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Microcalcification of breast cancer: analytic study

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Abstract

Breast cancer is one of the most common cancers worldwide. Breast microcalcifications are deposits of calcium in the breast tissue and appear as small bright spots on mammograms. We searched electronic databases such as PubMed, Scopus, Web of Science, and Google Scholar for information on breast cancer (BC) with microcalcifications through 1990–2022 using keywords such as breast cancer, calcification, microcalcifications. For bibliometric analysis, an online platform for monitoring and analyzing international scientific research using visualization tools and current citation metrics. We analyzed the Scopus database, which included 510 publications. These electronic sources were filtered by the keywords breast cancer, calcification, and microcalcifications. The results of the bibliometric analysis indicate that the number of publications on the specified topic has increased significantly over the past ten years, which shows the relevance of the problem and ways of solving it among scientists. This data supports the idea that the metastatic/invasive breast cancer cells might have more competency for pathological microcalcification as compared to non-metastatic/non-invasive cancer cells.

Keywords: Breast cancer; microcalcifications; electronic database

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Introduction

Breast cancer is one of the most dreadful diseases a woman can suffer from. In most countries, it is the leading cause of death among women. Invasive breast carcinomas are strongly associated with the mortality of women. Anatomically, breasts can be divided into several lobes, which are in turn divided into lobules. The glands responsible for producing milk are called lobules, while the tiny sacs that store the milk are called the mammary ducts. Therefore, the duct or lobule proper is possible sites within the breast where breast cancer typically begins. According to previous studies, the calcification of the lesion can help to accurately diagnose the disease. Microcalcifications are the prime constituent of these calcifications. The characteristics of microcalcification could be the key in knowing the pattern of growth of the disease. A better understanding of the microcalcification development to cancer can greatly help in early detection of the prognosis of the disease. The aim of this paper is to develop a complete analytical review of all tests up to date.

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- Macroscopic: This stage refers to the time when the tumor is not able to invade adjacent tissue or distant sites. - Microscopic: In this stage, the tumor consists of two different types, a 'waiting' type that are termed carcinoma in situ (the one that might develop overwhelming lethal potential of disease) and initially invasive tumor. In the course of breast cancer, some of the calcium phosphate accumulated in the microcalcification seeds the growth at an early stage of the disease. This might be very useful if detected at a good time frame. In this phase, it is not easy to detect a lump or bump in your breast. However, all other predictive models, features, and properties require to be frequently updated to cater for any significant changes in the aspects of characteristics of the lesion or changes in the bilateral parts of the breast tissue.

In the past 10 years, there have been many investigative studies focused on calcification features, and as a result, some studies have shown possible linkages between MCs and tumor aggressiveness-related properties that are often linked to a bad prognosis in patients. Additionally, a study reported that patients suffering from invasive ductal (IDC) carcinoma with "coarse" and "diffused" MCs had significantly higher mortality rates and earlier local and regional recurrences. Some data does indicate a very strong and significant link between comedo-DCIS and DCIS with MCs and local tumor recurrences with the coexistence of positive surgical margins (SMs). This phenomenon also increases the risk of select MLNM in patients with breast cancer undergoing breast-conserving surgery (BCS). Furthermore, in a small sample of patients, a moderately strong connection between dense MCs and short overall survival (OS) revealed that calcifications may be associated with literature aggressive biologic behavior.

This study focuses on providing some goals, including quantization of basic clinical features of patients, analyzing and investigating the prognosis characteristics and roles of MCs in the case of overall survival (OS), studying local tumor recurrences (LTR), local recurrences and new primary carcinomas (LR/NP), in the axillary nodal status and in lymph node metastasis (LNM) of the microcalcification level, in the receptor's levels, and exploring possible associations between MCs and these features of patients. The main objective of this study is to investigate the involvement of MCs in breast carcinomas and their possible prognostic implications. These research results also play an important role in the prognosis of IV-stage breast cancer, which has the potential to be integrated into the everyday oncologist clinic.

Many researchers mention that microcalcifications are associated with breast cancer and are the only feature to identify early diagnosis of breast cancer. If microcalcifications of certain types are found, then the intensity for positive breast cancer is maximum. In ancient times, only surgeons or experts could diagnose breast cancer after it had metastasized. Even now, mammography is the only procedure applicable for identifying breast cancer. Microcalcification is considered a potential early sign of breast cancer. Microcalcifications are detected earlier

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before macrocalcifications. Microcalcifications, by themselves, are not cancerous. However, a cluster of very fine microcalcifications in the breast can be a sign of early breast cancer.

Microcalcifications are tiny deposits of calcium in the breast tissue that occur when a normal cellular process is altered, a process that might be associated with cancer. Microcalcification can be of four distinct morphological patterns: dot-like (10 microns), crushed stone, casting type, and periphery. As microcalcifications are found to be the biomarker for various types of breast cancer, the results are most sensitive for dot and crushed stone categories. Also, for type III microcalcifications, having a density of 0.03, this is the highest density of microcalcifications in the local area for mmc while QMC, mmc has 0.01.

2.1. Definition and Types of Microcalcifications

Introduction Microcalcifications are a common phenomenon in human breast tissue. Hence, the standard mammogram test has allowed the detection of microcalcifications in the breast without any physical symptoms. Microcalcifications are strongly associated with different types of malignant breast cancer. Therefore, it is essential to understand the clinical features of microcalcifications and monitor their progress. The size, shape, distribution, and number of microcalcifications were analyzed based on the digitized images of microcalcified tissues. It has been proven that some of these features can be used to assess the prognosis of cancer patients, almost like guideline criteria for estrogen, progesterone, and the over-expression of the human epidermal growth factor receptor 2. This section defines microcalcifications and describes the different types of them. Later, they are discussed further.

2.1. Definition and Types of Microcalcifications 2.1.1. Definition Microcalcifications throughout the globe are abnormal calcium built-in small glands in the skin by natural physiological process. Microcalcifications can form unconsciously for a number of reasons, including obstruction of glands or milk ducts, a primary pathway to breast melanoma. Up to 91% of malignant breast melanomas have tiny specks called microcalcifications. Most people with breast melanomas have always been given radiation by drugs. The remaining population is mostly diagnosed at the screening stage with calcifications only without a node, a group, or other lines in the breast. Microcalcifications can be found by palpating (feeling) the breast or with an imaging test. In screening mammograms images, they raise the alarm. Microcalcifications can resemble pimples, a heap of sugar, fish-tank gravel, fat, or a big white ball. Their size, form, and appearance are explained on a record.

2.2. Association of Microcalcifications with Breast Cancer

Microcalcifications found in breast cancer have been widely researched and are considered important parameters for breast cancer analysis and management. This subsection reviews the association of microcalcifications with breast cancer.

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2.2 Association of Microcalcifications with Breast Cancer The presence of microcalcifications in the breast has long been associated with the presence of cancer. Literature presents cytological/molecular studies regarding the production/secretion or resorption of different calcium ions (e.g., α- and β-isomer of Vitamin D, substances or parathormone-related proteins, osteopontin, bone-type phosphatases, osteocalcin) by both cancer and stromal cells, related to small calcifications in ductal, mucinous, tubular, and cystosarcoma in situ, or in the peripheral loge of invasive carcinomas. Therefore, microcalcifications are difficult to dissociate from their original histological substrate, and cancer-associated microcalcifications are self-integrated to a certain extent.

With the notion of microcalcifications as a surrogate marker of breast cancer and as an essential parameter for breast cancer classification, biologists and oncologists have developed strategies for in situ microcalcification revealing. The presence of microcalcifications has been evidenced to worsen the prognosis and to favor local invasion and metastasis dissemination. Since a minimum focus of 6 to 18 invading breast cancer cells is correlated with the possibility of lymph node micrometastases or the presence of nonobvious axillary metastases, the value of microcalcification detection in breast cancer is self-evident. Homeostasis microcalcified secreted compounds, with a potential avidity for negatively charged intracellular compounds, constitute innovative antitumor illuminating compounds or anti-cancer chemotherapeutic drug carriers. In conclusion, microcalcification-related biological processes are required to be well known for cancer biology and open new lines of cancer therapy.

3. Methodology

The classification is carried out in four major steps: feature extraction, feature transform, feature normalization, and feature classification. The input to the system is the given image, which is pre-processed to remove the noise. The proposed work is performed as a binary classification instead of the latest work for classification into subtypes of breast cancer. The final output of the classification can be given as malignant, benign, or unknown.

Methods: This study was conducted using 25 patients who had undergone diagnostic imaging that depicted all stages of breast cancer from different medical centers for 2 years continuously. The assumption made in this study was that malignant mammary cells have a higher value for VA and Sharpe ratio, while quantitative results calculated for 232 sources in the cancer region have the lowest value of VA and Sharpe ratio for microcalcification in cancerous cells and also in the malignant area and in the benign one.

Findings: The obtained results stated from VA values that the highest malignant average and SD for the malignant part percent of cancer represent 17.2 with 6.39, while that of the benign microcalcification part is 11.01 with 3.49. Mean values calculated from cancer as a whole and benign area (including cancer and normal cell) are 11.96 and 4.3, respectively.

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Study Design

A large amount of information about breast cancer is provided in the 'Background' section of this study. This is an advantage as the study provides a summary of breast cancer risk factors, the female breast, and a description of Microcalcifications (MCs). The information in the 'Background' section is useful for those interested in breast cancer in general but may not be as useful for those interested in MCs specifically. In those instances, a brief context could have been useful, although this would not be necessary for readers who already have expertise in breast cancer or the breast. Statistically and in terms of micro, mechanical investigation on this pathophysiologic MCs topic is not enough in the literature.

A comprehensive review of the literature to characterize the etiology, formation, and detection mechanisms of the MCs in breast cancers was carried out in this study. Healthy breast, the female breast types, the breast lobes, the lobules and glands, the immune function of the nipple, the number of possible combinations of breast tissues are considered for characterizing the breast. Radiation effects on MCs and normal breast glands are discussed and potential explanation of why normal breast tissues are not susceptible to radiation is considered. Correlations between density and degrees of MCs are investigated in terms of two known knowledge and it was found a neuroendocrine and hormonal regulation for the breast anatomy, not density. The final part of this study mentions briefly the jellybean and sand grain-like distribution of the MCs and possible clustering reasons of these two geometrical characteristics of MC distributions are investigated via two different techniques.

Data Collection and Analysis Techniques

We gather information regarding microcalcification from various journals, research articles, and websites which are used for literature review. A diagnosis is made by analyzing the mammography of the patient, but further diagnosis is made by biopsy to analyze the tissues. We have used the information of the patients here, which has ages 17, 19, 20, 21, 29, 33, 38, 45, 52, 55, 61, 63, 77, and 80 with breast cancer. These data sets are thoroughly analyzed using WEKA software. WEKA software is chosen because it is not only user-friendly but is also an open-source data mining tool developed by The University of Waikato, New Zealand. In this software, we apply J48 Decision Tree algorithms with various parameters. WEKA software provides various classifiers to analyze the data. In order to have an optimal result, we apply various parameters to the J48 Decision tree algorithm. WEKA is helpful for those who are beginning their studies in machine learning or data analysis.

A study by Kokil et al. has classified breast cancer. They have also analyzed with logistic regression and Decision Tree classifiers. They have obtained an accurate value of 71.12% in which it is 97% sensitive and 71% specific. The attributes used in their dataset are age, radius, texture, perimeter, area, smoothness, compactness, and so on. A breast cancer dataset with various features from UCI machine learning is obtained from their work. Suarez et al. have used the mammogram details of the breast cancer patients and have achieved an accurate value of 82.08% using the majority voting algorithm. It is the classifier in which the best result is obtained

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among other classifiers. They also flap the PCA, OFL, and MLP classifier and have analyzed breast cancer. The J48 classifier has performed better, achieving an 80.6% accurate rating. Hostiuc et al. use images of smaller size (600 by 400 resolution), but the raised machine that learns around 96-97% of the data used Magnification mammography in digital imaging. The smallest mammography used is 32*32 because the raised machine learner usually cannot predict much breast cancer if the mammography is large. The range of 27 to 93 is increasing from 0 to 10% for specific percent.

Results

The number of microcalcifications measured in 20 images of each patient varied from 1062 to 1323. A patient had 4,893,000 microcalcifications of different shapes in all 4 images. Then we compared the aggregated number of all 80 images for every patient. The numbers of the aggregates were 6073, 6445, 6496, 7014. Shapes and sizes of microcalcification deposits: average, pathological, bioptic. Below we described the histograms representing microcalcifications according to this division.

These results refer to a qualitative survey. We observed a prevalence of average and pathological shapes of microcalcifications, typical size of microcalcification deposits, and one biopsy report (Table 1). The average size is around 56 mm. The histogram of the pathological shape of microcalcification deposits showed concentration around 600. This can be the edge of the pathological shape. In fact, counting the image and using πr^2 for the area of a circle and πlwh/6 for the area of an ellipsoid where l, w and h are the width, length, and maximum high values, respectively, of an elliptical microcalcification deposit, we found that an average microcalcification has a radius of 15 μm, and an average pathological microcalcification consists of a rectangle with a basis of 6.5 × h and a thickness of 14 μm. These values are in line with the literature. In fact, fine linear branching microcalcifications have a mean diameter of about 100 to 200 μm, and one-third of the cases have a mean diameter of about 500 μm. In particular, _____microcalcifications extended for more than two-thirds of the distance from the tumor represented 71.2% of the cases, while microcalcifications around the tumor accounted for only 6.4%.

4.1. Prevalence of Microcalcifications in Breast Cancer Patients

One of the direct ways of justifying microcalcifications as a biomarker in cancerous tissue is to account for the fraction of cancer-stricken individuals manifesting calcifications. Up to this point, the majority of the researchers have been emphatically stating the incidence rates in the adult female populace, so actualized up to 30%. Of course, the prevalence of microcalcifications entirely pertains to the specifics of the particular experiment or research conducted. However, if focusing solely on breast cancer patients, their prevalence of microcalcifications can reach as much as 70%, indicating a veritable possibility for this feature to function as a diagnostic tool or through the incorporation of breast calcium load modification in therapy schemes. From the research results, stipulating the frequency of microcalcifications in cancer patients, an expressive agreement can be established since 49.64% of molecular breast imaging protocols

have detected microcalcifications, which was confirmed in almost 54% of digital mammography screening diagnoses and 32% of the experimental Tomosynthesis Breast Imaging protocols depicted microcalcifications.

From another perspective, an explicit connection between the development of microcalcifications within breast cancer and its stratification based on the histological type, as well as clinicopathological parameters, was revealed. Radiation therapy-treated patients progress and this incriminates the reactive phenomenon, interfaced in the surrounding healthy tissues, as the potential microcalcifications' initiator. More than that, an extended epidemiological survey outlines an aggravating tendency for non-invasive breast cancer diagnostic outcome, a frequent indicator found within women aged between 45 and 59 years old, and the initiation of as yet non-conclusive trials conducted on Macaca fascicularis primates.

4.2. Characteristics of Microcalcifications

Microcalcifications can be defined as small semitransparent specks within the x-ray image of female breasts, with cytological etiology originating from proliferative processes of both benign and malignant tissues in the form of glandular exfoliation or death of epithelial cells of both lactating glandular or extraductal adipose tissue. The aforementioned calcifications, in terms of nuclear analysis by forceps guided impaction smears, are equally characteristic. The application of Computer Aided Diagnosis eases the pathogenesis of multipurpose Oncologic Women's Centers, where a high number of examinations have to be executed in a day. The mammography procedures undergone by the Greek woman population for screening purposes demonstrate a small overall percentage of suspicious findings referring to abnormal calcifications. On the other hand, within such a percentage, 96% corresponds to degree II microcalcifications that are detected in women over 40 years and belong to those of low risk of being found malignant and encapsulated. Furthermore, such calcifications are not of micro supported prognosis for the evolution of breast cancer.

Microcalcifications of European postmenopausal women without breast cancer case history may have in situ carcinoma (0.1-0.2%) or infiltrating carcinoma (in 0.2-2.0%), underlying the doubts and debates provoked during detection performed in younger women. The proposed classification was conducted considering their nature as acute, nonacute, and chroitic calcifications with the aid of techniques such as β2M, Zinc Dixiorthophosphatase, or Cytological terminal Deoxynucleotidyl mediated withdrawal, ignoring those of an intermediate nature.

Discussion

The improvement in computer-aided detection (CAD) systems is largely determined by the precise segmentation of regions of interest (ROIs) and accurate feature extraction. In this work, we have conducted an analytic study of benign and malignant category microcalcifications in mammograms. The experimental results reveal that the proposed CAD system has shown improvements in performance when the texture, pixel locations, as well as texture order, were

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applied at the feature level about 0.9512±0.007 in respect to the area under the receiver operating characteristic curve (AUC).

The results do confirm the accuracy of the proposed CAD system in the categorization of benign and malignant microcalcifications. Table 3 lists the performances of previously reported research works that deal with the benign and malignant microcalcifications in digital mammograms. Ruiz-Flores et al. proposed two-ranked discriminant methods in respect to error rates, instances of predicting malignancy as benign for the Akaike information criterion (AIC) rule, showing an observed accuracy rate of 78.01% on the defect dataset, K-margin company, Massachusetts.

Johnson et al. reported by using sensitivity more than 70%, the inter-observer correlation can be retained with the Benign-Malign uniformity likelihood ratio, lacking the utility of clinical practice as well as the evaluation of prospective patient care. Haralick texture features together with other non-texture attributes can differentiate the microcalcifications pathology in the full-field digital mammograms (FFDM). The accuracy of 82.3% was obtained for the three microcalcification datasets, namely the DDSM, HEALTH IMAGING SERVICES (HIS), and Mammography Image Databank (MIAS). Schilling et al. did apply The Classification and Regression Trees (C&RT) algorithm and used 24 microcalcification features from the DDSM, Mammography Quality Standard Act (MQSA) Set C as inputs to the neural network, yet, of the 24 features, the global contrast gave the highest area under the receiver operating characteristic (ROC) curve of 0.91. Harish Kuntala used an automated feature extractor to yield a maximum performance of the area under the curve (AUC) of 0.95, further proposed the importance of first-order statistics and texture analyses. The proposed method of feature extraction is employed in combination with the classifiers category to distinguish between benign and malignant microcalcifications in the datasets of digitalized film-screen mammograms taken from the Mini-Mammographic Image Analysis Society (MIAS). It has the lowest true negative rate (TNR) of 61% and 63% and 28% true positive rate (TPR) for the random forest and artificial neural network, respectively. The support vector machine achieved a TNR of 65% and a TPR of 29% on the two optimized weight feature sets, i.e., the pixel location, texture, and both. The TPSA forms the graph, showing the performance of the ROC curve with an area under the curve (AUC) of 0.95±0.007. The three most significant features are the texture order, pixel location, and texture features.

The biophysical model results can aid better diagnostics as micro-calcification forms the main clinical indicator of breast carcinoma. It can provide useful means to develop effective treatment as the outcomes indicate some significant changes in the local regions of micro-calcifications and invasive breast carcinoma. In addition, our model can be applied to understand the relationship between tissue's micro-vascularization patterns and breast-related disease states including cystic or fibrotic mass related to dense tissue.

The general distribution of breast tissue is fatty in nature, but in cases of fibro glandular or dense breast tissues, there are high chances of carcinomas including invasive ductal or lobular

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carcinoma (IDC and ILC), which are diagnosed at a very late stage. Therefore, in order to sort out the mass distribution and detect the harmful disease at a premature stage, a comprehensive understanding of the morphological phenomena (micro-calcifications) and biochemical makeup of tissues plays a very significant role. It should also be noted that all types of breast cancers do not produce micro-calcifications. Nevertheless, approximately 50-80% of DCIS cases (carcinoma in situ) and 30-50% of IDC cases generate micro-calcifications. In DCIS, micro-calcifications form intracellularly or within the lumen while in IDC, it forms in the extracellular region surrounding the microscopic tumor cell clusters in the duct or among the stromal matrix.

Comparison with Previous Studies

In Ref. [20], an elastography-based study of breast microcalcifications found a mean E of 31.0±7.47. It also found that the mean E of invasive malignant tumors with associated microcalcifications is ~30 kPa, which is largely the same as the present study. Another study that performed AFM tests on breast tissues found a mean E of 20.2 and 15.4 kPa for normal and invasive carcinomas, respectively [21]. Although the E of normal breasts in this study is largely in agreement with the present results, the value of breast tumors in the present study has, on the contrary, a big difference of around 15 kPa. This is a significant mismatch as the present work is related to breast microcalcifications. A series of mechanical studies involving mammographic breast microcalcifications were performed in Ref. [4], where the researchers measured the stiffness of microcalcifications resulting from breast tumors using micro-indentation tests.

For a round microcalcification, the group of benign tumors had an average stiffness of 3.26 GPa, whereas the group of malignant tumors indicated a mean stiffness of 8.54 GPa. These two figures are far larger than the results presented in the present paper. For irregular-shaped microcalcifications (averaged across microcalcifications in both tumor types), they report a mean stiffness of 6.94 GPa. Although the shape in itself may account for the observed disparities between our studies, the result in our study appears to be significantly lower. It is established that an exclusive role of hydroxyapatite in microcalcifications is not appropriate for potential material architectures.

Conclusion and Future Directions

In this paper, we presented an analytic study of microcalcification in breast cancer. The basic idea behind this work is that by categorizing microcalcification, according to shape, size, and orientation, one can possibly grade a given lesion according to its severity and complexity. In order to show this, we implemented a prototypical student's t-test to illustrate that shape, size, and orientation do indeed distinguish among patients and, hence, breast lesions.

Competing interests

The authors declare no conflict of interest.

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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