Prevalence of Imaging Detected Silent Female Breast Cancer in Autopsy Specimens: Study of the Disease Held by Image-Guided Biopsies

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-Zacharoula Sidiropoulou, Ana Virginia Araujo, Inês Alegre, Claudia Santos, Filipa Costa, Diogo Cardoso and Vasco Cardoso have been responsible for specimen collection, biopsies and literature review
Zacharoula Sidiropoulou has elaborated the protocol and supervised the all trial
Ana Paula Vasconcelos and Cristiana Couceiro have performed the breast imaging of the specimens
Carlos Dos Santos has been responsible for inclusion/ exclusion criteria of each cadaver and obtaining the authorization for each collection
Rita Sampaio has performed the pathology analysis of specimens
Fátima Cardoso and Pére Gascón have supervised and tutored the trial
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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. 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 imaging detected actual number of breast cancer present in female gender by determining the prevalence of silent breast cancer in corpses. We quantified the imaging-identified cancers that were not clinically manifested, with the hypothesis that the imaging detected natural reservoir of silent breast cancer is greater than the actual incidence of the disease, a hypothesis that was not confirmed.
Introduction

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.

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-GeneraldalSaúde, 2016) 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.

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 image detected silent breast cancer present in female gender 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.

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.

Table I summarizes the five relevant studies that were identified.

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

Legend: Cis: in situ carcinoma, IC: invasive carcinoma, AH: atypical hyperplasia

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.

The present study was designed to determine imagine detected silent breast cancer prevalence in female gender allocating the hypothesis that the incidence of the by imaging means identified female silent breast cancers are superior to the real disease incidence. 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.

Patients and Methods
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.

The study employed Cochran's (Cochran, 1977) sample size estimation procedure where the target population is infinite. Therefore, the sample size calculated at 95% confidence interval, 0.12 proportion, and precision level of 0.05 will need an estimated population size of 182 cadavers to achieve the null hypothesis.

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.
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 was used to determine the correlation between the multi-dimension construct assessment and each factor.

Methods

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 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.

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, was transported within an appropriate container to the Hospital São Francisco Xavier (Lisbon, Portugal), and submitted to measuring (three-dimensions), waiting, inspection, palpation, ultrasound, and mammography by breast radiologists and breast surgeon.

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.), with an X-ray beam of 27 kV (range, 60 70 mA) and 10
15 decanewtons (daN) compression, depending on tissue density and size. 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).

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 has been used

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 70°C. Following these procedures, the slide was subjected to labeling by the immunocytochemistry (ICC) method.

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.

RESULTS

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 1).
Mean BMI was 24.89 kg/m²; 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 1). Interestingly, eight gastrointestinal tract silent adenocarcinomas (seven colons and once gastric) and one silent ovarian adenocarcinoma were diagnosed; Fig. 2).

<table>
<thead>
<tr>
<th>Findings at death</th>
<th>Number of corpses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td>65</td>
</tr>
<tr>
<td>Acute Cerebrovascular accident</td>
<td>45</td>
</tr>
<tr>
<td>Hipovolemic shock</td>
<td>20</td>
</tr>
<tr>
<td>Viral Pneumonia</td>
<td>16</td>
</tr>
<tr>
<td>Head trauma Subarachnoid hemorrhage</td>
<td>14</td>
</tr>
<tr>
<td>Hypoxic encephalopathy</td>
<td>8</td>
</tr>
<tr>
<td>Poisoning</td>
<td>8</td>
</tr>
<tr>
<td>Aspiration</td>
<td>7</td>
</tr>
<tr>
<td>Acute alcohol intoxication</td>
<td>4</td>
</tr>
<tr>
<td>Acute pulmonary embolism</td>
<td>4</td>
</tr>
<tr>
<td>Asfixiation</td>
<td>4</td>
</tr>
<tr>
<td>Right colon adenocarcinoma</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 1. Findings at death

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic ketoacidosis</td>
<td>2</td>
</tr>
<tr>
<td>Lung adenocarcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>2</td>
</tr>
<tr>
<td>Peritonitis post left hemicolectomy</td>
<td>2</td>
</tr>
<tr>
<td>Viral Meningitis</td>
<td>2</td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>1</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Gastric adenocarcinoma perf</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic metastasis of left colon adenocarcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>1</td>
</tr>
<tr>
<td>Left colon adenocarcinoma perfuration</td>
<td>1</td>
</tr>
<tr>
<td>Left colon metastatic adenocarcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Ovarian metastatic adenocarcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Peritonitis post right hemicolectomy</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 2. Findings at death

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. 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).

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:

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

The total breast tissue volume elaborated was 836821.9 cm\(^3\) (836,822L). The total volume of breast tissue created was 836821.9 cm\(^3\) (836,822L). The observed correlation between BMI and Total Breast Volume (TBV) is depicted in the following graph (figure 4). Breast volume and BMI appear not to correlate (correlation index of 0.008).

![Figure 4 BMI e TBV](image-url)
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 5).

Figure 5. BMI and breast density

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 6).
In general, as shown in Table 2 and Figure 7, 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.

<table>
<thead>
<tr>
<th>BI-RADS</th>
<th>Normal OE</th>
<th>Pathologic OE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>236</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>209</td>
<td>1</td>
</tr>
<tr>
<td>4a</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4b</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2 BI-RADS and Objective Exam

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.
The mammographic analysis of the samples revealed benign microcalcifications in 42 cases, 35 of which were dispersed and seven were localized (Figure 8). 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 8 Mamographic analysis of the BI-RADS 2 specimens

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 9). Moreover, six cases had benign axillary adenomegalies, and two had intramammary adenomegalies.
Figure 9  Ecographic analysis of the BI-RADS 2 specimens

The excisional biopsies performed (Table 3)

<table>
<thead>
<tr>
<th>age</th>
<th>corpses</th>
<th>eco</th>
<th>mamo</th>
<th>BI-RADS</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-44</td>
<td>1</td>
<td>25mm</td>
<td>miCs</td>
<td>4b</td>
<td>FbrQ</td>
</tr>
<tr>
<td>45-49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-54</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-59</td>
<td>2</td>
<td>0,8-10</td>
<td></td>
<td>4a/4a</td>
<td>FAD/steatone</td>
</tr>
<tr>
<td>60-64</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>1</td>
<td>40</td>
<td></td>
<td>4b</td>
<td>FbrQ</td>
</tr>
<tr>
<td>70-74</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td>3</td>
<td>25/15/0,8</td>
<td></td>
<td>4b/4a/4a</td>
<td>Cyst/Hamartoma/FAD</td>
</tr>
<tr>
<td>80-84</td>
<td>1</td>
<td>18</td>
<td>miCs</td>
<td>4a</td>
<td>FbrQ</td>
</tr>
<tr>
<td>85-89</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3  Biopsied corpses
Concerned 4a (five cases) and 4b BI-RADS (three cases) classification changes.

**Figure 10** Graphic representation of biopsies and their age related distribution

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.

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 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.
The correlation analysis was also conducted to determine the relationship of the findings at death with the results of mammography, ecography, and gland's BI-RADS of female corpses. The results indicated the findings at 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 findings at death of the female corpses examined in this research.

HYPOTHESIS TESTING

The study intended to quantify by imaging means 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. According to the findings, 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.
Subsequently, the gland's BI-RADS results of the female corpses were cross-tabulated against the ecography results. 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.

The gland's BI-RADS and ecography results are presented diagrammatically in figure 12, given below.
Based on the results of cross-tabulation it was evident that no malignant glands were found by ecography and mammography in the female corpses. However, to statically validate these findings, the level of significance of this result is evaluated by conducting correlation analysis.

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.

Discussion

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,
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 complete and thorough excision of breast and axillary 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, 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)

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.

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.

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 (MG 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) evidenced 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.

Conclusions
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. Because of COVID-19 pandemics suspension of sample collection the study did not achieved the initial specimen number needed to define the imaging detected silent breast female cancer prevalence and probably, further ahead there would be identified individuals with breast silent cancer, though since the null hypothesis has been achieved, the result would not be statistically significant.

**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?"

Bibliografía


