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BIBLIOMETRIC ANALYSIS of the CHEK2 GENE ASSOCIATED with BREAST CANCER

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Abstract:
Cancer is currently a major public health problem worldwide. Approximately 20 per cent of people (up to the age of 75) develop cancer in their lifetime and 10 per cent of people worldwide die. In 2020, the number of cancer cases reached 19.3 million and nearly 10.0 cancer deaths. Breast cancer is the most frequently diagnosed cancer in women worldwide (2.26 million cases). In this article, we conducted a bibliometric analysis of 550 articles with the keywords "checkpoint kinase 2" and "breast cancer." The source of the articles was the Scopus database, and bibliometric laws were utilized to determine the growth trends in publications from 2018 to 2022, the most cited and prolific authors, as well as the articles and journals in this scientific field. An analysis of countries, organizations, publications, and keywords most frequently used by authors was also carried out. The study reveals an exponential trend in the number of publications on breast cancer and the CHEK2 gen.

Keywords: Breast cancer, gene CHEK2, malignant tumor, VOSviewer, bibliometrics.

Introduction

Nowadays, cancer is one of the most common diseases and a cause of high mortality [1] with an increasing trend among people [2].

Among many diseases, cancer has a major impact on the quality of life of violence. It should be noted that cancer is the second leading cause of death in humans after co ronary diseases.

Unfortunately,

scientists predict that by 2060, cancer may become the leading cause of death from disea se [3].

Breast cancer is a frequently diagnosed cancer worldwide among women [4]. Hereditary factors are of great importance in the treatment and study of breast cancer. The stability of the genome andthe constant support of the cell cycle by checkpoint medi ators play an important role in preserving the integrity of DNA [5].

Exposure to internal and external factorsleads to disruption of the cell cycle and DNA repair effectors [6] and increases the risk of cancer [7]. Biologically speaking, cancer cells develop when healthy cells mutate. Mutations in certain genes cause breast cancer [4]. The CHEK 2 (cell cycle checkpoint kinase 2) gene is one of these genes. CHEK2 is an important intermediate gene that plays an important role in DNA repair, stability and integrity [8]. When the cell is damaged, the CHEK2 gene prevents the cell cycle from progressing to mitosis and causes cell cycle arrest in the G1 phase [9]. The human CHEK2 gene also known as hCDS1 consists of 543 amino acids and is a low-penetrant cancer predisposition gene for many organs [10].

With the advent of bibliometrics, it became possible to link different subjects, to unite different fields of activity studying common topics [11]. Evaluative bibliometrics is a field of science that helps to evaluate and identify the most cited and recognized articles [12]. Over the past decades, many articles have been published on cancer and breast cancer predisposition genes [13,14,15]. Various studies have been conducted on different areas such as genetics, etiology, epidemiology of breast cancer, efficacy of treatments [10].

In this article, we performed a bibliometric analysis of articles on the association between CHEK2 (cell cycle checkpoint kinase2) gene mutations and breast cancer. This article was written using publicly available articles that do not contain protected health information.

2. MATERIALS AND MATHODS

Publications on breast cancer with mutation of gene CHEK2 were received from Scopus. VOSviewer and other online bibliometric analysis platforms were used to visualize and analyze the results. In this paper, bibliometric analysis and literature review were used to study CHEK2 (checkpoint kinase2). Using the online tool, Scopus database, more than 550 articles from 2018-2023 were retrieved and analyzed using the keywords "breast cancer, CHEK2 gene".In the next step, articles were categorized based on the year of publication. Then, a database was developed for all reviewed papers including the year of publication, author's name, country, journal name,doctype, result, subject articles and connection between articles using keywords. The extracted data is exported in CSV format. These exported data were processed using specialized software VOSViewer to calculate occurrences, relationships, and trends of key terms. VOSviewer software is used to analyze and visualize data related to key research terms extracted from the Scopus database that regroup high-quality publications. The VOSviewer software was developed using the Java programming language. This bibliometric tool uses a clustering algorithm based on the key term occurrence method.

3. RESULTS and DISCUSSION

3.1 PUBLISHED ARTICLES on CHEK2

Our studies in the field of self-education have allowed us to familiarize ourselves with articles published in the period from 2018 to 2022. As seen in Figure 1, the number of published articles has significantly increased, especially in the period from 2018 to 2019

and from 2020 to 2021. In 2019-2020 and 2021-2022, this indicator was relatively low. A general analysis leads to the conclusion that the number of articles dedicated to the subject of our research continues to grow over time. Perhaps, this is associated with a growing interest in the topic and the noticeable influence of the CHEK 2 gene on the expansion of research in the field of science and technology.

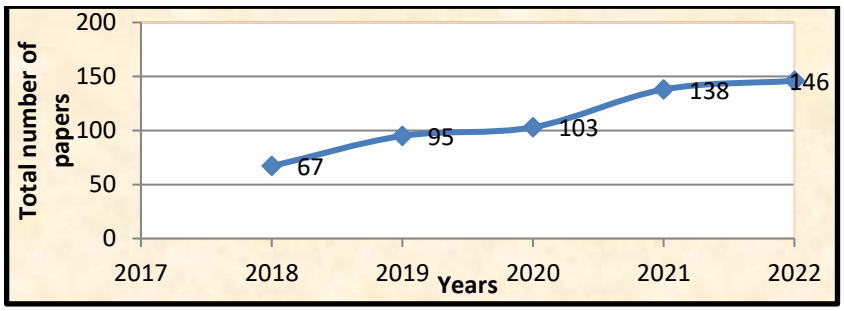

Figure 1. The number of papers on Checkpoint Kinase 2 and breast cancer published by year.

3.2 THE TYPE of PUBLICATIONS on CHEK2

We have analyzed over 550 articles published in the SCOPS database from 2018 to 2022(figure2). The results of our research indicate that out of the 550 articles, 415 are regular articles, comprising 76% of the total number of publications, which is the highest percentage. Reviews, while often receiving more citations, are relatively less frequently published in our case, constituting only 19% of the total publications. We explained this circumstance by noting that reviews require more information, analysis, and research time. It is important to note that the CHEK2 gene in the field of genetics is relatively "new" and understudied. Of the assessed and published 550 articles, 5% are represented by notes, letters, editorials, and conference papers. This suggests that research findings are predominantly disseminated by scientists in the form of articles.

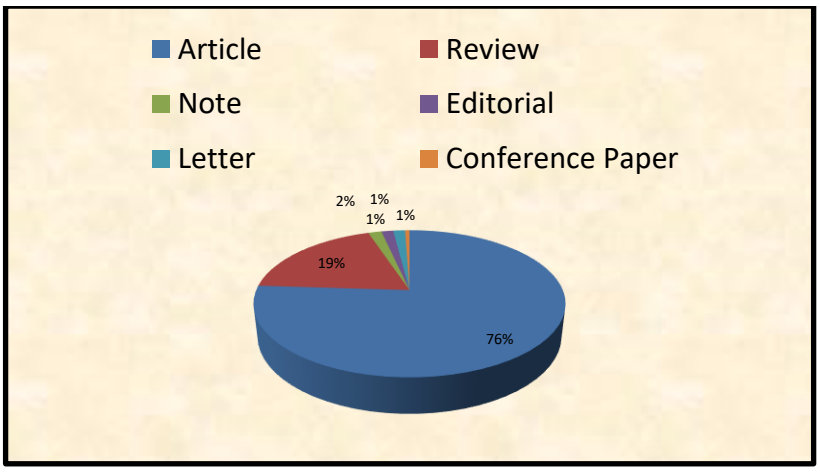

Figure.2. The type of publications on CHEK2

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3.3 TOP INSTITUTIONS PUBLISHED ARTICLES on CHEK2.

Scientific studies conducted in organizations on the topic of interest are depicted in Figure 3, reflecting the relationship between the number of studies and the organizations involved. As evident from the graph, organizations from the United States hold the top positions. The Memorial Sloan-Kettering Cancer Center in the USA occupies the highest position, represented by 29 studies. It is followed by the Harvard Medical School (USA) and the University of Cambridge (UK), each with 22 research projects, securing the second position. The overwhelming majority of scientific research is conducted in organizations located in the United States. Cancer research is considerably more complex in design compared to other areas of therapy, involving aspects such as criteria for selection, endpoints, and study locations[16]. The overall success rate in oncological research has been declining since 2015, reaching only 5.2% by 2021. Despite the increasing incidence of cancer each year, the success rate in the productivity of oncological research currently stands as one of the lowest in the world. As is well-known, scientific research in the field of oncology requires substantial funding. Most likely, this has become a reason for the fact that major research is conducted in economically developed countries, such as the United States, the United Kingdom, and Canada.

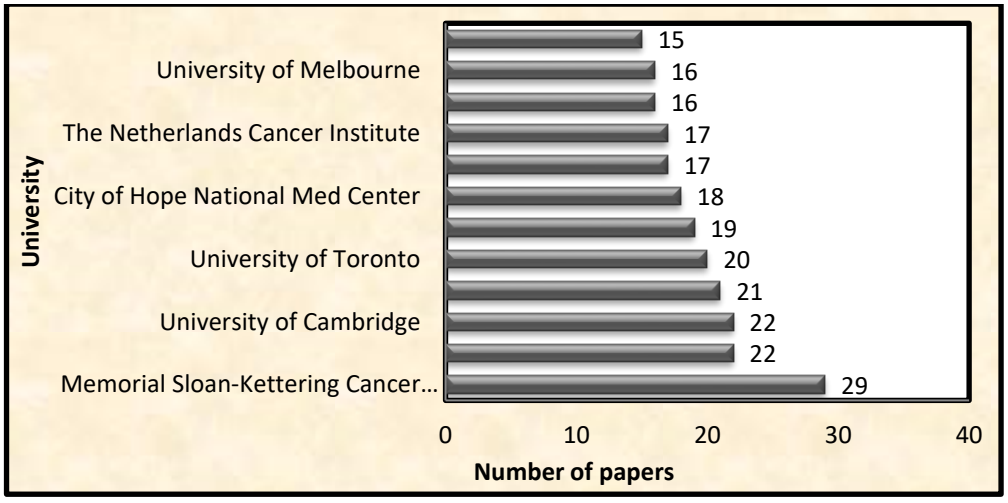

Figure.3. List of leading institutions publishing articles on CHEK2.

3.4 TOP AUTHORS PUBLISHED ARTICLES on CHEK2

Figure 4 presents the results of the analysis of authors who published the most articles on the researched topic. A total of 168 authors were identified. The most productive authors were Couch F.J. (n = 15), closely followed by Schmidt M.K. (n = 13). Moreover, many influential authors hail from the United States or the United Kingdom. Authors from China come next. It is noteworthy that while scholars from the United States or the United Kingdom constitute a significant portion of authoritative authors, many articles by scholars from China have higher citation values.

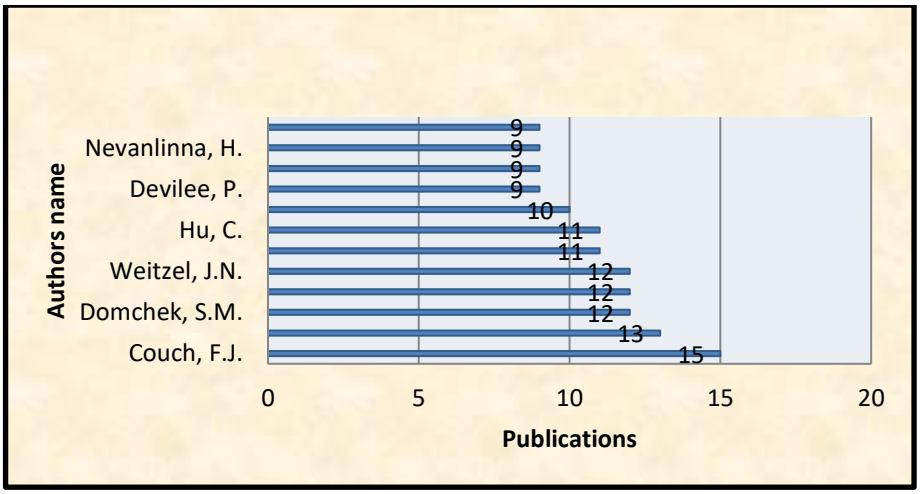

Figure.4. List of authors who have published articles on CHEK2 and breast cancer

3.4 TOP UNIVERSITIES PUBLISHED ARTICLES on CHEK2

Figure 5 provides an analysis of research institutions that have published the most articles on the researched topic. As indicated in the table, the top three institutions are the National Cancer Institute with the highest result (68), followed by the National Institutes of Health (61) in second place, and the National Science Foundation of China (29) in third place. Following them is AstraZeneca with 17 articles.

In this category, research institutes have remained in the first place, while universities have stayed in the last place. This trend emphasizes the understandable fact of the distinct goals between research institutes and universities.

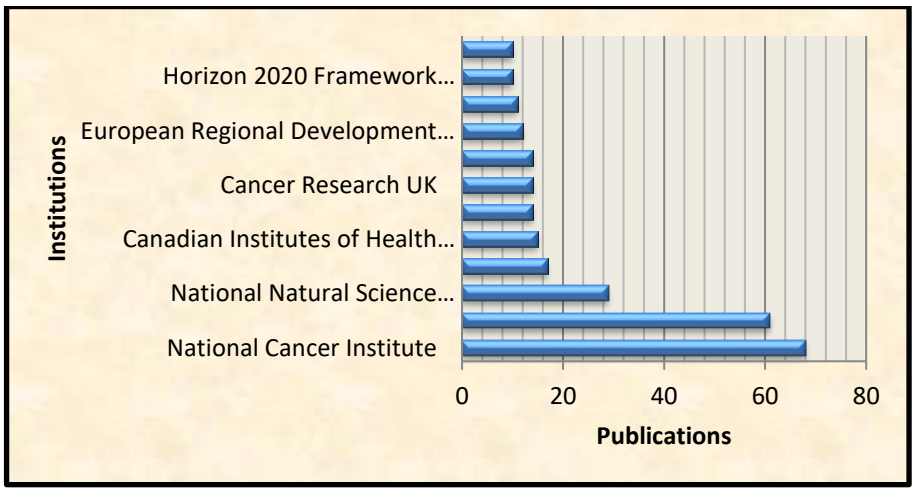

Figure.5. The list of research institutes that have published the highest number of articles on the topic of CHEK2 and breast cancer

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3.5 SCIENTIFIC FIELDS PUBLISHED ARTICLES on CHEK2

In Table (6), the results of the correlation between the researched topic and the field of science are presented. As expected, the majority of studies (49%) were conducted in the field of Medicine, followed by (39%) in the fields of Biochemistry, Genetics, and Molecular Biology. The remaining 12% are distributed among other scientific fields. It is known that genes play a crucial role in molecular biology, influencing various aspects. Scientific studies on the CHEK2 gene and research in the field of human health are closely intertwined. Most likely, this is the reason why primary research is conducted in the field of medicine.

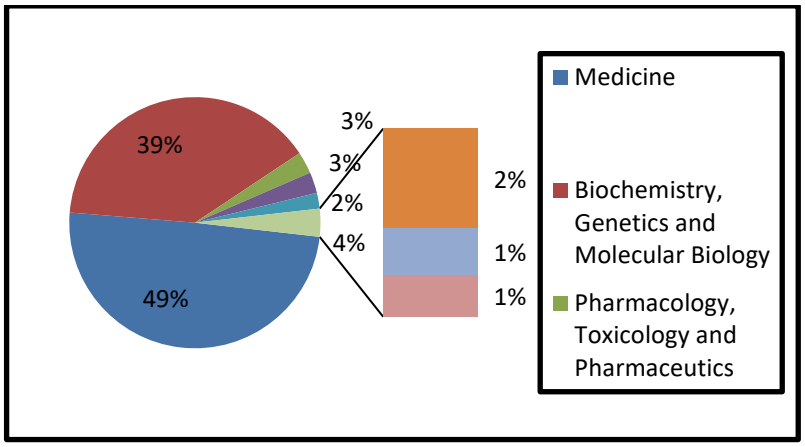

Figure.6. The relationship between the researched topic and the field of science

3.6 TOP JOURNALS PUBLISHED ARTICLES on CHEK2

The highest number of publications(Figure 7) on the topic we are studying was in the journal "Cancers" with an impact factor of 6.5, where 17% of the articles we investigated were published. Following that is the "International Journal of Molecular Sciences" with an impact factor of 6.2. The journal "Breast Cancer Research and Treatment" (with an impact factor of 4.6) published 13% of the articles we studied. It is unlikely to assert a direct correlation between the journal's impact factor and the number of articles. For instance, the journal "JAMA Oncology" has an impact factor of 28.4, yet only 9% of the publications were in this journal. This phenomenon underscores that the relevance of the journal to the nature of the research plays a crucial role, perhaps more than the journal's impact factor.

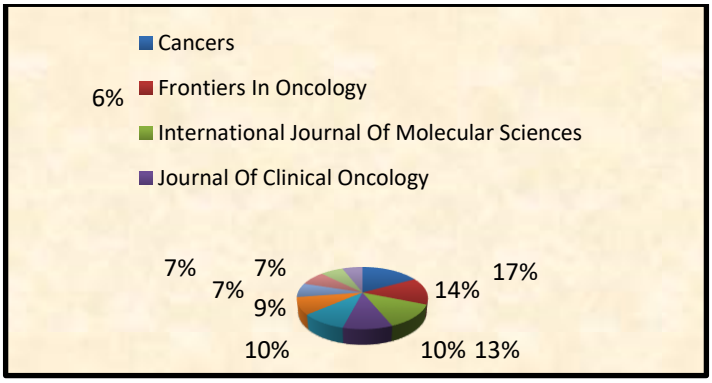

Figure.7. The list of journals publishing the most articles on the topic of CHEK2

3.7 TOP COUNTRIES PUBLISHED ARTICLES on CHEK2

In the 8th figure, as observed, the country that published the most articles is the United States, with 224 articles. China, making significant progress in many fields, occupies the second position with 66 articles. The United Kingdom is in the third position with 53 articles. The United States has led in the number of publications, scientific discoveries and, citations. This trend aligns with numerous other studies across various research domains[17]. None of the resource-limited countries participated as the primary author or leader in highly influential research. This trend has various reasons, with the distribution of funding by any country being the most crucial. In the United States, research and development are funded by multiple sectors, including the federal government, academia, business, non-profit organizations, and state governments, for various purposes. As a result, over the past decades, the United States has become a global leader in research and development[18].

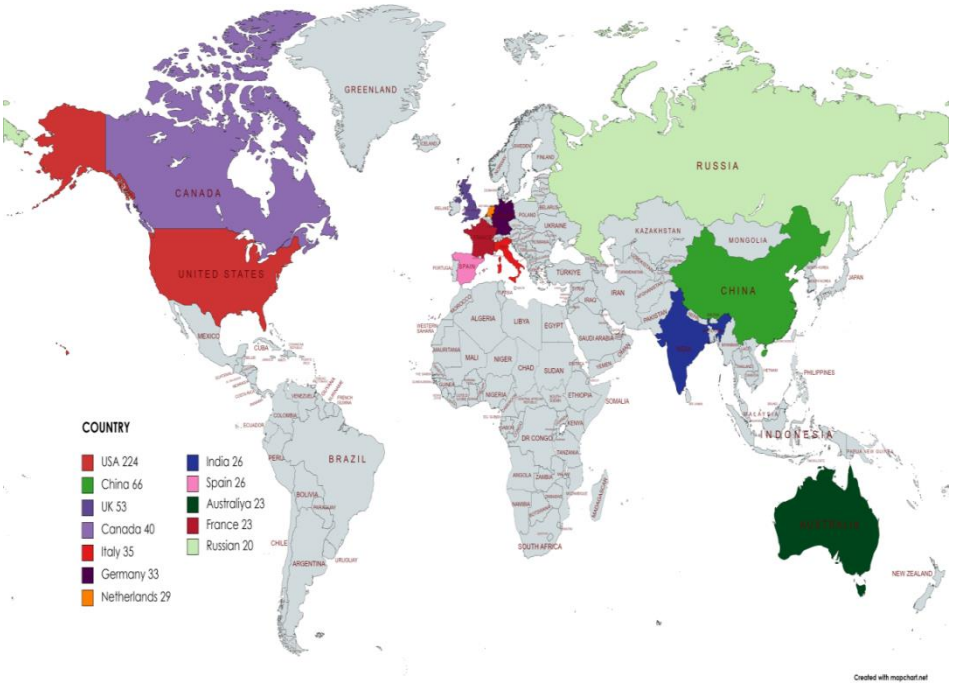

Figure. 8. The list of countries publishing the most articles on the topic of CHEK2

3.8 TOP PUBLICATIONS RECEIVED the HIGHEST CITATIONS on CHEK2

From 550 articles, we selected the top 10 most cited (table1). Among them, 6 received more than 500 citations. Leading the list is the review titled "Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis" with 1031 citations, published in the journal "Genes and Diseases" (IF 6.8). Following that is the review "ROS and the DNA damage response in cancer," published in the journal Redox Biology (IF 10). The article "A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal" was published in the

journal "Modern Pathology" from the United States and Canada (IF 7.5). All selected articles were published in English. Despite publications in this field predominantly taking the form of articles, 3 out of the top 4 most cited publications turned out to be reviews. This may be explained by the fact that reviews provide more extensive information and knowledge. It is important to note that the journal's impact factor (IF) is not always directly correlated with the number of citations a specific publication receives. Regarding the distribution of scientific output by countries, a large number of articles on this topic were published in journals from the United States. However, the most cited review was from a Chinese journal (Genes and Diseases), emphasizing the active participation of Chinese scholars in genetics research [7].

Table 1. List of highly cited papers on gen CHEK2

Title	Year	Source	Cited by	Type
ROS and the DNA damage response in cancer	2019	Redox Biology	837	Review
A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal	2018	Modern Pathology	620	Article
State-of-the-art strategies for targeting the DNA damage response in cancer	2019	Nature Reviews Clinical Oncology	595	Review
Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis	2018	Genes and Diseases	522	Review
Breast cancer risk genes - Association analysis in more than 113,000 women	2021	New England Journal of Medicine	358	Article
BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors	2019	Genetics in Medicine	311	Article
Cancer therapy shapes the fitness landscape of clonal hematopoiesis	2020	Nature Genetics	235	Article
Genetic testing and results in a population-based cohort of breast cancer patients and ovarian cancer patients	2019	Journal of Clinical Oncology	200	Article
TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes	2020	Journal of Clinical Oncology	196	Article
Feasibility and utility of a panel testing for 114 cancer-associated genes in a clinical setting: A hospital-based study	2019	Cancer Science	178	Article

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3.9 KEYWORDS ANALYSIS

Using VOSviewer, we conducted a keyword co-occurrence analysis. A total of 6578 author keywords were identified, and 25 keywords appeared more than 212 times. The network of relationships among these keywords is shown in Figure 9. Figure 9 displays four colors, representing four clusters, with connections between keywords illustrated by lines. The keyword "checkpoint kinase 2" (TLS 16550) was used 544 times and positioned in the central position of the green cluster, which focuses on the diagnosis of breast cancer. Other keywords in this cluster include "breast cancer," "BRCA1," "human," "protein P53," and so on. The blue cluster, with the central keyword "BRCA1" (TLS 1236), was used 34 times and is oriented towards the cancer mechanism. It includes keywords such as "protein," "cancer patient," "ATM protein," "BRCA2," and so on. In the red cluster, the central keyword "female" (TLS 13046) was used 396 times and forms a cluster with words like "gen," "adult," "breast cancer," and so on. The yellow cluster's central keyword is "gene mutation" (TLS 5720), used 189 times, connecting and forming a cluster with words like "human," "CHEK2," "female," "genetics," "BRCA1,2," and so on.

During the analysis of the most frequently used keywords, the following results were identified. The term "checkpoint kinase 2" was most frequently used (544 occurrences), followed by the term "human" (539 occurrences). It's noteworthy that the keyword "breast cancer" occupies the fourth position (418 occurrences). Recent studies prove that the CHEK2 gene is one of the hereditary gene markers in various types of cancer. This is likely the reason why the words "human" and "female" appear and are used more frequently than the keyword "breast cancer." It is known that breast cancer is primarily diagnosed in adults. Therefore, we believe that the words "female" and "adult" form a separate cluster. Recent studies show that the CHEK2 gene is closely related to the BRCA1 and BRCA2 genes. These genes are also major gene markers in breast cancer. Therefore, when entering the term "checkpoint kinase 2," the terms "BRCA1" and "BRCA2" are encountered more frequently than other genes. In our case, the terms "BRCA1" and "BRCA2" formed a separate cluster. Finally, the words "gene mutation," "clinical article," "mastectomy," and "mammography" formed a separate cluster [19,20].

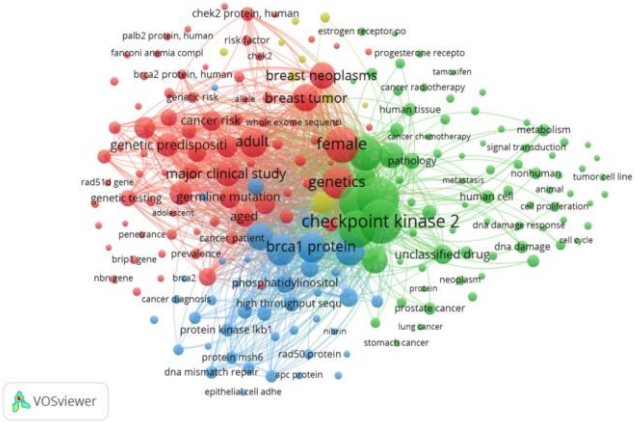

Figure.9. Analysis of the correlation of keywords

4. CONCLUSION

This bibliometric analysis provides an overview of publication results with the keywords "checkpoint kinase 2" and "breast cancer" worldwide. We analyzed articles from 2018 to 2022. It is worth noting that over the past few years, interest in the CHEK2 gene and its association with breast cancer has been growing steadily. The United States is the leading country in producing scientific knowledge. However, in recent years, China has made a significant contribution to the development of science in many fields.

The most significant authors are F.J. Couch and M.K. Schmidt. The keywords "checkpoint kinase 2" and "breast cancer" were chosen as key terms. The key term "checkpoint kinase 2" is more frequently associated with the words "human" and "female." As scientific research requires significant resources, low-income countries are not included in this category.

Citations of articles on this topic have been increasing each year, which can be attributed to the growing interest in the CHEK2 gene.

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