MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE SUMY STATE UNIVERSITY MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

2, Rymskogo-Korsakova st., Sumy 40007, Ukraine e-mail: EUMJ@med.sumdu.edu.ua

eumj.med.sumdu.edu.ua ISSN: 2663-5909 (print)

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ABSTRACT

DOI: https://doi.org/10.21272/eumj.2022;10(4):300-308

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BREAST CANCER WITH MICROCALCIFICATES: A BIBLIOMETRIC ANALYSIS

Introduction. Microcalcifications in breast tissue are an important marker of the tumor process and are crucial for early diagnosis of this pathology. Detection of microcalcifications in the breast gland using mammography is of great importance in the diagnosis of breast cancer (BC), especially in the early stages. The presence of microcalcifications in the mammary gland indicates a worse prognosis, mainly due to a higher frequency of lymph node invasion and rapid metastasis.

The objective of the paper is the bibliometric analysis and research of data on the pathomorphological characteristics of breast cancer with biomineralization.

Materials and methods. The authors searched for information on BC in electronic databases such as PubMed, Scopus, Web of Science, and Google Scholar using key terms such as "breast cancer," "calcification," "microcalcifications". For bibliometric analysis, we used SciVal (Scopus) online platform for monitoring and analyzing international scientific research using visualization tools and modern citation metrics and VOSviewer tool for building and visualizing bibliometric networks.

Results. The presence of microcalcifications in the mammary gland correlates with a worse prognosis, especially due to a higher frequency of lymph node invasion and rapid metastasis.

It is important to distinguish microcalcifications by type and origin, as they can be an indicator of differential diagnosis of the pathological process in the tissue of the gastrointestinal tract, namely, benign and malignant pathology.

We performed a bibliometric analysis of the scientific sources of the Scopus database, which included 924 publications. The main keywords for the bibliometric analysis were "breast cancer", "calcification", "microcalcifications". The results of the analysis indicated that the number of publications on the specified subject had increased over the past 10 years, which showed the relevance of the problem among scientists.

Among the most interesting areas, we singled out the papers devoted to the classification of breast cancers, early diagnosis of breast cancer, and classification of biomineral deposits.

In order to build and visualize bibliometric networks, we used the VOSviewer publication activity tool.

Conclusions. For the period of 1967–2022, we identified 4 chronological stages from the bibliometric analysis results in the Scopus database, which included: 1) radiological methods of research – mammography, 2) pathomorphological assessment of cervical cancer and calcifications, 3) study of BC progression biomarkers, 4) prognostic assessment of BC depending on metastasis and survival. We divided all publications into 6 thematic clusters: 1) classification of biominerals, 2) mammography, 3) physico-chemical composition of calcifications, 3) ductal neoplasia of the breast, 4) biopsy, 5) metastasis of cervical cancer, 6) calcium hydroxyapatite.

Keywords: breast cancer, microcalcifications, bibliographic analysis, hydroxyapatite, oxalate.

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РАК ГРУДНОЇ ЗАЛОЗИ З МІКРОКАЛЬЦИФІКАТАМИ: БІБЛІОМЕТРИЧНИЙ АНАЛІЗ

Вступ. Наявність мікрокальцифікатів у тканині грудної залози (Γ 3) ϵ важливим маркером пухлинного процесу та для ранньої діагностики цієї патології. Виявлення мікрокальцинатів у грудній залозі за допомогою мамографії має велике значення в діагностиці раку грудної залози ($P\Gamma$ 3), особливо на ранніх стадіях. Наявність мікрокальцифікатів у грудній залозі вказує на гірший прогноз, в основному через більшу частоту інвазії лімфатичних вузлів та швидке метастазування.

Метою роботи ε бібліометричний аналіз та дослідження даних щодо патоморфологічних характеристик раку грудної залози з біомінералізацією.

Матеріали та методи: авторами було проведено пошук інформації стосовно раку грудної залози (РГЗ) в електронних базах даних, таких як PubMed, Scopus, Web of Science та Google Scholar, за такими ключовими термінами, як «рак грудної залози», «кальцифікація», «мікрокальцифікати». Для бібліометричного аналізу застосовувалися онлайн-платформа для моніторингу та аналізу міжнародних наукових досліджень з використанням інструментів візуалізації та сучасних метрик цитування SciVal (Scopus) та інструмент для побудови та візуалізації бібліометричних мереж VOSviewer.

Результати. Наявність мікрокальцифікатів у грудній залозі корелює з гіршим прогнозом, особливо через більшу частоту інвазії лімфатичних вузлів та швидке метастазування.

Важливо розрізняти мікрокальцифікати за типом і походженням, так як вони можуть бути індикатором диференційної діагностики патологічного процесу у тканині Γ 3, а саме доброякісної та злоякісної патології.

Ми зробили бібліометричний аналіз наукових джерел бази даних Scopus, які включали 924 публікацій. Основними ключовими словами для бібліометричного аналізу були «рак грудної

залози», «кальцифікація», «мікрокальцифікати». Результати аналізу свідчать про те, що кількість публікацій на зазначену тематику має тенденцію до зростання за останні 10 років, що вказує на актуальність проблематики у науковців.

Серед найбільш цікавих напрямів публікаційної активності ми виділяємо роботи присвячені класифікації пухлин ГЗ, ранній діагностиці РГЗ, класифікації біомінеральних депозитів.

Для побудови та візуалізації бібліометричних мереж ми використали інструмент публікаційної активності VOSviewer. За період 1967–2022 рр. з результатів бібліометричного аналізу у базі даних Scopus за ключовими словами ми виділили 4 хронологічні етапи, які включають наступне: 1) радіологічні методи дослідження — мамографія, 2) патоморфологічна оцінка РГЗ та кальцифікатів, 3) дослідження біомаркерів пухлинної прогресії РГЗ, 4) прогностична оцінка РГЗ в залежності від метастазування та виживаності. Всі публікації ми розділили на 6 тематичних кластерів: 1) класифікація біомінералів, 2) мамографія, 3) фізико-хімічний склад кальцифікатів, 3) протокова неоплазія грудної залози, 4) біопсія, 5) метастазування РГЗ, 6) гідроксиапатит кальцію

Ключові слова: рак грудної залози, мікрокальцифікати, бібліографічний аналіз, гідроксиапатит, оксалат.

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How to cite / Яκ цитувати статтю: Kolomiiets O, Moskalenko R. Breast cancer with microcalcificates: a bibliometric analysis. *EUMJ*. 2022;10(4):300-308

DOI: https://doi.org/10.21272/eumj.2022;10(4):300-308

INTRODUCTION / BCTYII

Breast cancer is one of the most common cancers worldwide. The disease is the leading cause of death from cancer in women in more than 100 countries [1, 2].

Microcalcifications in the tissue sample are an important marker of the pathological process. Microcalcification's presence in the tumor tissue is a criterion for determining the stage of the disease and for early diagnosis of this pathology [3]. Detection of microcalcifications in the breast using mammography is crucial in diagnosing breast cancer, especially in the early stages. Breast cancer microcalcifications are usually associated with degenerative-necrotic changes in tumor tissue [4]. Microcalcifications in the breast correlate with a worse prognosis, especially due to a higher frequency of lymph node invasion and rapid metastasis [5].

Objective. The work aims to carry out a bibliometric analysis and study of data on the

pathomorphological characteristics of BC with biomineralization.

Materials and methods

We searched electronic databases such as PubMed, Scopus, Web of Science, and Google Scholar for information on breast cancer (BC) with microcalcifications for the period 1967–2022 using key terms 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, SciVal (Scopus) and a tool for building and visualizing bibliometric networks, VOSviewer were used.

We used Scopus database bibliometric tools to analyze the year, source, type of study, subject area, and country of the publication. The VOSviewer system from the University of Leiden (http://www.vosviewer.com/) was used to generate and visualize the bibliometric network.

The results and discussion

Physico-chemical classification of biominerals

Biologically, biomineral deposits are divided into two main types: type I, consisting of calcium oxalate (CO), and type II, consisting of hydroxyapatite (HA). Classification is based on chemical composition and mammographic characteristics, including morphology, distribution, and density. Research data indicate that type II is often associated with malignant lesions of the gastrointestinal tract [5, 6].

CO is produced by apocrine cells and is most often associated with benign changes in breast tissue. CO cannot be metabolized by mammalian cells, indicating that its presence metabolically affects epithelial cells and can induce proliferation and c-Fos overexpression in MCF-7 cells [6, 7].

Biominerals of type I have an amber color, are partially transparent and have the form of pyramidal structures with a flat surface. Minerals of type II are white-gray in color, opaque, respectively, spindle-shaped or egg-shaped with an irregular surface [5, 8]. When analyzing the majority of studies, it can be asserted that the presence of calcium oxalate is more common in benign breast pathology or non-invasive carcinomas in situ, and the presence of HA is associated with both benign and malignant breast pathology [9].

Type II calcifications can be associated with benign and malignant breast formations; they are present in benign tumors such as fibroadenomas, fibroadenosis, and sclerosing adenosis and are related to invasive cancer in experimental models necrosis and fibrosis [10–12].

Not only the detection of microcalcifications but also their specific properties are important. The morphology of biomineral deposits can indicate a malignant process in the breast. Recently, many studies have indicated a connection between histopathological variants and microcalcifications' physicochemical compositions.

Pathomorphological classification of breast pathology

According to pathomorphological characteristics, the pathology of the breast is divided into malignant and benign, which is the basis for verifying the diagnosis, treatment, and prognosis. Benign pathology of the gastrointestinal tract is represented by: benign epithelial proliferative and precancerous diseases (ductal hyperplasia, atypical ductal hyperplasia, columnar epithelium disease), adenomas, adenomas, benign sclerosing diseases, benign papillary tumors, epithelial-myoepithelial tumors, fibroepithelial

tumors (fibroadenoma and phylloid tumor), hamartomas The most frequent malignant diseases of the breast include invasive carcinoma of the breast, ductal carcinoma in situ (DCIS), non-invasive lobar neoplasia, malignant papillary tumors, neuroendocrine tumors and cancers of rare types (acinar carcinoma, adenocystic, secretory, mucoepidermoid, polymorphic and high cell carcinoma with inverted polarity [13, 14].

We paid considerable attention to the problem of biomineralization in this study (from physicochemical features to the mechanisms of their formation and clinical diagnostic features) since there are data on the important role of microcalcifications and calcification in general in the diagnosis and prognosis of the course of breast tumors.

X-ray criteria for the differences in calcifications

Currently, 30-50% of non-palpable breast cancer is detected exclusively by identifying calcifications on mammography [3, 6, 15]. Welldescribed radiological criteria help distinguish benign calcifications from potentially malignant ones. Mammography is the primary method for assessing these changes. According to the fifth version of the Breast Imaging Reporting and Data System (BI-RADS), biominerals are classified as benign and suspicious. There are five categories of distribution: diffuse, segmental, regional, grouped, and linear. Benign calcifications on mammography are usually more extensive, rougher, rounder with smooth edges, and easier to see than malignant calcifications. Calcifications associated malignancy are typically small and require magnification to be well visualized. Suspicious morphology includes a gross heterogeneous appearance, amorphous nature, thin pleomorphic elements, and finely branched calcifications [3]. Morphologically, biominerals with thin linear branches are associated with worse results than non-linear biominerals [6].

Detection and interpretation of calcinates represent a complex problem, so radiological and pathological evaluations are crucial for accurately diagnosing these lesions. The type and composition of biominerals, including the determination of their biochemical nature, may improve their predictive value.

Mechanism of formation of calcifications

The researchers' immediate attention is focused on studying the molecular mechanism involved in forming biominerals. The mechanism of regulation of pathological biomineralization can be similar to physiological bone mineralization [9, 15].

Overexpression of bone matrix proteins sialoprotein, osteopontin (OPN), and osteonectin was detected in the biopsies of BC [16]. Rizwan et al., in their studies, indicate that inhibition of the OPN gene reduces the formation of calcium hydroxyapatite in BC cells. This study describes a direct relationship between calcium deposition and the ability of BC cells to metastasize to distant organs and lymph nodes. Under the influence of specific stimuli, breast epithelial cells that undergo epithelial-mesenchymal transition (EMT) cells with transform into an osteoblast-like phenotype can influence the formation of biominerals in breast tissue [17]. The main molecular mechanism of phenotype change in EMT is the loss of epithelial cell markers, such as E-cadherin and cytokeratin, and their replacement by mesenchymal markers - vimentin, nuclear β-catenin, smooth muscle actin, and fibronectin. This pathological transformation leads to the activation of signaling pathways reorganization of the cytoskeleton, increased expression of genes encoding MMPs, which participate in the degradation of the extracellular matrix and basement membrane [9].

The role in the metastatic spread of breast cancer cells is still being studied, but studies show that the OPN gene binds to cell surface integrins (β 1 and β 2 integrins) and CD 44 [16, 17]. It is the connection of OPN with the cell surface of the CD 44 receptor and damage to the epithelial-mesenchymal transition with subsequent cell

transformation that is the trigger for the initiation and adhesion of the cell matrix in various types of tumors, which leads to the invasion and metastasis of malignant tumors [9, 18].

The primary mechanism of the formation of biominerals is still poorly understood. According to recent studies, bone morphogenetic protein 2 (BMP-2) plays a role in the formation of microcalcifications. BMPs are growth factors of the TGF-β superfamily and are a specific and key regulator of osteoblasts. BMP-2 can encourage the cells of BC to acquire osteoblastic characteristics, which leads to the formation of microcalcifications [19]. A recent study also showed that active processes of microcalcification are caused by osteoimmunological disorders [20]. Tumorassociated macrophages are the main types of tumors that penetrate the immune cells of the extracellular environment and accumulate around microcalcifications in BC. High APM levels are associated with a poor prognosis. APMs implicated in breast cancer include a spectrum with M1-like and M2-like phenotypes. They may exhibit antitumor potential (M1-like phenotype) or be responsible for increased cancer cell growth (M2-like phenotype), most of which have an M2-like phenotype (CD163). In studies, it is believed that BMP-2 is mainly secreted by the cells of the tumor microenvironment but not by the breast cancer tumor cells themselves. It is known that tumor-associated macrophages are essential component of the tumor microenvironment and can secrete BMP-2, which contributes to calcification [19].

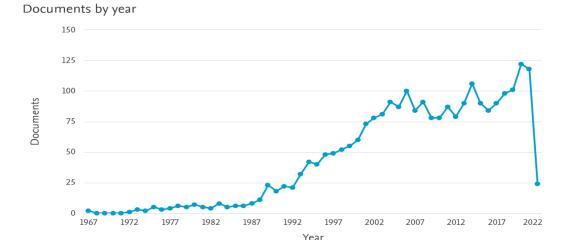


Figure 1 – The result of visualization of the publication chronology for 1967–2022 using the tools of bibliometric analysis of the Scopus database

Bibliometric analysis of scientific literature

We analyzed the Scopus database, which included 924 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 (Fig. 1).

The pathological biomineralization of breast cancer is actively studied by scientists from the United States of America, China, and Great Britain.

After studying the results of the bibliometric analysis of 924 publications of the Scopus database

using the tools of the SciVal service for the keywords "breast cancer" and "calcification" for the period 1967–2022, it was established that the vast majority belong to the field of medicine. In addition, 27 thematic clusters can be identified in the specified area, most of which belong to the field of medicine, computer science, engineering, material science, physics, and a few – mathematical sciences. Among the most exciting areas of publishing activity, we should highlight the works devoted to BC: the classification of breast tumors, early diagnosis of BC, and classification of biomineral deposits (Fig. 2).

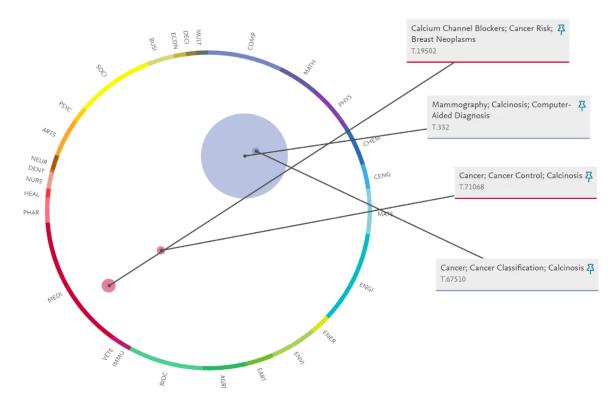
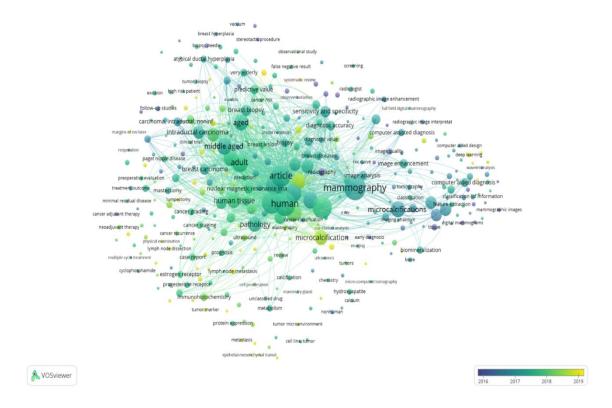


Figure 2 – The result of visualization of the distribution of publications by topics and clusters using SciVal bibliometric analysis tools

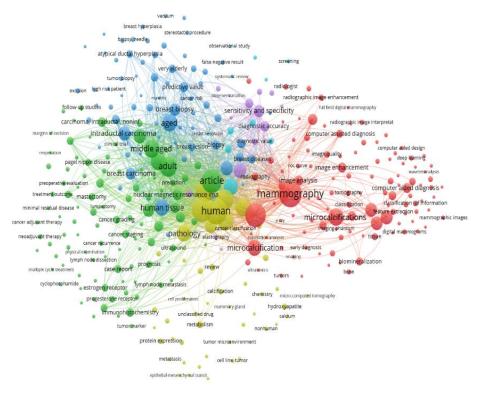
We also analyzed the publication activity of 1967–2022 on the research topic using the VOSviewer tool for building and visualizing bibliometric networks. As a result of the bibliometric analysis of 924 publications in the Scopus database using the keywords "breast cancer" and "calcification," we identified four chronological stages, which include: 1) radiological research methods – mammography, research using clinical and histological methods, 2)

pathomorphological evaluation of BC and calcifications, 3) study of biomarkers of tumor progression of BC, 4) predictive assessment of BC depending on metastasis and survival (Fig. 3). The data of the publication were also divided into six thematic clusters: 1) classification of biominerals, 2) mammography, 3) physicochemical composition of calcifications, 3) ductal neoplasia of the breast, 4) biopsy, 5) metastases of BC, 6) calcium hydroxyapatite (Fig. 4).

& VOSviewer



 $Figure \ 3-The \ result \ of \ visualization \ of \ the \ patterns \ of \ the \ chronological \ development \ of \ this \ topic \ using \ VOS viewer \ bibliometric \ analysis \ tools$



Figure~4-Visualization~result~of~the~thematic~distribution~of~pathological~biomineralization~of~breast~cancer~using~VOSviewer~bibliometric~analysis~tools

Limitations. This research includes publications only in the Scopus database from 1967 to 23.04.2022.

CONCLUSIONS / BИСНОВКИ

The presence of biominerals in tumor tissue is an important marker in diagnosing BC. It is a criterion for determining the disease's stage and early diagnosis.

The results of the analysis of scientific sources of the Scopus database by keywords in the period from 1967 to 23.04.2022 indicate that the number of publications on the specified subject has a tendency to increase over the past ten years, which shows the relevance of the issues and ways of solving them among scientists.

Among the most exciting publication areas, we single out works devoted to BC: the classification of breast tumors, early diagnosis of BC, and classification of biomineral deposits.

Using the tool for building and visualizing bibliometric networks VOSviewer of publication activity for the period 1967–2022 in the researched

topics of BC calcification, we identified four chronological stages, which include: 1) radiological research methods - mammography research using clinical and histological methods, 2) pathomorphological evaluation of BC calcifications, 3) research of biomarkers of tumor progression of BC, 4) prognostic evaluation of BC depending on metastasis and survival, as well as published data on six thematic clusters: 1) classification of biominerals, 2) mammography, 3) physicochemical composition of calcifications, 3) ductal neoplasia of the mammary gland, 4) biopsy, 5) metastasis of BC, 6) calcium hydroxyapatite.

The most relevant today is the early diagnosis of breast cancer, as well as factors that affect the deterioration of prognostic criteria, such as survival and metastasis in such patients, which is associated with the formation of biomineral deposits in the breast tissue.

CONFLICT OF INTEREST / KOHФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

FUNDING / ДЖЕРЕЛА ФІНАНСУВАННЯ

The work is a fragment and was carried out with the support of the research topic "The state of mineralized tissues when using new composites with Ag+ Cu2+ nanoparticles" (state registration number No. 0121U100471).

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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Одержано 29.08.2022 Затверджено до друку 11.09.2022

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