	11.1%	44.4%	22.2%	22.2%	100.0%

Glands * Ecography Crosstabulation

			Ecography		
			Intramammary lymphnodes	Axilary lypmhnodes	Total
Glands	Bi-RADS 1: no alterations found	Count	1	1	2
		% within Glands	50.0%	50.0%	100.0%
		% of Total	20.0%	20.0%	40.0%
	BI-RADS 2: benign findings	Count	2	1	3
		% within Glands	66.7%	33.3%	100.0%
		% of Total	40.0%	20.0%	60.0%
Total		Count	3	2	5
		% within Glands	60.0%	40.0%	100.0%
		% of Total	60.0%	40.0%	100.0%

Silent female breast cancer

Correlations

Correlations

		Glands (Bi-RADS)	Age	Weight	BMI
Glands (Bi-RADS)	Pearson Correlation	1	-.008	-.037	.143*
	Sig. (2-tailed)		.860	.441	.031
	N	433	433	425	226
Age	Pearson Correlation	-.008	1	-.030	.008
	Sig. (2-tailed)	.860		.542	.902
	N	433	434	426	226
Weight	Pearson Correlation	-.037	-.030	1	.175**
	Sig. (2-tailed)	.441	.542		.009
	N	425	426	426	220
BMI	Pearson Correlation	.143*	.008	.175**	1
	Sig. (2-tailed)	.031	.902	.009	
	N	226	226	220	226

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

		DeathCause	Mammography	Ecography	Glands (Bi-RADS)
DeathCause	Pearson Correlation	1	.164	-.094	-.088
	Sig. (2-tailed)		.058	.333	.067
	N	434	135	108	433
Mammography	Pearson Correlation	.164	1	-.003	.127
	Sig. (2-tailed)	.058		.985	.143
	N	135	135	37	135
Ecography	Pearson Correlation	-.094	-.003	1	.328**
	Sig. (2-tailed)	.333	.985		.001
	N	108	37	108	108
Glands (Bi-RADS)	Pearson Correlation	-.088	.127	.328**	1
	Sig. (2-tailed)	.067	.143	.001	
	N	433	135	108	433

Correlations

		DeathCause	Mammography	Ecography	Glands (Bi-RADS)
DeathCause	Pearson Correlation	1	.164	-.094	-.088
	Sig. (2-tailed)		.058	.333	.067
	N	434	135	108	433
Mammography	Pearson Correlation	.164	1	-.003	.127
	Sig. (2-tailed)	.058		.985	.143
	N	135	135	37	135
Ecography	Pearson Correlation	-.094	-.003	1	.328**
	Sig. (2-tailed)	.333	.985		.001
	N	108	37	108	108
Glands (Bi-RADS)	Pearson Correlation	-.088	.127	.328**	1
	Sig. (2-tailed)	.067	.143	.001	
	N	433	135	108	433

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

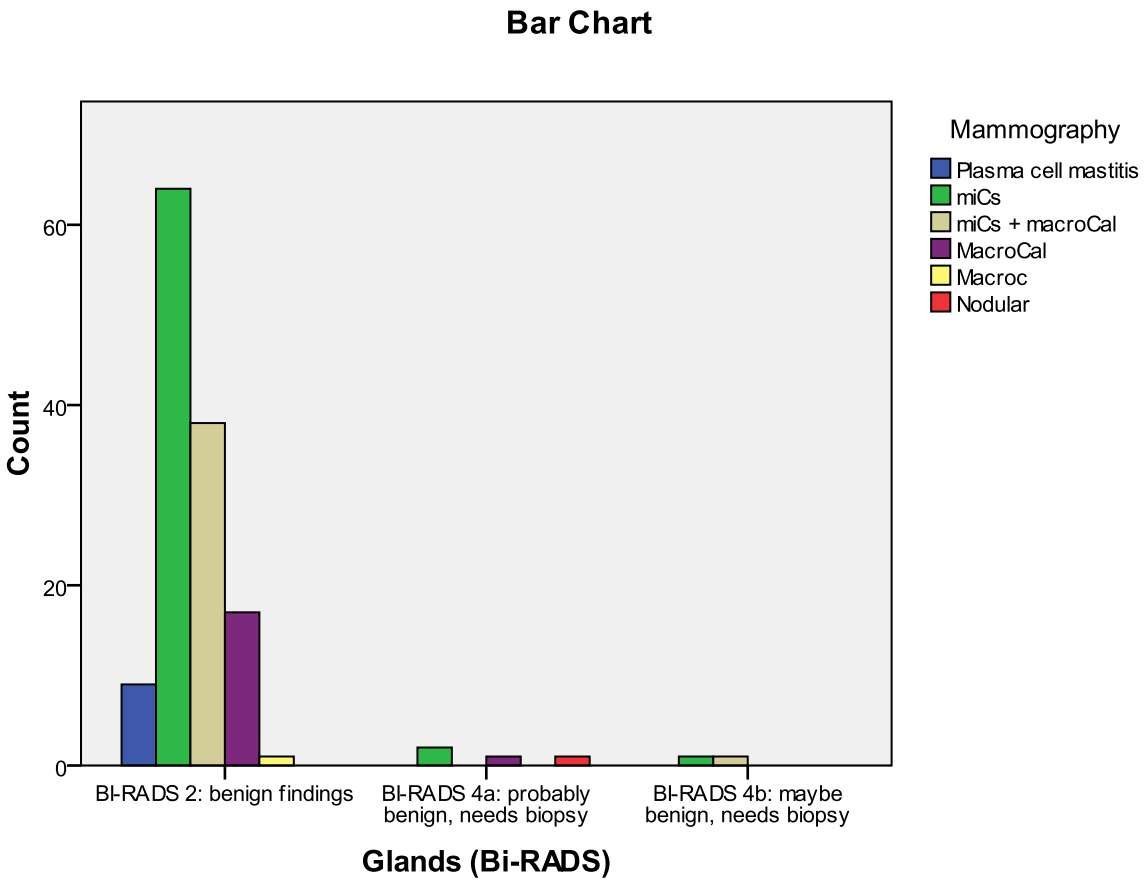
		Glands (Bi-RADS)	Ecography	Mammography
Glands (Bi-RADS)	Pearson Correlation	1	.328**	.127
	Sig. (2-tailed)		.001	.143
	N	433	108	135
Ecography	Pearson Correlation	.328**	1	-.003
	Sig. (2-tailed)	.001		.985
	N	108	108	37
Mammography	Pearson Correlation	.127	-.003	1
	Sig. (2-tailed)	.143	.985	
	N	135	37	135

**. Correlation is significant at the 0.01 level (2-tailed).

Cross Tabs

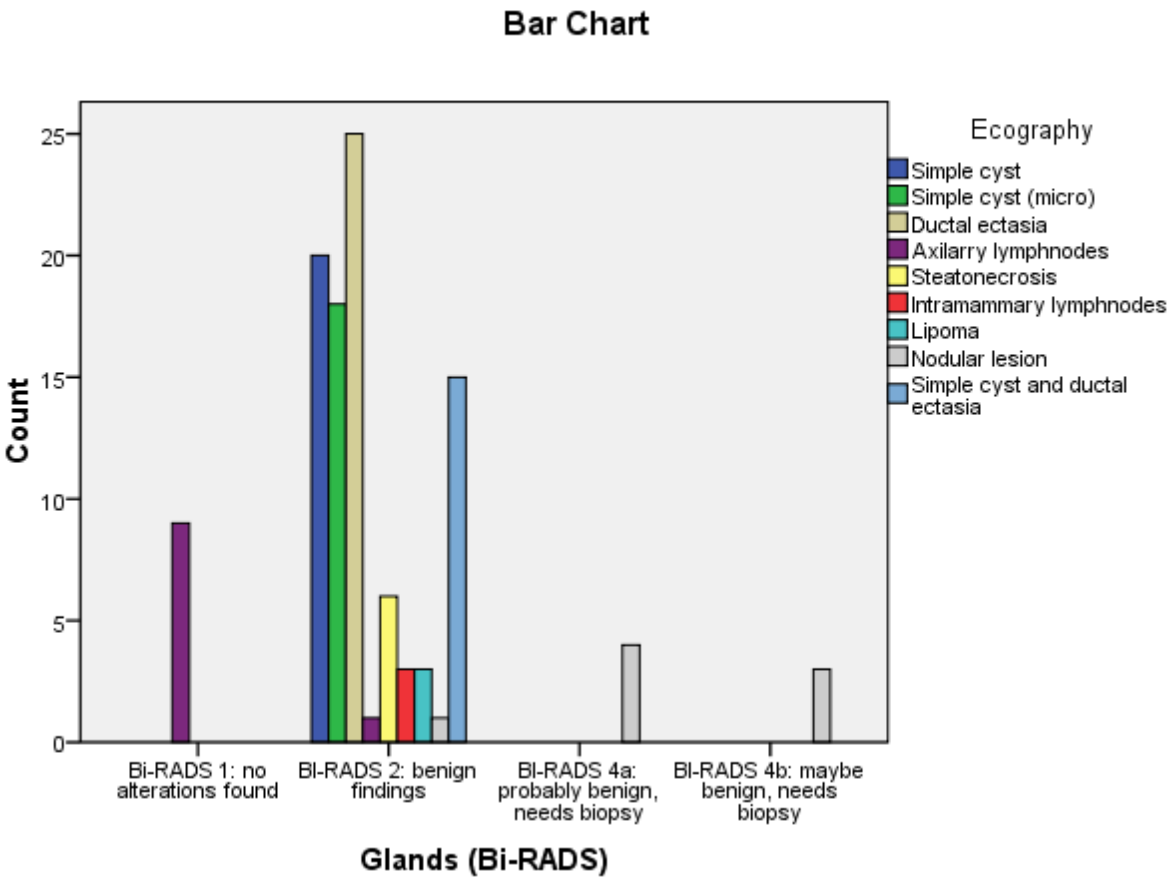
Glands (Bi-RADS) * Mammography Crosstabulation

			Mammography						
			Plasma cell mastitis	miCs	miCs + macroCal	MacroCal	Macroc	Nodular	Total
Glands (Bi-RADS)	BI-RADS 2: benign findings	Count	9	64	38	17	1	0	129
		% within Glands (Bi-RADS)	7.0%	49.6%	29.5%	13.2%	.8%	.0%	100.0%
		% of Total	6.7%	47.4%	28.1%	12.6%	.7%	.0%	95.6%
	BI-RADS 4a: probably benign, needs biopsy	Count	0	2	0	1	0	1	4
		% within Glands (Bi-RADS)	.0%	50.0%	.0%	25.0%	.0%	25.0%	100.0%
		% of Total	.0%	1.5%	.0%	.7%	.0%	.7%	3.0%
	BI-RADS 4b: maybe benign, needs biopsy	Count	0	1	1	0	0	0	2
		% within Glands (Bi-RADS)	.0%	50.0%	50.0%	.0%	.0%	.0%	100.0%
		% of Total	.0%	.7%	.7%	.0%	.0%	.0%	1.5%
Total		Count	9	67	39	18	1	1	135
		% within Glands (Bi-RADS)	6.7%	49.6%	28.9%	13.3%	.7%	.7%	100.0%
		% of Total	6.7%	49.6%	28.9%	13.3%	.7%	.7%	100.0%


Bar Chart
Mammography
Plasma cell mastitis
miCs
miCs + macroCal
MacroCal
Macroc
Nodular
Count
60
40
20
0
BI-RADS 2: benign findings
BI-RADS 4a: probably benign, needs biopsy
BI-RADS 4b: maybe benign, needs biopsy
Glands (Bi-RADS)

Glands (Bi-RADS) * Ecography Crosstabulation

			Ecography									
			Simple cyst	Simple cyst (micro)	Ductal ectasia	Axilarry lymphnodes	Steatonecrosis	Intramammary lymphnodes	Lipoma	Nodular lesion	Simple cyst and ductal ectasia	Total
Glands (Bi-RADS)	Bi-RADS 1: no alterations found	Count	0	0	0	9	0	0	0	0	0	9
		% within Glands (Bi-RADS)	.0%	.0%	.0%	100.0%	.0%	.0%	.0%	.0%	.0%	100.0%
		% of Total	.0%	.0%	.0%	8.3%	.0%	.0%	.0%	.0%	.0%	8.3%
	BI-RADS 2: benign findings	Count	20	18	25	1	6	3	3	1	15	92
		% within Glands (Bi-RADS)	21.7%	19.6%	27.2%	1.1%	6.5%	3.3%	3.3%	1.1%	16.3%	100.0%
		% of Total	18.5%	16.7%	23.1%	.9%	5.6%	2.8%	2.8%	.9%	13.9%	85.2%
	BI-RADS 4a: probably benign, needs biopsy	Count	0	0	0	0	0	0	0	4	0	4
		% within Glands (Bi-RADS)	.0%	.0%	.0%	.0%	.0%	.0%	.0%	100.0%	.0%	100.0%
		% of Total	.0%	.0%	.0%	.0%	.0%	.0%	.0%	3.7%	.0%	3.7%
	BI-RADS 4b: maybe benign, needs biopsy	Count	0	0	0	0	0	0	0	3	0	3
		% within Glands (Bi-RADS)	.0%	.0%	.0%	.0%	.0%	.0%	.0%	100.0%	.0%	100.0%
		% of Total	.0%	.0%	.0%	.0%	.0%	.0%	.0%	2.8%	.0%	2.8%
Total		Count	20	18	25	10	6	3	3	8	15	108
		% within Glands (Bi-RADS)	18.5%	16.7%	23.1%	9.3%	5.6%	2.8%	2.8%	7.4%	13.9%	100.0%
		% of Total	18.5%	16.7%	23.1%	9.3%	5.6%	2.8%	2.8%	7.4%	13.9%	100.0%


Bar Chart
Count
25
20
15
10
5
0
Bi-RADS 1: no alterations found
BI-RADS 2: benign findings
BI-RADS 4a: probably benign, needs biopsy
BI-RADS 4b: maybe benign, needs biopsy
Glands (Bi-RADS)
Ecography
Simple cyst
Simple cyst (micro)
Ductal ectasia
Axilarry lymphnodes
Steatonecrosis
Intramammary lymphnodes
Lipoma
Nodular lesion
Simple cyst and ductal ectasia

Oneway analysis of variance

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
Mortality (deaths due to breast cancer per year)	HHIC	153	17.8555	5.35863	.43322	16.9996	18.7114	11.44	70.70
	IHIC	128	16.5451	3.49469	.30889	15.9338	17.1563	10.83	30.88
	LHIC	107	16.0089	1.83969	.17785	15.6563	16.3615	11.73	21.93
	Total	388	16.9139	4.10305	.20830	16.5044	17.3235	10.83	70.70
Incidence (new cases of breast cancer per year)	HHIC	129	85.6995	14.53618	1.27984	83.1672	88.2319	54.22	120.49
	IHIC	111	73.9474	13.96007	1.32503	71.3215	76.5733	46.61	96.69
	LHIC	94	55.1324	12.03364	1.24118	52.6677	57.5972	37.32	86.37
	Total	334	73.1912	18.40915	1.00730	71.2097	75.1726	37.32	120.49

Test of Homogeneity of Variances

	Levene Statistic	df1	df2	Sig.
Mortality (deaths due to breast cancer per year)	6.075	2	385	.003
Incidence (new cases of breast cancer per year)	3.598	2	331	.028

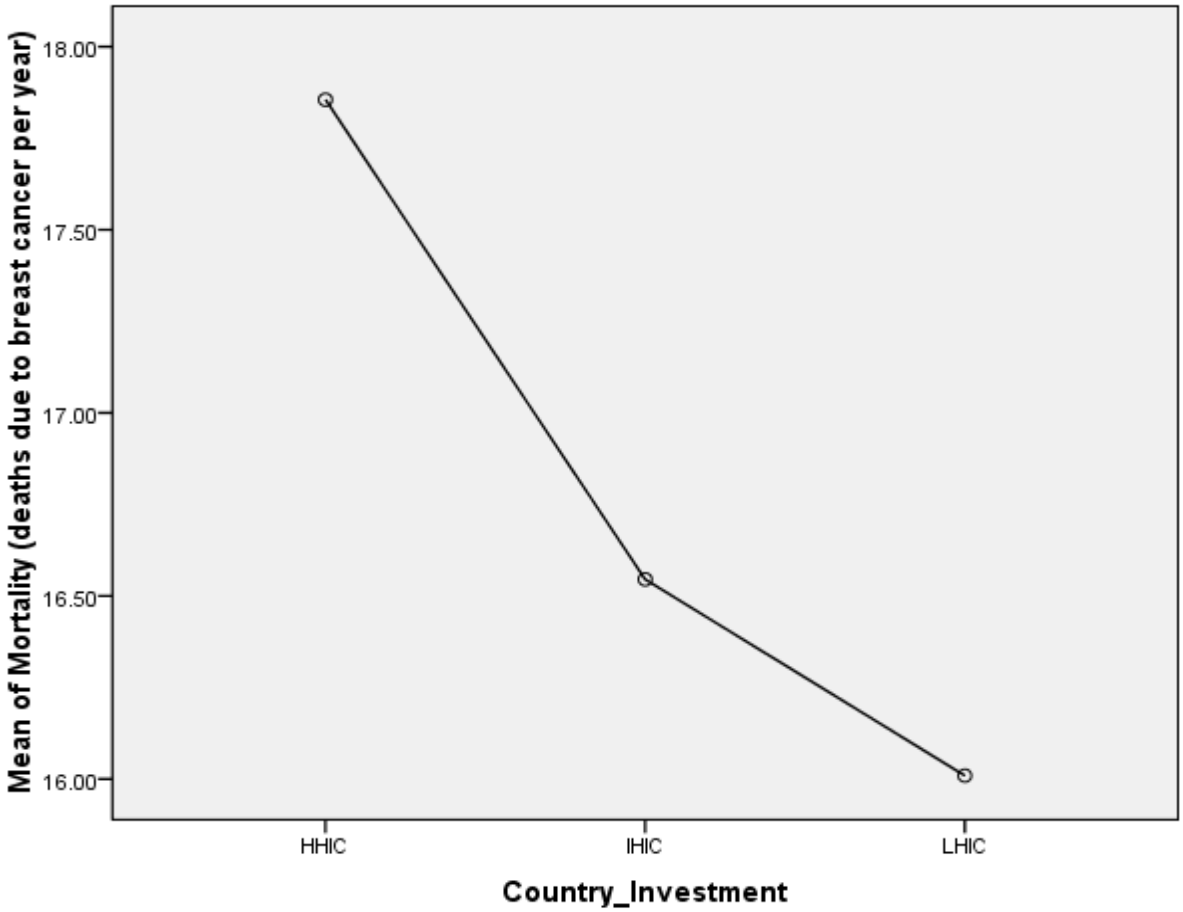
ANOVA

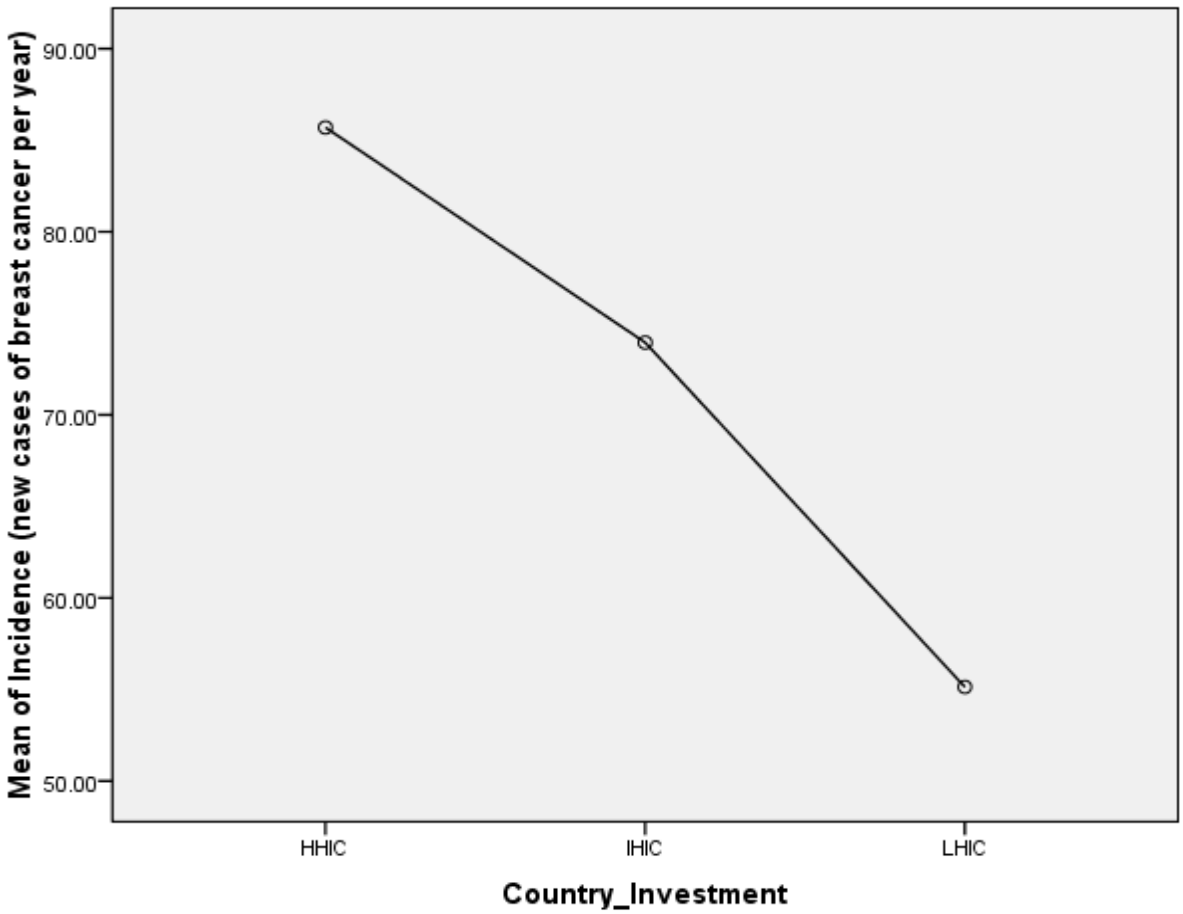
		Sum of Squares	df	Mean Square	F	Sig.
Mortality (deaths due to breast cancer per year)	Between Groups	240.700	2	120.350	7.385	.001
	Within Groups	6274.457	385	16.297		
	Total	6515.157	387			
Incidence (new cases of breast cancer per year)	Between Groups	50901.756	2	25450.878	135.983	.000
	Within Groups	61950.833	331	187.163		
	Total	112852.589	333			

Robust Tests of Equality of Means

		Statistic[a]	df1	df2	Sig.
Mortality (deaths due to breast cancer per year)	Welch	8.049	2	242.198	.000
Incidence (new cases of breast cancer per year)	Welch	149.658	2	217.617	.000

a. Asymptotically F distributed.


Mean of Mortality (deaths due to breast cancer per year)
18.00
17.50
17.00
16.50
16.00
HHIC
IHIC
LHIC
Country_Investment


Mean of Incidence (new cases of breast cancer per year)
90.00
80.00
70.00
60.00
50.00
HHIC
IHIC
LHIC
Country_Investment