Original Article

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Trends and Implications of Studies on Advanced Glycation End Products (AGEs) and Cancer: Bibliometric Analysis

İleri Glikasyon Son Ürünleri (AGE'ler) ve Kanser Üzerine Yapılan Çalışmaların Eğilimleri ve Sonuçları: Bibliyometrik Analiz

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ABSTRACT

Objective: This study aims to analyze the current status of studies on the relationship between advanced glycation end products (AGEs) and cancer and to reveal the main trends in the field, the prominent authors, papers, affiliations, countries and collaborations and the most popular keywords related to the subject and changes in the popularity of keywords over time. In this context, the study aims to guide researchers who want to focus on the relevant field, and provide a basis for future research by facilitating access to information in the field.

Methods: Raw data were taken from the Web of Science (WoS) Core Collection database on April 30, 2024, and analyzed with programs such as Bibliometrix and VOSviewer. The data of the year 2024 were not included to be accurate regarding annual calculations.

Results: The first study on the subject in WoS was published in 1994. The United States of America (USA), China, and Japan stood out among countries, with Takeuchi M., Yamagishi S., and Kuniyasu H. among authors, and Kurume University among the institutions. The most collaboration on the subject was between the USA and China as countries and between Yamagishi S., and Matsui T. as authors.

Conclusion: Results from this bibliometric analysis emphasize the expanding importance of AGEs in cancer studies, pointing to potential avenues for further investigation and collaborative efforts in.

Keywords: Bibliometric analysis, cancer, oncology, advanced glycation end products, rage, nutrition

ÖZ

Amaç: Bu çalışmanın amacı ileri glikasyon son ürünleri (AGE) ve kanser ilişkisi üzerine yapılan çalışmaların mevcut durumunu analiz etmek ve alandaki ana eğilimleri, öne çıkan yazarları, makaleleri, kurumları, ülkeleri ve iş birliklerini ve konuyla ilgili en popüler anahtar kelimeleri ve anahtar kelimelerin zaman içinde popülerliğindeki değişimi ortaya koymaktır. Bu bağlamda, çalışma ilgili alana odaklanmak isteyen araştırmacılara rehberlik etmeyi ve alandaki bilgilere erişimi kolaylaştırarak gelecekteki araştırmalar için bir temel sağlamayı amaçlamaktadır.

Yöntemler: Ham veriler 30 Nisan 2024'te Web of Science (WoS) Core Collection veritabanından alınmış, Bibliometrix ve VOSviewer gibi programlarla analiz edilmiştir. Yıllık hesaplamalar açısından doğru olması için 2024 yılı verileri dahil edilmemiştir.

Bulgular: WoS'da konuyla ilgili ilk çalışma 1994 yılında yayınlanmıştır. Ülkeler arasında Amerika Birleşik Devletleri (ABD), Çin ve Japonya, yazarlar arasında Takeuchi M., Yamagishi S. ve Kuniyasu H. ve kurumlar arasında Kurume Üniversitesi öne çıkmaktadır. Konuyla ilgili en fazla iş birliği; ülkeler olarak ABD ve Çin arasında, yazarlar olarak Yamagishi S. ve Matsui T. arasındadır.

Sonuç: Bu bibliyometrik analizden elde edilen sonuçlar, AGE'lerin kanser çalışmalarındaki artan önemini vurgulayarak, daha fazla araştırma ve iş birliği çabası için potansiyel yollara işaret etmektedir.

Anahtar Kelimeler: Bibliyometrik analiz, kanser, onkoloji, ileri glikasyon son ürünleri, öfke, beslenme

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Introduction

Advanced glycation end products (AGEs) are a group of reactive compounds formed as a result of the non-enzymatic glycation of free amino groups of proteins and carbonyl groups of reducing sugars, known as the Maillard reaction (1,2). They can also form during non-enzymatic glycation and oxidation of lipids or nucleotides with sugars (3). Ne-(carboxyethyl)lysine, Ne-(carboxymethyl)lysine, fructosyl-lysine, and pyrraline are well-known types of AGEs (4). The formation of AGEs can occur exogenously during food processing, especially through heat treatment, or endogenously in the body due to high amounts of sugar intake (5,6). AGEs threaten human health in various ways by causing glycative stress (7). They are pro-inflammatory and pro-oxidant compounds that influence numerous biological responses by activating the receptor AGE (RAGE). They are causal in many chronic diseases, including cancer (8). Cancer, characterized by abnormal cell growth and proliferation beyond normal limits, which can subsequently invade surrounding tissues, is also referred to as malignant tumors and neoplasms (9). Recommendations are given to guide a healthy life to prevent cancer, such as changing nutritional patterns, reaching and maintaining a healthy body weight, reducing alcohol consumption, and increasing physical activity (10).

This study aims to analyze the current state of research on AGEs and cancer, revealing the main trends and identifying gaps in this field. The analysis may guide researchers who want to engage in this field and direct them to the right resources. In this context, the study's results will provide an idea of which articles and authors future researchers should focus on. As a result, this study aims to provide a basis for future research by facilitating access to information in the field.

Methods

This search was conducted in the Web of Science (WoS) Core Collection database on April 30, 2024. The search strategy and exclusion criteria are detailed in Table 1.

We searched the search query in title, abstract, and keywords without language restriction since all documents already contain English titles, abstracts, and keywords. Initially, 1,284 documents were identified. The data for 2024, when we conducted the analysis, were not included to be accurate regarding annual calculations, and the number of documents decreased to 1262. In order to address the historical development and evolution of research on AGEs and cancer, we did not choose to limit the study to a specific time period. The WoS database began indexing studies on this topic in 1994, and we considered this year as the starting point for analysis. By not applying a time restriction, we aimed to assess the progression of the field and identify key milestones that may have influenced the current state of research. Finally, arrangements were made according to document type. There were 1161 published documents from 584 sources related to "AGEs and cancer" from 1994 to 2023, and 242 were review articles.

Statistical Analysis

This study is based on bibliometric analysis, which does not involve conventional statistical hypothesis testing. Instead, descriptive bibliometric indicators such as the number of publications, citations, collaboration networks, and keyword

Table 1. The search strategy

OR		OR		OR	Excluded
advanced glycation end product$ glycosylation product$ glycoxidation product$ carboxymethyl-lysine carboxyethyl-lysine fructosyl-lysine pyrraline	And	cancer$ *carcinoma* tumor$ tumour$ neoplasm$ neoplasia neoplastic malignancy malignancies malignant melanoma leukemia lymphoma carcinogenesis onco*	Not	tumor necrosis factor tumour necrosis factor	Final publication year 2024 Meeting abstract Proceeding Paper Early access Editorial material Book chapters Letter Correction Data paper Note Publication with Expression of concern Retracted publication Retraction

: Was used to include all morphological variants of a word stem (e.g., onco for "oncology", "oncogene", etc., and *carcinoma* for all compound terms containing "carcinoma")
$: was used to include both singular and plural forms of words (e.g., cancer$ retrieves both "cancer" and "cancers"; tumor$ retrieves "tumor" and "tumors")
These wildcard characters ensured a comprehensive and inclusive search strategy by capturing different forms and variants of key terms, OR: Odds ratio

co-occurrence were analyzed. Raw data were exported in "plain.txt" format from WoS. These indicators were processed using WoS, RStudio 4.3.3 (Bibliometrix package) (11) and VOSviewer 1.6.20 (12) software. Besides, Microsoft Excel 365 was used for tabular presentations. No inferential statistical tests (e.g., t-tests, ANOVA) were conducted, as the objective was to evaluate publication and citation patterns rather than test statistical hypotheses.

Ethics Statement

This study does not involve human participants, animal experiments, or private or sensitive data collection. It is a bibliometric analysis based entirely on publicly available data from the WoS database. Therefore, ethical approval and informed consent were not required.

Results

Analysis of Documents

Figure 1 shows the number of documents produced on the subject by year. The first publication on the topic started in 1994 with 1 article. The number of publications increased over time and reached a peak of 106 documents in 2021. The annual growth rate was 16.46%.

While "local citation score (LCS)" reflects the citations made by the documents in the collection coming from WoS, the total citations (TC) they receive from documents indexed in WoS are called "global citation score (GCS)", also known as "TC". The top 10 most cited documents in terms of TCs in our data set are given in Table 2.

In Figure 2, 21 documents from our data set are visualized according to their citation relationships to each other and listed chronologically from left to right. The arrows show who is citing whom, and the direction of the arrow points to the document cited. The sizes of the nodes represent the LCS, Supplementary Table 1 is a detailed explanation of Figure 2. In this case, the article "Blockade of RAGE-amphoterin signaling suppresses tumor growth and metastases" published by Taguchi in 2000, ranked first in terms of both LCS and GCS.

Figure 3 shows the density analysis of the most cited references cited by the WoS collection. While some of these documents are already in our collection, some are from outside. The top 10 most local cited references are given in Supplementary Table 2.

Analysis of Authors

The number of authors publishing on "AGE and cancer" was 5789. The top 3 authors in terms of production were Yamagishi S. (n=28), Takeuchi M. (n=27), Kuniyasu H. (n=16). Figure 4 shows the authors and their publications over time. The line represents an author's timeline. The size of the circles represents the number of articles produced in the relevant year, and the color darkness represents the annual average number of citations for these articles.

Table 3 lists the top 10 authors according to their local impact. The ranking of the authors, whose h-indexes are calculated according to the number of articles related to the subject and the citations they receive from other authors in the collection, shows the author's local impact.

According to the results of the co-authorship analysis, 79 co-authors made at least five publications related to the subject together. Some of these 79 authors were not connected, and the largest set of connected items consisted of 7 authors (Figure 5). These seven authors were grouped into 2 clusters according to their relationships with each other. The authors in the first cluster were Takeuchi M., Sakasai-Sakai A., Takata T., and Takino J., and the authors in the second cluster were Yamagishi S., Matsui T., and Fukami K.

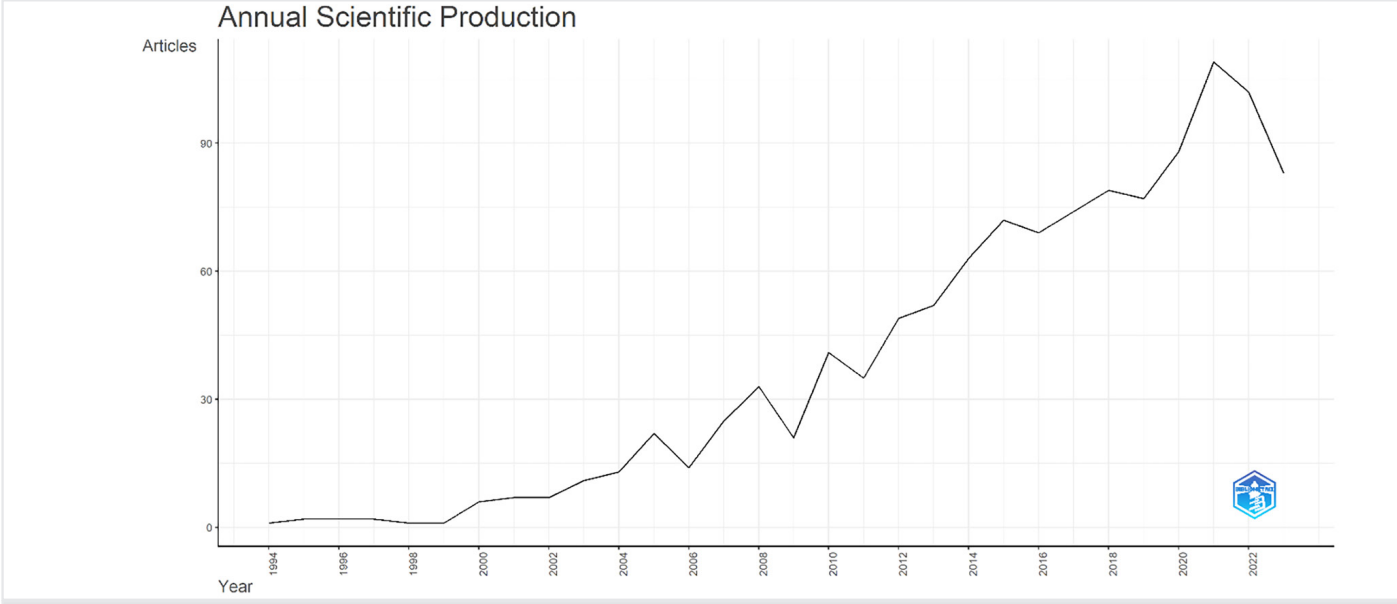

Figure 1. Annual scientific production

In Figure 5, colors ranging from purple to yellow provide information about the year of publication. The size of the nodes represents the number of documents that the authors have collaborated on regarding the subject; the lines between the nodes represent the connections between the collaborating authors; and the thickness of the lines represents the strength of these connections. In this respect, Yamagishi S., and Matsui T. had the closest collaboration. The ranking of these seven authors according to total link strength (TLS) was: Takeuchi M. (TLS=29) Yamagishi S. (TLS=22), Sakasai-Sakai A. (TLS=21), Takata T. (TLS=16), Takino J. (TLS=16), Matsui T. (TLS=15), and Fukami K. (TLS=9).

Analysis of Sources

The top 10 most productive sources were the International Journal of Molecular Sciences (n=34), PLoS One (n=22), Biochemical and Biophysical Research Communications (n=21), Scientific Reports (n=18), Journal of Biological Chemistry (n=15), Cells (n=14), Nutrients (n=13), Cancers (n=12), Medical Hypotheses (n=12), and Molecules (n=12), respectively. The production of these resources over time is given in Figure 6. While the International Journal of Molecular Sciences had eight publications in 2018, it experienced a turning point, increased rapidly in production, and ranked first with 34 publications in 2023. Journal of Biological Chemistry, Medical Hypotheses, Biochemical and Biophysical Research Communications, PLOS ONE, and Molecules have not published new publications on

Table 2. Top 10 most global cited documents

Author	Year	Title	TC	TC per year
Taguchi A	2000	Blockade of RAGE-amphoterin signalling suppresses tumour growth and metastases	1072	42,88
Bierhaus A	2005	Understanding RAGE, the receptor for advanced glycation end products	1010	50,50
Donato R	2013	Fuctions of S100 proteins	965	80,42
De Vos VM	2022	Gut microbiome and health: mechanistic insights	601	200,33
Van Remmen H	2003	Life-long reduction in MnSOD activity results in increased DNA damage and higher incidence of cancer but does not accelerate aging	564	25,64
Vauzour D	2010	Polyphenols and human health: prevention of disease and mechanisms of action	546	36,40
Huttunen HJ	2000	Coregulation of neurite outgrowth and cell survival by amphoterin and S100 proteins through receptor for advanced glycation end products (RAGE) activation	503	20,12
Lotze MT	2007	The grateful dead: damage-associated molecular pattern molecules and reduction/ oxidation regulate immunity	475	26,39
Negre-Salvayre A	2008	Advanced lipid peroxidation end products in oxidative damage to proteins. Potential role in diseases and therapeutic prospects for the inhibitors	464	27,29
Sinha P	2008	Proinflammatory S100 proteins regulate the accumulation of myeloid-derived suppressor cells	448	26,35

TC: Total citation

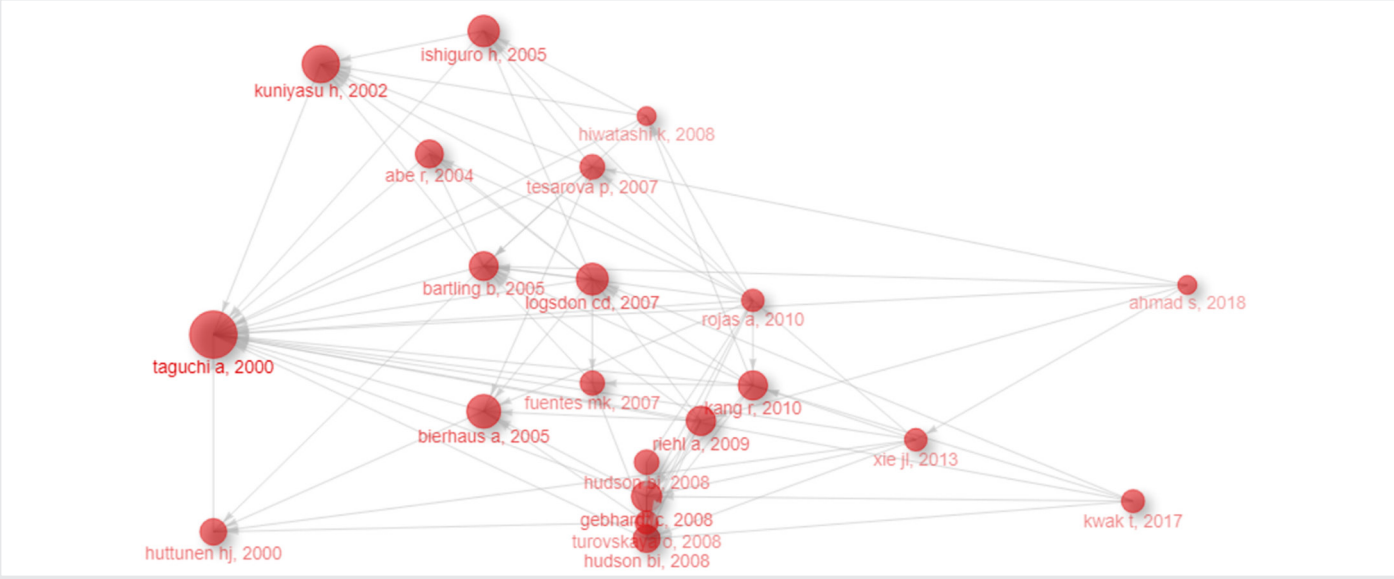

Figure 2. Historiograph of the documents

the subject after certain years, and the number of publications has remained constant.

The top 10 sources, according to their local impact, are given in Table 4. Among the top 10 sources in production, Cells, Cancers, and Molecules could not rank in the top 10 regarding local impact. Although Oncology Letters, Cancer Letters, and Carcinogenesis were not in the top 10 regarding production, they managed to be in the top 10 regarding local impact.

Analysis of Affiliations

The top 20 affiliations that published the most on "AGE and cancer" and their number of publications are shown in Figure 7.

Figure 8 shows the analysis of the collaborations. There were 114 affiliations that made at least five publications together related to the subject. Some 114 affiliations were not connected, and the largest set of connected items consisted of 104. These 104 affiliations were grouped under 11 clusters according to their relationships with each other.

In Figure 8, the size of the nodes represents the number of documents that the affiliations have collaborated on, the lines between the nodes represent the connections between the collaborating affiliations, and the thickness of the lines represents the strength of these connections. The top 5 affiliations according to their TLS were China Medical University, Taiwan (TLS=34), Asia University, Taiwan (TLS=26), Kurume University, Japan (TLS=25), National Chung Hsing University, Taiwan (TLS=25), Taichung Veterans General Hospital, Taiwan (TLS=19), respectively. The top 5 affiliations with the closest collaboration in terms of link strength (LS) were Kurume University-Hokuriku University (LS=8), National Tsing Hua University-China Medical University Taiwan (LS=8), Asia University Taiwan-China Medical University Taiwan (LS=8), National Chung Hsing University-Taichung Veterans General Hospital (LS=8),

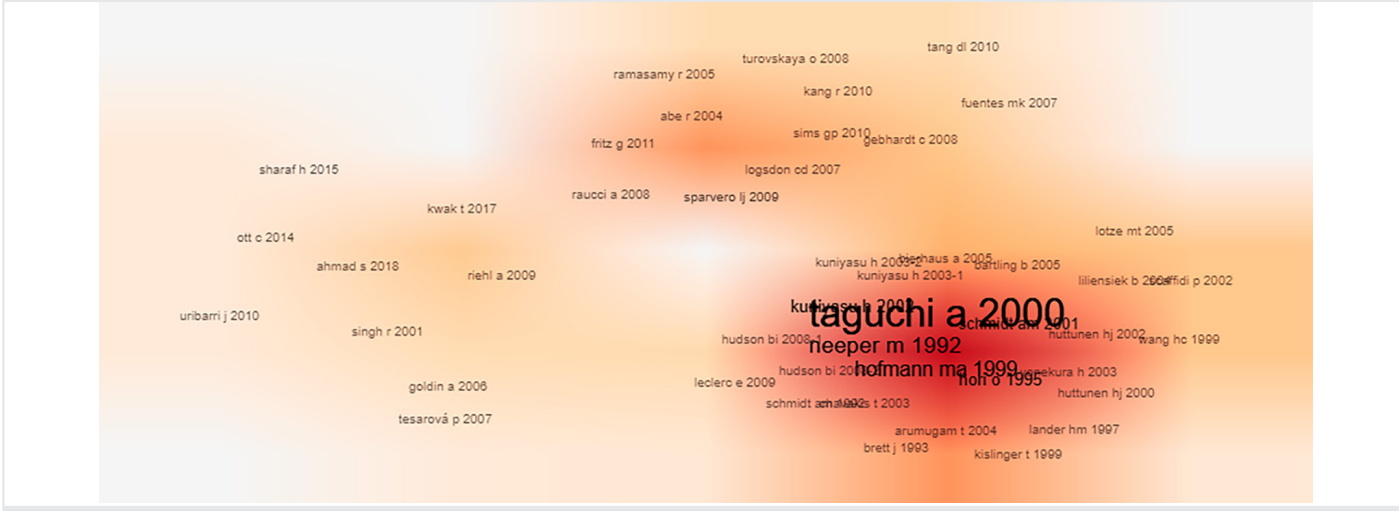

Figure 3. The density of most cited references which cited by the data set obtained from WoS

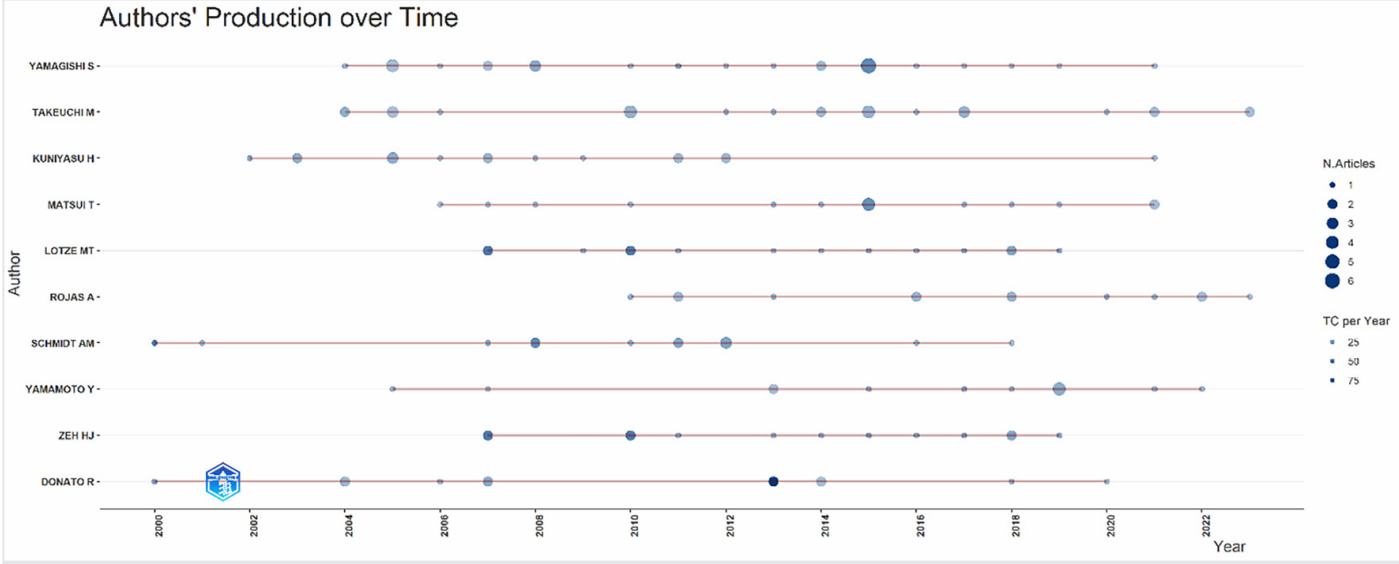

Figure 4. Authors' production over time

and Hiroshima Int University-Kanazawa Medical University (LS=7), respectively.

Analysis of Countries

Figure 9 shows the top 10 countries of the corresponding authors. Single-country publications (SCP) provide information about national collaboration, while multiple-country publications (MCP) provide information about international collaboration. The MCP and SCP rates of countries are shown in Supplementary Table 3. Countries with an MCP rate of 50% and above have high international collaboration (13). In this respect, the United Kingdom (UK) exceeded the threshold. The MCP ratios of China, the United States of America (USA), and Japan were 10%, 27.4%, and 10.3%, respectively.

Table 3. Author's local impact

Author	h-index	TC	NP	PY start
Takeuchi M	19	875	27	2004
Yamagishi S	19	1344	28	2004
Kuniyasu H	13	1136	16	2002
Lotze MT	13	2124	14	2007
Donato R	12	2288	12	2000
Zeh HJ	12	2039	13	2007
Matsui T	11	534	15	2006
Riuzzi F	11	1610	11	2004
Schmidt AM	11	2367	13	2000
Sorci G	11	2070	11	2000

TC: Total citation, NP: Number of paper, PY: Publication year

The top 10 countries that received the most citations on the subject are given in Figure 10. The first three most cited countries were the USA, China, and Japan. When we ranked them in terms of the average number of citations per article (CPA), the top 10 were Finland (CPA=136.90), Belgium (CPA=130.80), Ireland (CPA=99.30), New Zealand (CPA=94.00), the Netherlands (CPA=90.10), Switzerland (CPA=87.70), the UK (CPA=80.40), France (CPA=65.90), the USA (CPA=59.60), and Germany (CPA=58.70).

Figure 11 shows collaboration between countries. Countries that collaborated more are marked in dark blue. The thickness of the connections represents the strength of collaboration. Supplementary Table 4 lists the ranking of the top 10 country pairs according to their frequency of collaboration.

Analysis of Author's Keywords

Figure 12 shows the word cloud, which consists of the author's keywords. The size of the words represents their frequency of use. The first 10 most frequently used keywords were rage (n=232), AGEs (n=96), cancer (n=90), high mobility group box 1 (HMGB1) (n=81), inflammation (n=72), ages (n=63), oxidative stress (n=60), diabetes (n=52), glycation (n=48), and breast cancer (n=40).

Figure 13 shows the trend of the author's keywords used over the years. The three most popular keywords per year used at least five times are shown in the figure. The location of the circles indicates the year in which the keywords were most popular, while the size of the circles represents the frequency of use of these keywords. The smallest circles belonged to the words "immunohistochemistry", "blood-brain barrier" and "glycoxidation" which were used five times each, and the largest circle belonged to the word "rage", which was used 232 times.

In Figure 14, keywords are divided into 9 clusters according to their co-occurrence. While different colors represent different

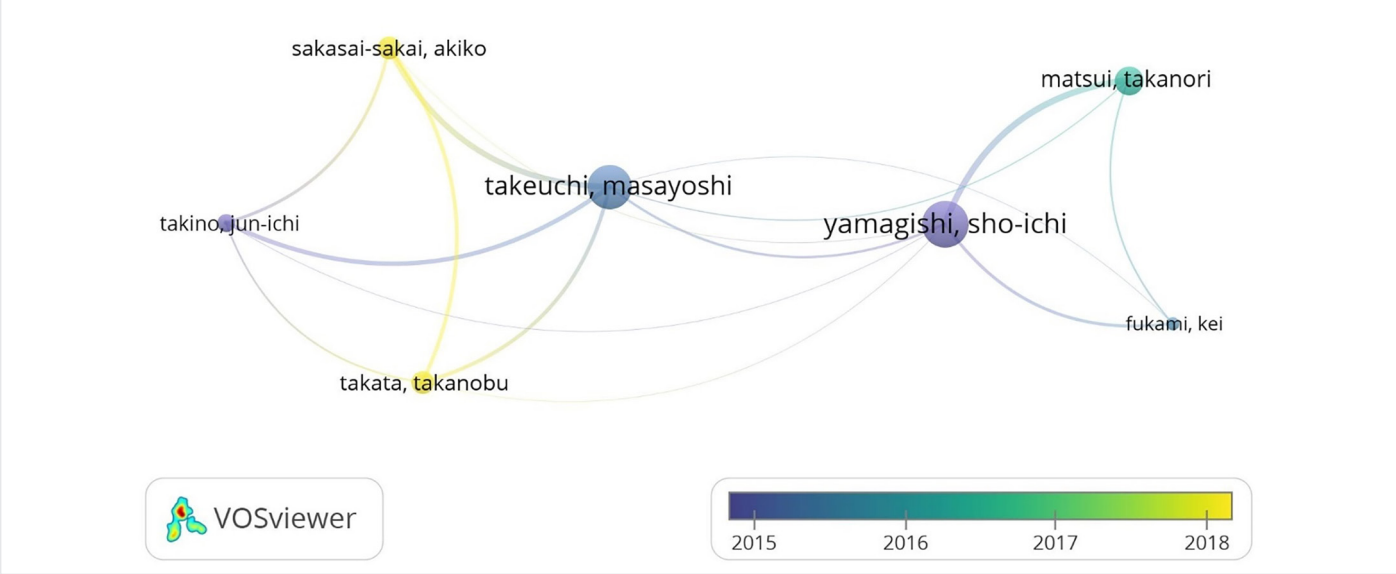

Figure 5. Co-authorship analysis of authors

clusters, the size of the nodes represents the TLS. The top 10 keywords in terms of TLS are rage, cancer, HMGB1, ages, AGEs, inflammation, diabetes, oxidative stress, glycation, and apoptosis, respectively. Lines between nodes show the recurrent relationship between words, meaning that the thicker the line, the more frequently the words were used together. Detailed information about Figure 14 is included in Supplementary Table 5.

Discussion

We have reported an increase over time in publications on AGEs and cancer; this trend has also been observed in bibliometric analyses of cancer and nutrition (14-16) and AGEs in obesity (17). According to the World Health Organization, approximately 1 in 5 people develop cancer in their lifetime. The International Agency for Research on Cancer projections for 2022 highlight the urgent need to address the escalating burden of cancer (18). The significance of cancer prevention and control was underscored at the third UN High-Level Meeting on Noncommunicable Diseases in 2018 (19) and the UN High-Level Meeting on Universal Health Coverage in 2019 (20). These factors likely contributed to the pronounced surge in publications observed between 2019 and 2021. Also, the dominance of ultra-processed foods rich in AGEs in the global food supply chain may have paved the way for more research over time (21,22). More than 35 million new cancer cases are projected to occur by 2050, representing a 77% increase from the estimated 20 million cases in 2022. This rapid escalation in the global cancer burden reflects both demographic aging and shifts in individuals'

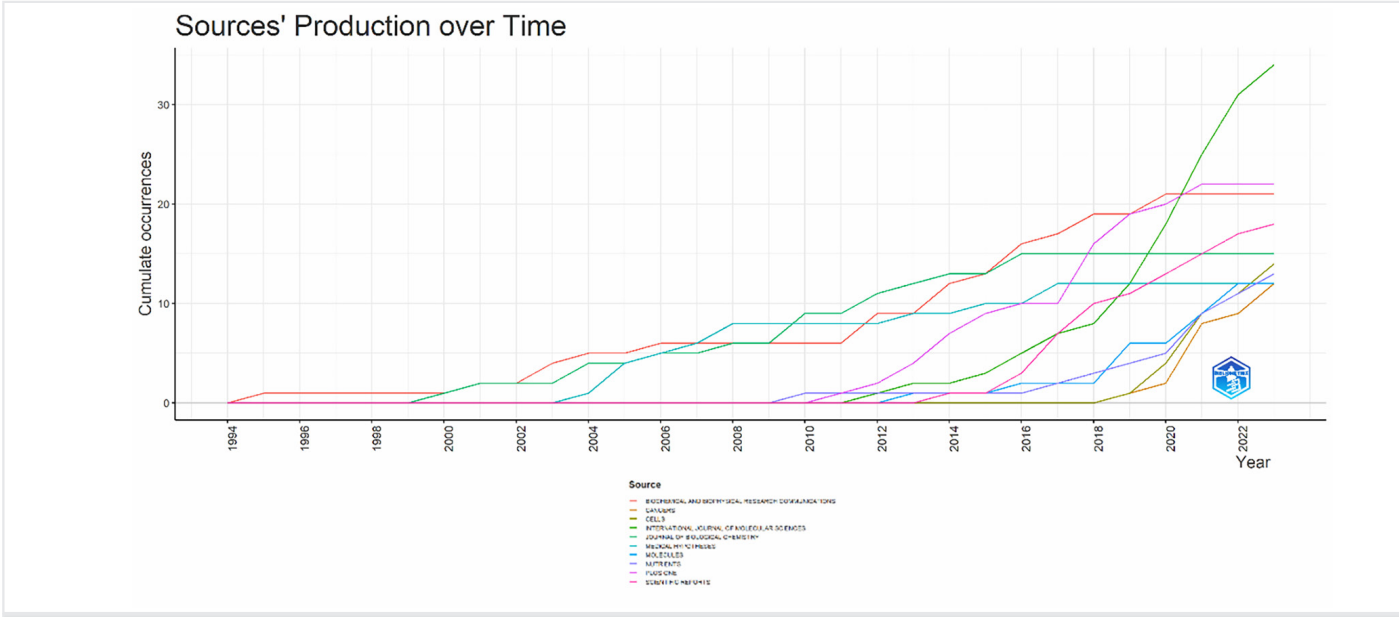

Figure 6. Sources' production over time

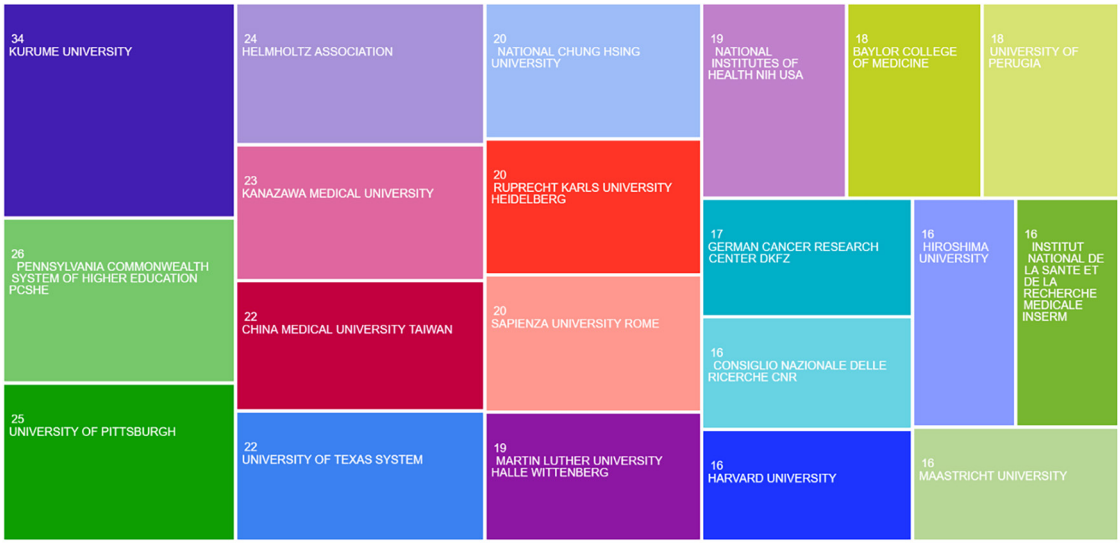

Figure 7. Publication of affiliations

Table 4. Sources' local impact

Sources	h-index	TC	NP	PY start
International Journal of Molecular Sciences	17	751	34	2012
Journal of Biological Chemistry	15	1742	15	2000
Biochemical and Biophysical Research Communication	14	716	21	1995
PLoS One	13	463	22	2011
Scientific Reports	11	405	18	2014
Medical Hypotheses	9	274	12	2004
Nutrients	9	761	13	2010
Oncology Letters	9	214	11	2012
Cancer Letters	8	361	8	2003
Carcinogenesis	8	775	9	2005

TC: Total citation, NP: Number of paper, PY: Publication year

exposure to risk factors (18). Given this context, research into the relationship between AGEs and cancer is anticipated to continue to garner significant attention in the years ahead.

The most cited study regarding TCs showed that co-localization of RAGE and amphoterin, also known as HMGB1, at the leading edge of advancing neurites contributes to cellular migration and pathologies such as tumor invasion. The authors also reported that RAGE-amphoterin blockade reduced the growth and metastasis of implanted and spontaneous tumors in susceptible mice (23). Amphoterin is a protein that enhances process elongation and migration in embryonic neurons and tumor cells by binding to RAGE, a multiligand transmembrane receptor (24).

The most cited document per year was a review article about gut microbiome and health. This study mentioned that AGEs interact with the colon epithelium by activating RAGE and increasing intestinal permeability, which in turn causes bacterial toxins to leak into the systemic circulation. It was also stated that

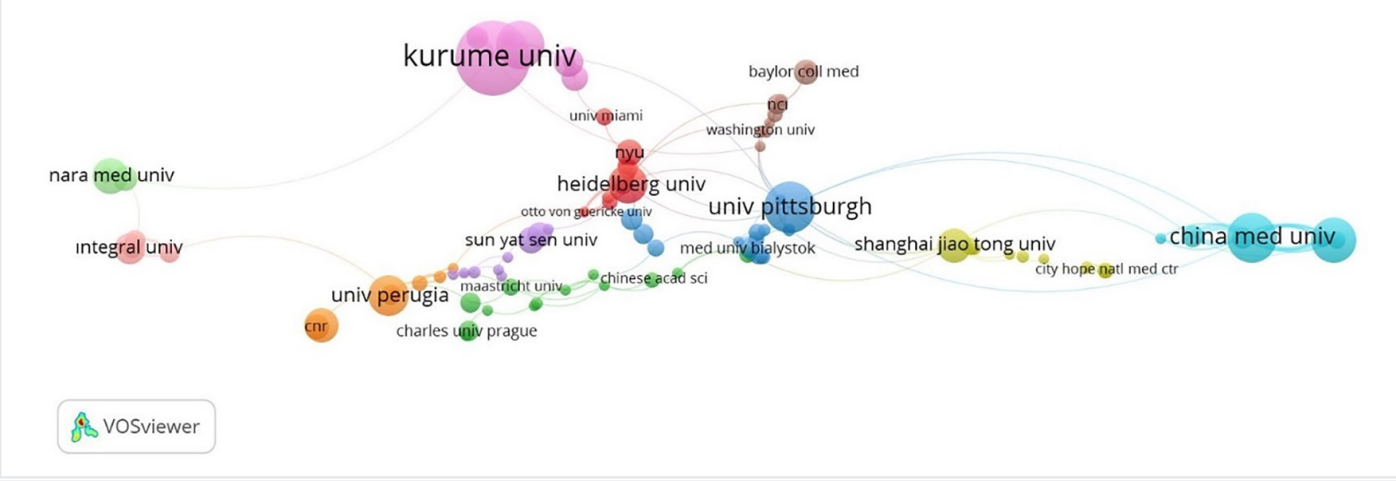

Figure 8. Collaboration of affiliations

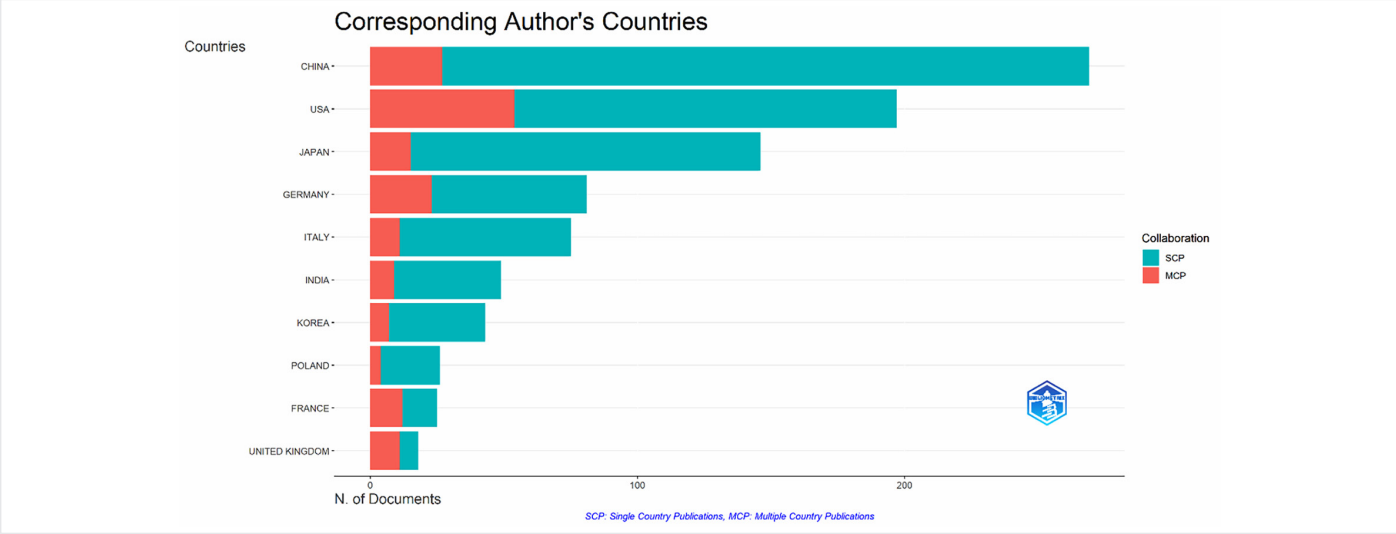

Figure 9. Top 10 corresponding authors' countries.
SCP: Single-country publications, MCP: Multiple-country publications

Escherichia coli could respire fructoselysine, a type of AGE, but this substance can be converted to butyrate by members of the genus Intestinimonas spp. in a new way as well (25).

The Journals Nutrients, PLoS One, Medical Hypotheses, and Scientific Reports, which ranked among the top 10 most productive sources in our study, were also in the top 15 in a bibliometric analysis of AGE and obesity (17). In a separate analysis on cancer and nutrition, Nutrients was among the top 10 sources (15), and in another, Nutrients, PLOS ONE, and Cancers were in the top 10 (16). As can be seen in Figure 6, some journals do not publish new studies related to the subject. If this continues, changes are expected in the list of the most productive sources.

Among the top 10 most influential authors, Schmidt AM., Yamagishi S., and Takeuchi M. (Table 3) were also prominent in another bibliometric analysis on AGE and obesity (17).

Kurume University, which has the most publications related to the subject, was ranked 3rd in terms of LS, and the institution it collaborated with the most was Hokuriku University. Kurume University is a prestigious university in Japan, founded in 1928 as Kyushu Medical School (26). The University of Texas System, in the top 10 regarding the number of publications in our collection, was also among the top 10 institutions in a bibliometric study analyzing the top 100 most cited articles (27). The University of Texas System was founded on September 15, 1883, in a real sense (28).

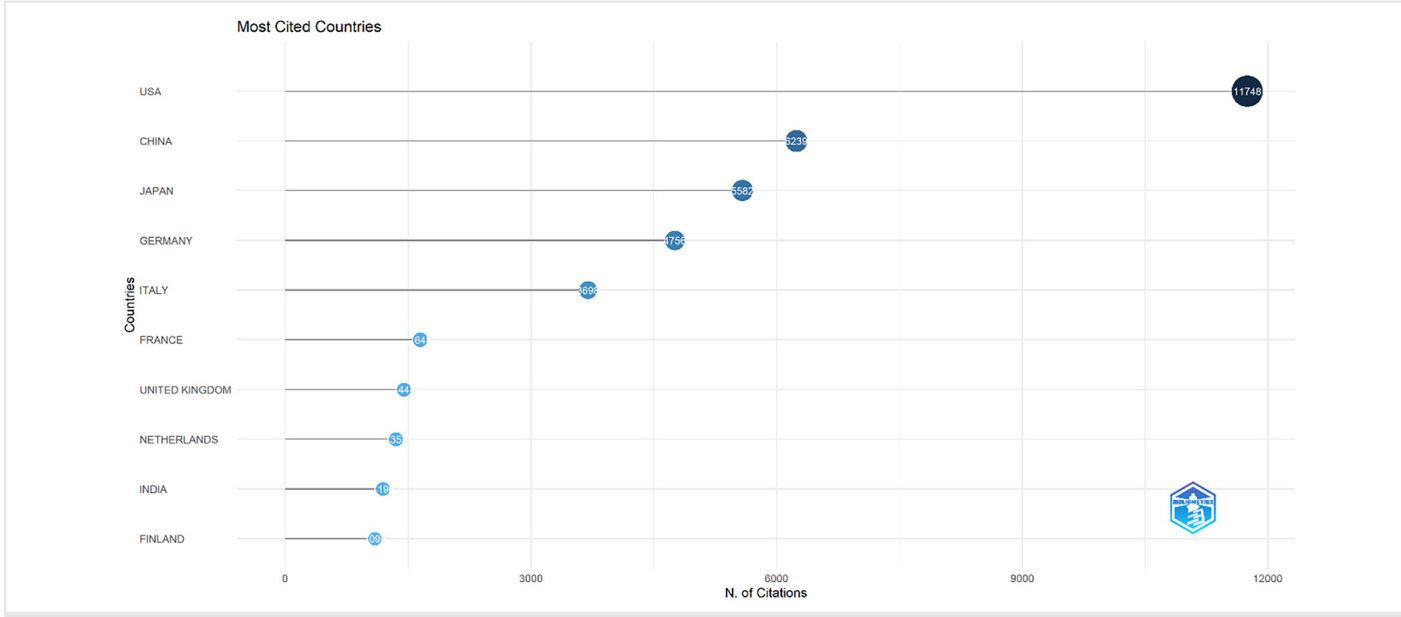

Figure 10. Most cited countries

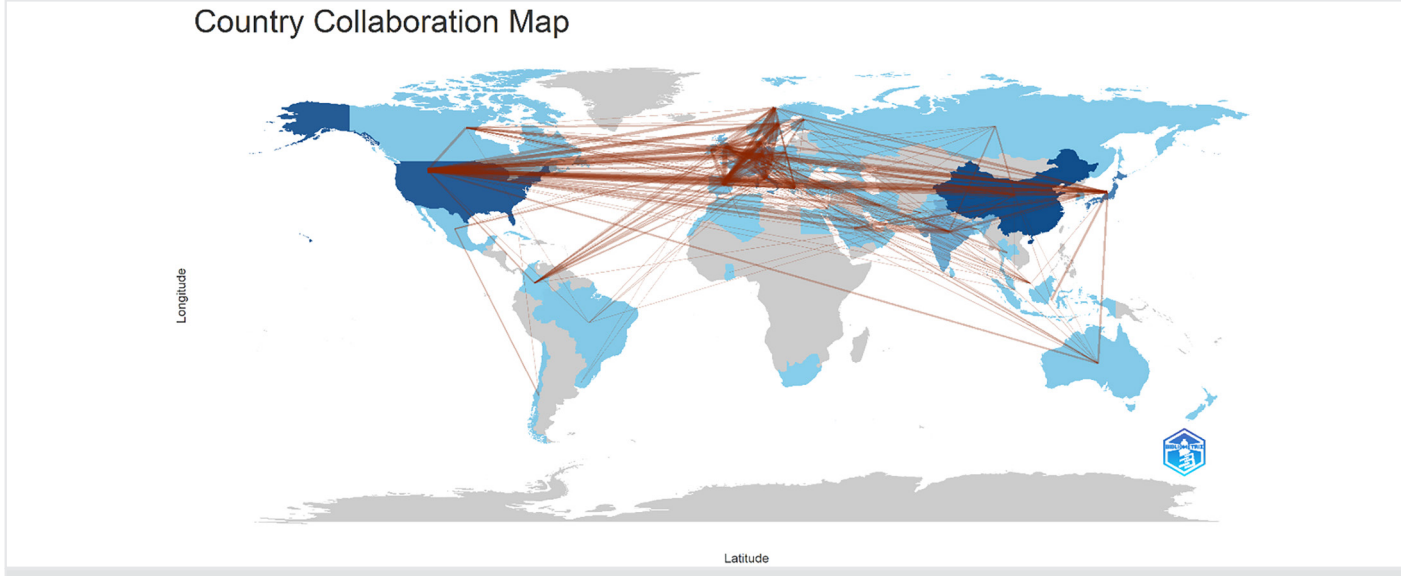

Figure 11. Country collaboration map

Although the most influential authors and the most productive institutions in the field were from Japan, as a result of the country analysis, Japan ranked 3rd in terms of both production and citations. The USA and China took the first two places. Our findings align with other bibliometric analyses on cancer and nutrition, where China, the USA, Japan, Germany, Italy, France, and the UK ranked among the top 10 (14-16). In the bibliometric analysis on AGE and obesity (17), the top 10 most cited countries included the USA, UK, Italy, Germany, Japan, China, France, the Netherlands, and India, as in our study. Cancer is the leading cause of death in China and developed countries (29). In 2019, when looking at the leading causes of premature death (between the ages of 30-70) in 183 countries, cancer ranked first in China, the USA, and Japan (30).

Supplementary Table 4 shows the top 10 most collaborative country pairs. Similar to our findings, a cancer and nutrition bibliometric study identified Italy-Germany, Italy-UK, UK-Germany, and UK-Spain as key collaborations (15). In our study, the USA and China were the leading cooperative countries, with the USA collaborating with various nations in the top four pairs. However, when the MCP rates of the countries are examined, it is seen that only the UK passes the 50% threshold and that international cooperation could be much higher. Despite the collaborative efforts observed among certain country pairs, there remains a need for increased international cooperation to address the complex challenges associated with AGEs and cancer.

The most frequently used keyword in our collection was "rage". This situation is natural, as in many studies, the mechanism of disease formation is explained through the activation of RAGE (8,23,25). Besides, the presence of breast cancer in the top 10 most frequently used keywords indicates that this type of cancer has been studied more than other types of cancer.

Figure 12. Word cloud of author's keywords

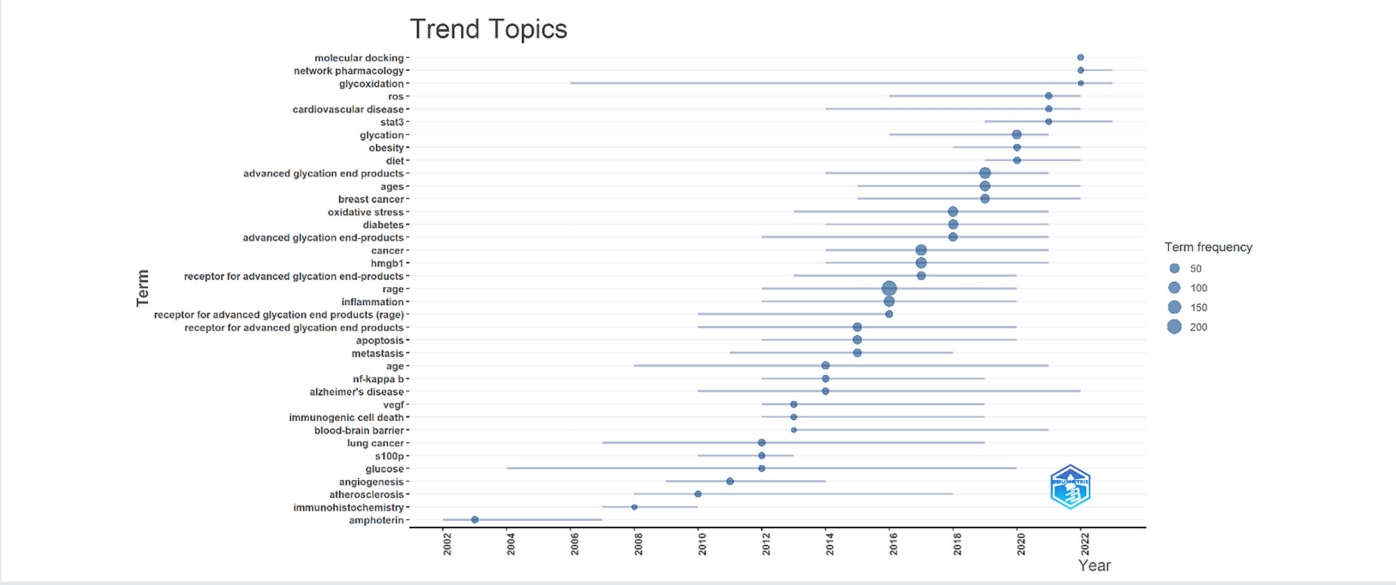

Figure 13. Trend topics of author's keywords

When the co-occurrence analysis of authors' keywords is examined in Figure 14, although different types of cancer are located in different clusters, all cancer types are in a central position. In this study, nine clusters emerged from the co-occurrences of keywords (Supplementary Table 5), and four study areas were revealed from these clusters.

In the first cluster, the research area includes studies and meta-analyses examining the relationship between cancer and diabetes, the effect of polymorphism in RAGE on cancer, and the effect of AGE, hyperglycemia, and glycation biomarkers in cancer formation. Gene polymorphisms in different parts of RAGE significantly increase the risk of cancer (31-33). A study examining the link between cancer and diabetes shows that patients with diabetes have a higher risk of developing cancer and that cancer patients with diabetes have higher mortality than cancer patients without diabetes (34).

In the second cluster, the research area examines cell migration, cell differentiation, and cell proliferation by induction RAGE and toll-like receptors by HMGB1. It also examines the effects of S100 proteins on malignant tumor proliferation, cell migration, metastasis, and the effects of factors promoting epithelial-mesenchymal transition (EMT) on micrometastasis. High mobility group box 1 is a pro-inflammatory cytokine and pro-angiogenic factor that can signal through RAGE and the toll-like receptors (35,36). It induces EMT, which plays an important role in cancer progression, especially colorectal cancer, through signaling pathways that increase the levels of snail, nuclear factor (NF)-kappaB, and matrix metalloproteinase 7 (36).

In the third cluster, the research area consists of studies examining the effect of the formation and accumulation of methylglyoxal, a strong inducer of AGEs, on diabetes and cancer formation, intervention studies that prevent the formation of methylglyoxal, and epidemiological studies on different types of cancer. An epidemiological study conducted in Japan examining dietary AGEs and cancer risk found a significant positive association between liver cancer risk and AGE consumption (37). Dietary intake of AGEs negatively affects the liver and increases the development of non-alcoholic fatty liver disease (38). Similarly, dietary AGE intake increases the risk of breast cancer (39). These results are intriguing, but studies on dietary AGEs and cancer are insufficient. Keywords such as "diet", "nutrition" or "dietary AGE" did not appear in the top 10 most frequently used authors' keywords, and Figure 13 shows that the word "diet" appeared in trends only between 2019-2022. These results support the idea that there are insufficient studies on dietary AGEs. Although some studies have shown a relationship between dietary AGE consumption and cancer risk, the formation mechanism has not been revealed. As a result, more studies on dietary AGEs are needed.

In the fourth cluster, the study area examines the effect of RAGE and amphoterin, on tumor invasion and metastasis of different types of cancer. Besides, S100 proteins, especially S100B, are abundantly expressed in the nervous system and are thought to function as cytokines with neurotrophic and neurotoxic effects. S100B is a signaling receptor for the toxic effects of RAGE (24).

When the trend topics graph in Figure 13 is examined, it seems that studies on amphoterin have not been studied as of 2007, but the keyword "amphoterin" referred to as "HMGB1" in the current literature. The keywords "immunohistochemistry", "angiogenesis", "atherosclerosis" and "S100p" are fields of study that are a little more of the past. Studies that reveal the relationship between glycation, diabetes, and cancer via AGEs in

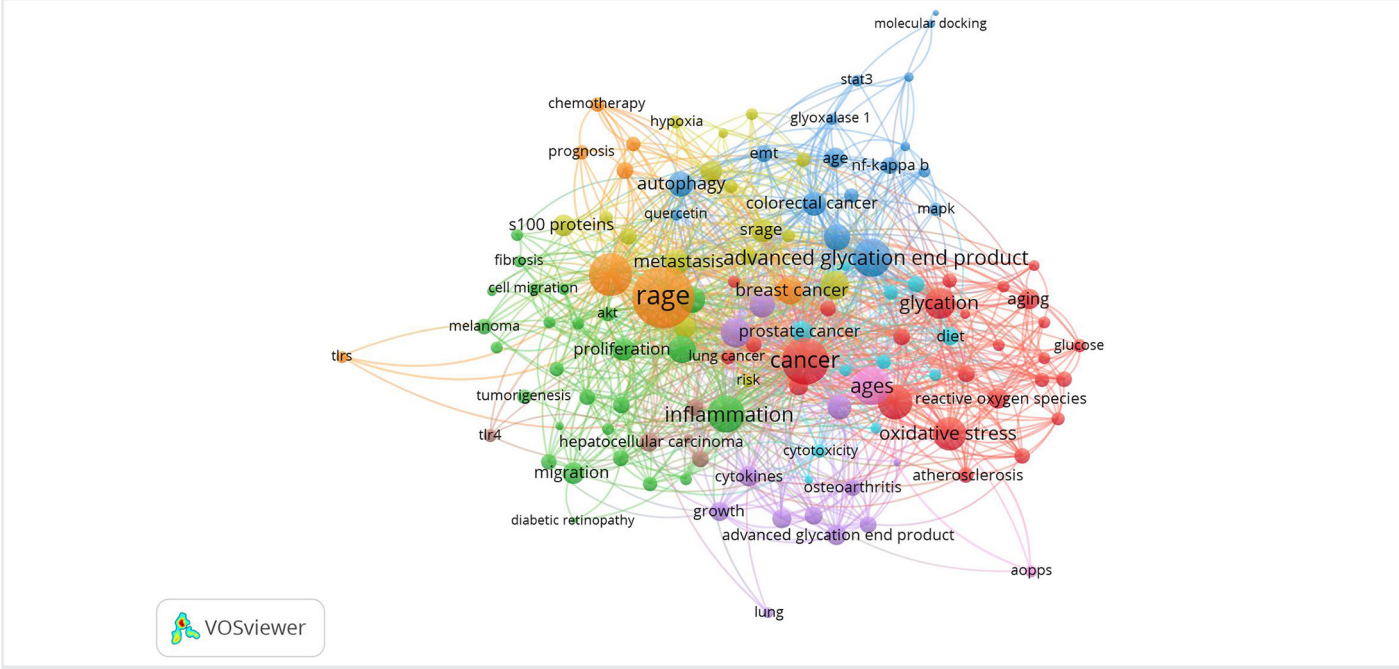

Figure 14. Co-occurrence analysis of author's keywords

the third cluster, are among the recently studied topics. Although "molecular docking" was among the trending keywords in 2022, this issue was not focused on much afterward. Network pharmacology, a term that has gained popularity recently, is an evolving approach used to explore the possible effects and mechanisms of natural products by conducting system-wide analyses of gene sets in herbs (40). Recent studies in our dataset have revealed that various active ingredients influence multiple mechanisms in the body, with some showing anticancer effects through the AGE-RAGE signaling pathway (40-42). Another currently popular keyword in our data was "signal transducer and activator of transcription 3 (STAT3)". The primary signaling pathways through which AGEs increase RAGE expression are NF-kappaB and STAT3 (43). In recent years, some cancer mechanisms have been explained through RAGE and STAT3 signaling pathways, and therefore STAT3 has become a popular word in current studies (44,45).

Generally, there is no keyword standard in the data set examined. The term "advanced glycation end product" is used alongside variations like "age," "ages," "AGEs," and "advanced glycation end-product," leading to similar keywords being grouped together. The lack of standardization in keyword usage underscores the importance of adopting consistent terminology to facilitate information retrieval and enhance the visibility of relevant research. To avoid this situation, authors can choose the most frequently used version of the keyword for their study through bibliometric research before publishing.

This study is the first bibliometric analysis of AGE and cancer. The fact that the WoS is a prestigious database with scientifically high-quality studies is one of the strengths of our study. Another strength of our study is that two researchers checked the data set separately, and the search strategy was created in great detail. Additionally, we could access more studies because we did not impose any language restrictions.

Study Limitations

The limitation of our study is that we only conducted bibliometric analysis based on the WoS database and did not include other publications on the subject from different databases. The exclusive use of the WoS database was primarily due to its high-quality, peer-reviewed content, and it is a widely accepted source for bibliometric analysis. Furthermore, WoS provides a comprehensive dataset for research in biomedical and health fields. However, future studies may consider incorporating additional databases for a broader comparison.

Conclusion

This bibliometric analysis highlights the growing significance of research into the relationship between AGEs and cancer, revealing key global trends in the field. While studies are increasing, much remains to be understood, particularly regarding the impact of dietary AGEs on cancer. The results underscore the need for greater international collaboration, with a special emphasis on expanding research in low- and middle-income countries. AGEs are emerging as a critical target for cancer prevention and treatment, reinforcing the importance of multidisciplinary studies to explore their biological effects in greater detail.

Our findings suggest that research on the AGEs-cancer connection will continue to expand. Studies focusing on molecules like RAGE and HMGB1 in cancer progression and metastasis have gained prominence. Further clinical validation of these targets could enhance treatment strategies. Future research will not only deepen our understanding of cancer's biological mechanisms but also help develop novel prevention and treatment approaches.

Ethics

Ethics Committee Approval: This study does not involve human participants, animal experiments, or private or sensitive data collection. It is a bibliometric analysis based entirely on publicly available data from the Web of Science database. Therefore, ethical approval were not required.

Informed Consent: This study does not involve human participants, animal experiments, or private or sensitive data collection. It is a bibliometric analysis based entirely on publicly available data from the Web of Science database. Therefore, informed consent were not required.

Footnotes

Authorship Contributions

Concept: Ş.N.D., Ş.A., Design: Ş.N.D., Ş.A., A.A.U., Data Collection or Processing: Ş.N.D., Analysis or Interpretation: Ş.N.D., Ş.A., A.A.U., Literature Search: Ş.N.D., A.A.U., Writing: Ş.N.D., A.A.U.

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Supplementary Tables: https://d2v96fxpocvxx.cloudfront.net/bd1986e1-0bc1-4f4d-af66-3a184850a065/content-images/26c9a403-44ff-48b3-bc57-81d72e6e8ef2.pdf