Brief Communication

Unraveling links between aging, circadian rhythm and cancer: Insights from evidence-based analysis

Dechao Feng[1,2,3*], Yuhan Xiao[1*], Jie Wang[1*], Ruicheng Wu[1*], Zhouting Tuo[4], Koo Han Yoo[5], Wuran Wei[1], Dilinaer Wusiman[6,7], Zhipeng Wang[8], Dengxiong Li[1], Yubo Yang[9], William C. Cho[10], Mang Ke[3]

[1]Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu 610041, China; [2]Division of Surgery & Interventional Science, University College London, London W1W 7TS, UK; [3]Department of Urology, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Taizhou 317000, China; [4]Department of Urology, the Second Affiliated Hospital of Anhui Medical University, Hefei 230601, China; [5]Department of Urology, Kyung Hee University, Seoul 130-701, South Korea; [6]Department of Comparative Pathobiology, College of Veterinary Medicine, Purdue University, West Lafayette, IN, 47907, USA; [7]Purdue Institute for Cancer Research, Purdue University, West Lafayette, IN 47907, USA; [8]Department of Urology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu 610072, China; [9]Department of Urology, Three Gorges Hospital, Chongqing University, Chongqing 404000, China; [10]Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong SAR, China

*These authors contributed equally to this work.

Correspondence to: Dechao Feng. Department of Urology, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Taizhou 317000, China; Division of Surgery & Interventional Science, University College London, London W1W 7TS, UK; Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu 610041, China. Email: fdcfenix@stu.scu.edu.cn; Dengxiong Li. Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu 610041, China. Email: dengxiongli.ymedx@gmail.com; Yubo Yang. Department of Urology, Three Gorges Hospital, Chongqing University, Chongqing 404000, China. Email: potatobo@126.com; William C. Cho. Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong SAR, China. Email: williamcscho@gmail.com; Mang Ke. Department of Urology, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Taizhou 317000, China. Email: kem@enzemed.com.

Abstract

Aging and circadian rhythms have been connected for decades, but their molecular interaction has remained unknown, especially for cancers. In this situation, we summarized the current research actuality and problems in this field using the bibliometric analysis. Publications in the PubMed and Web of Science databases were retrieved. Overall, there is a rising trend in the publication volume regarding aging and circadian rhythms in the field of cancer. Researchers from USA, Germany, Italy, China and England have greater studies than others. Top three publication institutions are University of California System, UDICE-French Research Universities and University of Texas System. Current research hotspots include oxidative stress, breast cancer, melatonin, cell cycle, calorie restriction, prostate cancer and NF-KB. In conclusion, results generated by bibliometric analysis indicate that many approaches involve in the complex interactions between aging and circadian rhythm in cancer. These established and emerging research directions guide our exploration of the regulatory mechanisms of aging and circadian rhythms in cancer and provide a reference for developing new research avenues.

Keywords: Aging; circadian rhythm; human cancer; bibliometric analysis; oxidative stress

Submitted May 07, 2024. Accepted for publication Jun 10, 2024.
doi: 10.21147/j.issn.1000-9604.2024.03.09
View this article at: https://doi.org/10.21147/j.issn.1000-9604.2024.03.09

Introduction

How to expand the human lifespan is an interesting and everlasting topic. Age has already been demonstrated to be a risk factor of many human diseases because an increased susceptibility to infection and the onset of disorders like chronic kidney disease (1), neuromuscular dysfunction and cancers including cancer located in colorectum, breast, as well as different physiological changes like circadian rhythm systems are characteristics of aging (2-4). Around 20% of the world's population will be 65 years or older by 2030 (5). Thus, with population ages worldwide, the influence of global disease burden on national healthcare system is expected to be more pronounced.

Currently, malignant tumor research is increasingly focusing on ageing and circadian rhythm (6). Actually, circadian rhythm is dysregulated in age-related diseases and treatment, including a variety of malignant tumors (6,7). An increasing number of studies link the changes of circadian rhythm systems at the molecular, circuit and behavioral levels to normal aging and aging-related diseases (8). Furthermore, Blacher *et al*. found that the loss of diurnally rhythmic innate immune responses was linked to ageing, and the deterioration in homeostatic immune responses was linked to a startling absence of circadian gene transcription in old *vs*. young tissue macrophages (9). According to their findings, disturbance of circadian innate immune homeostasis was associated with loss of rhythmic Kruppel-like factor 4 expression in aged macrophages, which may be a mechanism underlying the aging-related decline in protective immunological responses (9). Therefore, we suppose that there is an inseparable relationship among aging, circadian rhythm and cancers and we summarized the current research actuality and problems in this field using the bibliometric analysis.

Materials and methods

Publications in the PubMed and Web of Science databases were retrieved from the beginning of the database to August 25, 2023. Aging, cancer and circadian rhythm were the used keywords. Detailed research strategy could be seen in *Supplementary materials*. A total of 1,059 publications were obtained initially and we finally analyzed 976 studies using Citespace v6.2.R4 after limiting the literature type as article and review and removing duplicates (10). We also used VOSviewer and pajek to better present our data (11). We analyzed the commons between aging and circadian rhythm in cancer from the distribution of years, authors, institutions, research hotspots and evolution trends of international researches, in order to understand the research strength, development momentum, hotspots and evolution trends in this field.

Results

Publication landscape

Research in this field could be traced back to 1979 and the publication trends could be classified into three stages (*Figure 1A*). In the first stage, researches in this field from 1979 to 1992 were low. In the second stage, from 1993 to 2004, this topic is steadily developed. During this period, the number of papers published was relatively stable, basically maintained at 10–20 per year. In the third stage, this subject experiences a rapid rising period since 2005. Overall, the number of articles on this research topic is increasing, and the number of articles published in the past three years is more than 60, indicating that the current field has become a hot topic in the research of international scholars. As of August 2023, the number of papers published in 2023 was still above 50, indicating that this field is likely to become the core of future research. Researchers from USA, Germany, Italy, China and England have greater studies than others (*Figure 1B*). Top three publication institutions are University of California System, UDICE-French Research Universities and University of Texas System (*Table 1*). Notably, Universite Paris Saclay shows close collaborations with Assistance Publique Hopitaux Paris (APHP), Hopital Universitaire Paul-Brousse – APHP, Universite Paris Cite and UDICE-French Research Universities (*Figure 1C*). Top authors in this field are presented in *Table 1*. Author co-occurrence network (*Figure 1D*) indicated that Mirza-aghazadeh-attari, Mohammad had tight collaboration with Yousefi, Bahman and Majidinia, Maryam. Similar collaboration relationship could be seen between Levi, Francis and Innominato, Pasquale F, Komarzynski, Sandra, Hardeland, Ruediger and Clairambault, Jean. The expertise of authors could be classified into four types: 1) circadian rhythm for cancer treatment research. Innominato, Pasquale F, and Levi, Francis have conducted in-depth research on the application and mechanism of circadian rhythm in cancer treatment; 2) association of clock gene expression with cancer and metabolism. Mazzoccoli, Gianluigi focused on the relationship between clock gene expression and cancer,

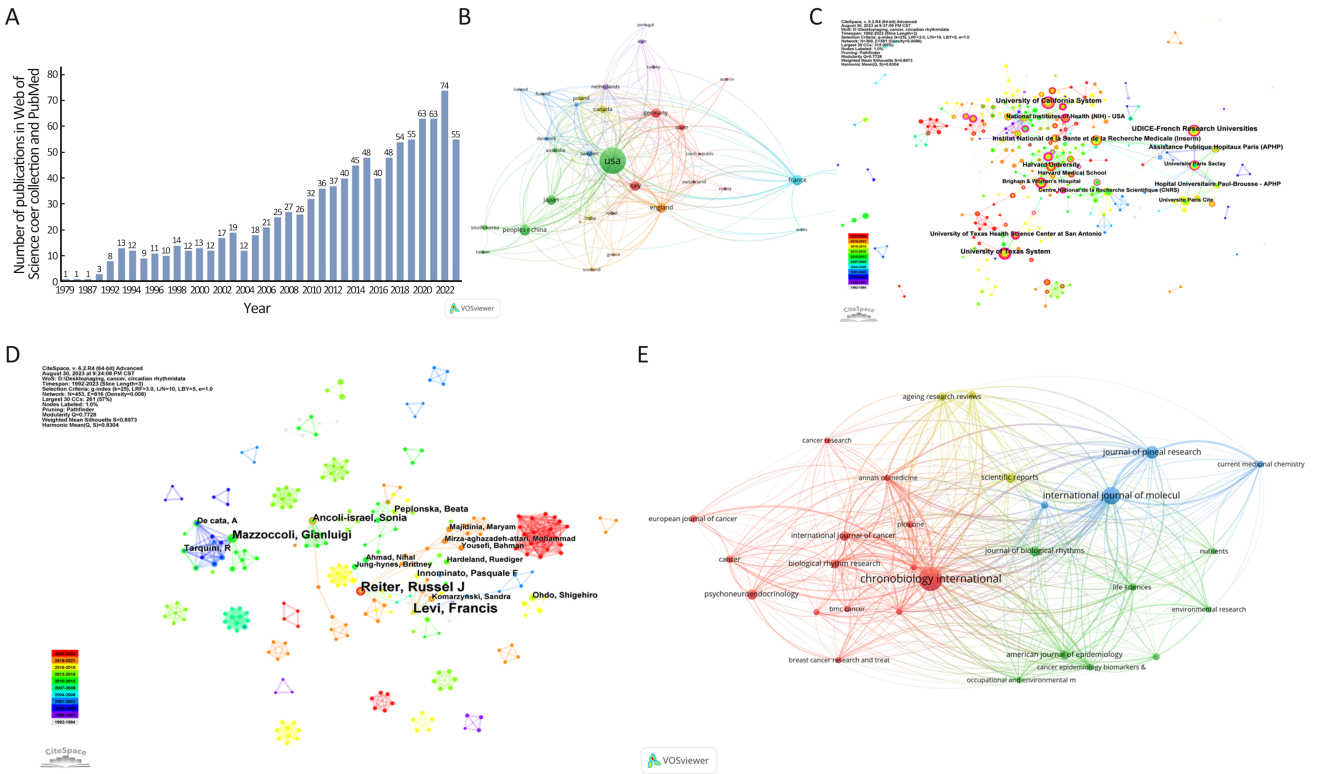

Figure 1 Publication landscape. (A) Column plot showing the number of studies published by year; (B) Country collaboration network; (C) Institution collaboration network; (D) Researcher collaboration network; (E) Co-occurrence map of journals.

Table 1 Top ten publication journals, cited-institutions and cited-authors

Rank	Top ten journals			Top ten institutions		Top nine authors	
	Journal name	Publications	IF	Institution	Publications	Author	Publications
1	Chronobiology International	47	2.8	University of California System	57	Reiter, Russel J	27
2	International Journal of Molecular Sciences	28	5.6	UDICE-French Research Universities	52	Levi, Francis	26
3	Journal of Pineal Research	17	10.3	University of Texas System	48	Mazzoccoli, Gianluigi	15
4	Journal of Biological Rhythms	11	3.5	Institut National de la Sante et de la Recherche Medicale (Inserm)	42	Ancoli-israel, Sonia	10
5	Psychoneuroendocrinology	11	3.7	Harvard University	38	Innominato, Pasquale F	7
6	Scientific Reports	11	4.6	Assistance Publique Hopitaux Paris (APHP)	37	Tarquini, R	7
7	International Journal of Cancer	10	6.4	Hopital Universitaire Paul-Brousse - APHP	32	Peplonska, Beata	7
8	American Journal of Epidemiology	9	5.0	National Institutes of Health (NIH) - USA	30	Ohdo, Shigehiro	6
9	Biological Rhythm Research	9	1.1	University of Texas Health Science Center at San Antonio	30	De cata, A	6
10	Ageing Research Reviews	8	13.1	Harvard Medical School	28	–	–

IF, impact factor.

metabolic rhythms, and immune function, while Ohdo, Shigehiro concentrated to the strategy influenced by the clock gene expression; 3) sleep and metabolism. Reiter, Russel J focused on the mechanism of melatonin in endocrinology and metabolism and its impact on the field of neuroscience, while Ancoli-israel, Sonia focused on the relationship between sleep and aging; and 4) night shiftwork and tumor or metabolism. Peplonska, Beata studied the effects of night shiftwork on cancer, nutrition, and endocrine metabolism in nurses. The top journals published studies in this topic are Chronobiology International [impact factor (IF) 2.8], International Journal of Molecular Sciences (IF 5.6) and Journal of Pineal Research (IF 10.3) and so on (*Figure 1E*, *Table 1*).

Research hotspots and trends

Keywords co-occurrence network showed the keywords about this topic in last three decades (*Figure 2A*). Keyworks with high frequency are circadian rhythm, aging, breast cancer, oxidative stress, gene expression, melatonin, colorectal cancer, prostate cancer and metastatic colorectal cancer, indicating that current researchers in this topic mainly focus on the influence of oxidative stress, gene expression or melatonin on the above cancers, especially for breast cancer. Additionally, most keywords occurred in recent years which was consistent with the publication trends. Based on the keywords co-occurrence, we conducted keywords cluster analysis (*Figure 2B*). Nuclear factor (NF) kappa B, cell cycle and calorie restriction (CR) are the research focus in recent years. Each cluster is composed of several closely related words. The smaller the clustering number is, the more keywords the cluster contains (*Table 2*). According to the results of publication trends, we conducted keyword evolving network analysis under different cluster subjects in three stages, namely from 1979 to 1992 (*Figure 2C*), from 1993 to 2004 (*Figure 2D*) and from 2005 to 2023 (*Figure 2E*). Moreover, keywords burst analysis also could help us know the research hotspots and their evolution in this field (*Figure 2F*). Notably, oxidative stress is the recent research hotspot in this topic, indicating that its related pathways might play an important role in aging, circadian rhythm and cancers.

Discussion

In this study, we used thorough search criteria and rigorous reviews to obtain a total of 976 literature sources from the PubMed and Web of Science databases, spanning from 1979 to 2023. Over the years, substantial investigation and progress have been made within the realm of aging, circadian rhythms, and their association with cancers. Overall, there is a rising trend in the publication volume regarding aging and circadian rhythms in the field of cancer. This trend can be roughly divided into three periods: a period of neglect (1979 to 1992), a period of stable growth (1993 to 2004), and a period of rapid expansion (2005 to 2022). From 1979 to 1992, the low annual publication count suggests that researchers were neglecting this field. This may have been due to the fact that the mechanisms of biological rhythms were not yet fully elucidated at that time, and research on aging was also in its early stages. Consequently, it was challenging for researchers to establish a mechanistic connection between aging and biological rhythms during this period. After 1992, the number of publications per year has been experiencing rapid growth, reflecting a continuous increase in researchers' attention to this field. In 2017, the Nobel Prize in Physiology or Medicine was jointly conferred upon Jeffrey Hall, Michael Rosbash, and Michael Young in recognition of their collective efforts in elucidating the fundamental mechanism underpinning the circadian rhythms (12). This further promoted research on aging and circadian rhythms in tumors, reaching its peak in 2022. Furthermore, we conducted an analysis of the countries and institutions that made the most significant contributions to the topic, revealing that the USA is the leading contributor in this field. Among the top 10 institutions with the highest publication volume, six of them are from USA, which indicates their significant role in the development of this field.

For keywords co-occurrence network analysis, we found that the most frequently occurring keywords include circadian rhythm, aging, breast cancer, oxidative stress, gene expression (such as *NF-κB*), cell cycle, melatonin, colorectal cancer, prostate cancer and metastatic colorectal cancer. These frequent keywords signify that contemporary researchers primarily emphasize the impact of oxidative stress, gene expression, or melatonin on the above cancer types, with a notable emphasis on breast cancer. Aging is driven by hallmarks consisting of genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis (13). Recently, Cellular Senescence Network (SenNet)

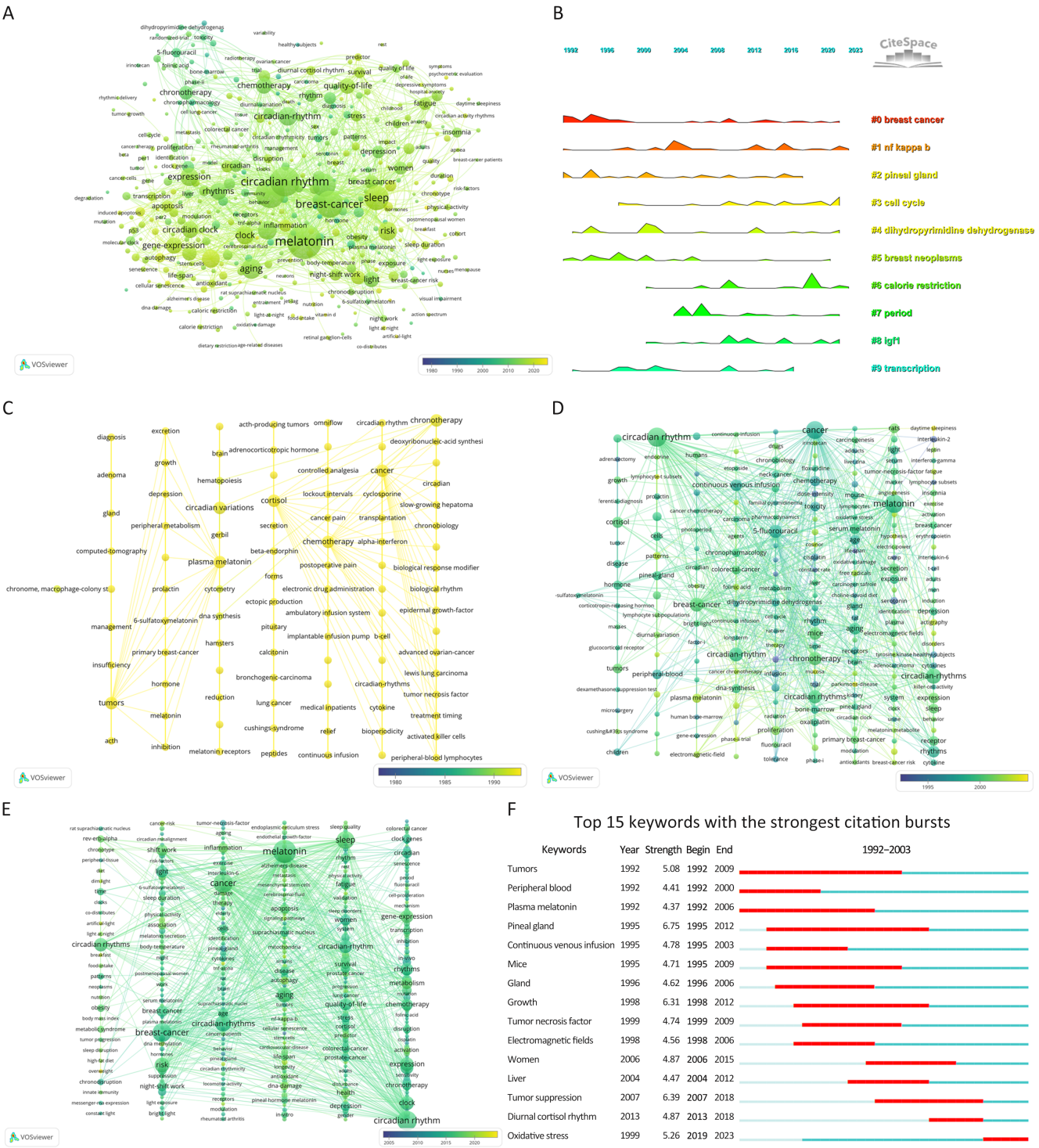

Figure 2 Research hotspots and trends. (A) Keywords co-occurrence network (1979 −2023); (B) Sierra figure showing keywords cluster; (C) Keywords evolving network analysis (1979−1992); (D) Keywords evolving network analysis (1993−2004); (E) Keywords evolving network analysis (2005−2023); (F) Keywords burst analysis.

Consortium provided nine hallmarks of cellular senescence which included cell cycle arrest, senescence-associated secretory phenotype (SASP), nuclear changes, cell surface markers, changes in cell morphology, increased lysosomal

Table 2 Cluster details of keywords

Cluster ID	Cluster size	Silhouette	Median (year)	Cluster name	LLR (top three keywords)
0#	38	0.915	2001	Breast cancer	Breast cancer, circadian rhythms, mortality
1#	38	0.897	2009	NF-κB	NF-κB, aging, safety
2#	30	0.874	2003	Pineal gland	Pineal gland, hormone, DNA
3#	30	0.863	2014	Cell cycle	Cell cycle, cellular senescence, cancer risk factors
4#	28	0.890	2004	Dihydropyrimidine dehydrogenase	Dihydropyrimidine dehydrogenase, 5-fluorouracil, pharmacokinetics
5#	28	0.896	1999	Breast neoplasms	Breast neoplasms, electromagnetic fields, night work
6#	27	0.856	2015	Calorie restriction	Calorie restriction, night-shift work, aryl hydrocarbon receptor
7#	26	0.932	2008	Period	Period, bone formation, genes
8#	26	0.897	2012	IGF1	IGF1, GH, actigraphy
9#	24	0.768	2004	Transcription	Transcription, liver, *in vivo*

LLR, log-likelihood rate; IGF1, insulin-like growth factor 1; GH, growth hormone.

content, metabolic adaptations, the DNA damage response, and upregulation of anti-apoptotic pathways (14). The hallmarks and key words co-occurrence network analysis results reflected the research process, hotspots, and directions of aging and circadian rhythm in cancer. At initiation (1992), researchers just realized that aging represented a foremost risk factor across various cancer types, correlating with an elevated incidence of cancer that typically reaches its peak around the age of 85 years (4,15). Thus, they focused on key words "tumors". Similar to aging (1992), researchers who observed that disruptions in circadian rhythms, such as shift work, influence tumor development have employed methods like measuring peripheral blood and plasma melatonin to assess circadian rhythms (16). Over time (1995), with the expansion of research methods, understanding of circadian rhythms has deepened, leading to the increasing prominence of keywords such as "pineal gland", "glandular tissue", and "mice" in the cancer literature. Subsequently, researchers began exploring specific regulatory mechanisms, leading to the emergence of more contemporary keywords such as "cell cycle", "proliferation", "insulin-like growth factor 1", and "tumor necrosis factor (TNF)" in the cancer literature. These results correspond to the hallmarks of aging and senescent cells, including cell cycle arrest, chronic inflammation, stem cell exhaustion, mitochondrial dysfunction, altered intercellular communication, SASP, and changes in cell morphology, which promoted cancer research. For instance, senescence is typically characterized by cell cycle arrest, elevated expression of certain genes (such as *P16*, *P21*, and *P53*), affecting tumor development and progression (17). SASP contained regulatory cytokines (including TNFs) involved in tumor progression and treatment efficiency (17,18). In addition, these keywords also reflect the research progress on circadian rhythms in cancer. For instance, circadian rhythm gene *RORα* could affect tumor progression by influencing the NF-κB-derived cholesterol metabolism of CD8+ T cells (19). Chromosomal instability regulated the cGAS-STING pathway and the non-canonical NF-κB pathway in cancer cells by activating the interleukin (IL)-6/signal transducer and activator of transcription pathway, affecting the progression of cancer (20). Interestingly, oxidative stress-derived senescent breast epithelial cells would affect the efficacy of doxorubicin through the modulation of the NF-κB/IL-8 pathway (21). The components of SASP have a lot common with chronic inflammation, which has highly correlation with oxidative stress in cancers through activating transcription factors such as NF-κB, and P53 (22). This evidence indicates that research on the interrelationship between aging and circadian rhythms, and their roles in cancer, has progressed from simple phenotypic observations to explorations at the mechanistic level. Based on these findings, research has intensified. Some studies continue to delve into the mechanisms and regulatory networks affecting aging and circadian rhythms in tumors (mentioned by keywords "liver", "diurnal cortisol rhythm", and "women"), while others have begun manipulating aging and circadian rhythms to influence tumor biology (mentioned by keywords "tumor suppression").

Cellular senescence contains heterogeneity: different

cells, organs, sex, and senescent stages exhibited various senescent biomarkers (23,24). Similarly, circadian rhythm also influences various pivotal cellular processes, including but not limited to nutrient metabolism, redox regulation, autophagy, and DNA damage repair and so on (25). Therefore, current research further explores the mechanisms and regulatory networks affecting aging and circadian rhythms in cancer from multiple perspectives. Of these, CR has been identified as a recent hotpot. Research group from Shogo Sato and Guiomar Solanas unveil that although core clock machinery remained robustly oscillatory in aged stem cells and liver cells, tissue-specific rewiring of rhythmic transcriptomes is related to aging and more importantly, they found that CR can prevent this age-related rewiring and restore diurnal timing homeostasis (26). Liver-specific rhythmic pathways include nicotinamide adenine dinucleotide metabolism/biosynthesis, protein acetylation and chromatin modification and CR restores homeostatic function (inflammation and DNA damage for aged epidermal stem cells and inflammation and inefficient autophagy for aged muscle stem cells, respectively) and response to oxidative stress (27). Importantly, global protein acetylation is also seen in histone marks, indicating a clear connection between this and how CR activates the genes responsible for metabolic rhythm (27). Sirtuins, which target histones or non-histone proteins and are nicotinamide adenine dinucleotide+-dependent histone deacetylases, are hypothesized to be involved in the interaction between circadian rhythms and aging (28). Overall, we suppose that current findings indicate a potentially vital role of oxidative stress-energy metabolism in aging and circadian rhythm in cancers (29).

Aging is a multifaceted phenomenon marked by the deceleration or modification of cellular and physiological processes as time progresses. This leads to a diminished cellular function, heightened vulnerability to diseases, and ultimately culminates in the organism's death (6,30). Furthermore, keywords burst analysis also showed that oxidative stress is the recent research hotspot in this topic. It has been proven that oxidative stress plays an important role in the mechanism of aging (31). One of senescent cell hallmarks is metabolic adaptations which mainly include mitochondrial dysfunction-induced oxidative stress (14,32). Oxidative stress is an imbalanced condition which pertains to the physiological and pathological reactions of cells and tissues within the organism in response to the generation of reactive oxygen species and reactive nitrogen species (33). It arises when the organism encounters detrimental stimuli from both its internal and external surroundings and when the production rate of oxygen radicals surpasses the body's capacity to eliminate them through its antioxidant mechanisms, resulting in the accrual of a substantial quantity of oxygen radicals and consequently the initiation of oxidative stress (17,34). In our recent work, we discussed the complex interactions between oxidative stress and senescence in cancer (17). Senescence induced by oxidative stress could prevent tumorigenesis, while SASP promoted cancer occurrence (35). Furthermore, oxidative stress-derived cancer cell senescence would result in drug resistance, while inhibiting the senescence could recover this kind of resistance (36). These results indicated that oxidative stress-derived senescence significantly affected carcinogenesis and cancer progression, and treatment efficiency. In addition, there is a close relationship between circadian rhythm and oxidative stress (37). A study examined the effects of H2O2-induced oxidative stress on Drosophila melanogaster at various time intervals within a 24-h cycle. Their investigation revealed a noteworthy disparity in mortality rates between flies treated during the daytime compared to those treated during the nighttime. However, they found that flies lacking the protein PER did not show a difference in mortality between daytime and night-time exposure to H2O2, which directly proved that these effects were related to the circadian rhythm (38). In tumor, many antioxidants and protective enzymes involved in preventing oxidative stress have been found to exhibit diurnal rhythmicity, with their expression levels showing abnormal expression compared to a healthy state. For example, researchers have explored the relationship between differences in antioxidant and protective enzyme levels and circadian rhythms in rats with and without breast tumors. They found that compared to the control group, rats in the tumor group exhibited delayed peak times in the levels of superoxide dismutase, catalase from *micrococcus lysodeikticus*, glutathione peroxidase 4, and lipid peroxidation in their blood. Additionally, the average level of lipid peroxidation increased, while the activities of superoxide dismutase, catalase from *micrococcus lysodeikticus*, glutathione peroxidase 4 decreased. This suggests a correlation between decreased antioxidant levels and increased lipid peroxidation in the process of breast cancer development in rats (39). In another our work, we discussed the function of circadian rhythms in tumor microenvironment (40). Of these, we found that circadian rhythm genes influenced the efficacy of anti-tumor drugs by modulating oxidative stress levels (41). This series of

studies show that circadian rhythm disruption and aging might lead to tumor occurrence and development through oxidative stress-related signal pathways, thus indicating the important role of oxidative stress in tumor research in the future. For instance, we might target the process of oxidative stress to reverse aging or resume circadian rhythm to enhance anti-tumor effect with or without other therapeutics. Moreover, exogenous melatonin increased 30-d lifespan and decreased oxidative stress and inflammation in all examined animal tissues and melatonin is also said to have anti-aging effects and to alter immunological responses (42). Based above results, we may get two suggestions: 1) oxidative stress maybe a key connection point between senescence and circadian rhythms in cancer, which worth to further explore; and 2) our bibliometric analysis results are reliable and has significant value to provide research directions.

Bibliometric analysis provides us with the current research landscape of aging and circadian rhythm in the field pan cancer. However, it was quite difficult to analyze them with specific indicators like cancer stages, grades, types as bibliometric analysis was conducted by the special software integrating the current publications. Aging and circadian rhythms have long been associated, but the molecular mechanisms of how they interact have remained a mystery, especially for human cancers as this is our current cognition, that unknown and known demarcation line, lifelike with the demarcation line which dies equally is fuzzy. It is of high interest that whether the tissue-specific circadian reprogramming during aging can also be used to cancer treatment with or without other therapies like immunotherapy. We think that melatonin and its derivatives might set an example and warrant further research.

Conclusions

Results generated by bibliometric analysis indicate that many approaches involve in the complex interactions between aging and circadian rhythm in cancer. These established and emerging research directions guide our exploration of the regulatory mechanisms of aging and circadian rhythms in cancer and provide a reference for developing new research avenues.

Acknowledgements

This study was supported by the Chinese Scholarship Council (No. 202206240086); Zhejiang Province Public Welfare Technology Application Research Project in China (No. TGY23H160090 and No. LGF21H160029); Taizhou Science and Technology Project, Zhejiang Province (No. 20ywb12) and Program for Talents of Chongqing University Three Gorges Hospital (No. 2022YJKYXM-036).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Yin S, Zhou Z, Fu P, et al. Roles of extracellular vesicles in ageing-related chronic kidney disease: Demon or angel. Pharmacol Res 2023;193:106795.
2. Duffy JF, Zitting KM, Chinoy ED. Aging and circadian rhythms. Sleep Med Clin 2015;10:423-34.
3. Yang Y, Gao Z, Huang A, et al. Epidemiology and early screening strategies for colorectal cancer in China. Chin J Cancer Res 2023;35:606-17.
4. Xu H, Xu B. Breast cancer: Epidemiology, risk factors and screening. Chin J Cancer Res 2023;35:565-83.
5. Feng D, Li D, Shi X, et al. A gene prognostic index from cellular senescence predicting metastasis and radioresistance for prostate cancer. J Transl Med 2022;20:252.
6. Chen W, Wang Y, Zheng J, et al. Characterization of cellular senescence in radiation ulcers and therapeutic effects of mesenchymal stem cell-derived conditioned medium. Burns Trauma 2023;11:tkad001.
7. Feng D, Xiong Q, Zhang F, et al. Identification of a novel nomogram to predict progression based on the circadian clock and insights into the tumor immune microenvironment in prostate cancer. Front Immunol 2022;13:777724.
8. Mattis J, Sehgal A. Circadian rhythms, sleep, and disorders of aging. Trends Endocrinol Metab 2016; 27:192-203.
9. Blacher E, Tsai C, Litichevskiy L, et al. Aging disrupts circadian gene regulation and function in macrophages. Nat Immunol 2022;23:229-36.
10. Synnestvedt MB, Chen C, Holmes JH. CiteSpace II: visualization and knowledge discovery in bibliographic databases. AMIA Annu Symp Proc 2005;

2005:724-8.
11. van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics 2010;84:523-38.
12. Burki T. Nobel Prize awarded for discoveries in circadian rhythm. Lancet 2017;390:e25.
13. López-Otín C, Blasco MA, Partridge L, et al. Hallmarks of aging: An expanding universe. Cell 2023;186:243-78.
14. Suryadevara V, Hudgins AD, Rajesh A, et al. SenNet recommendations for detecting senescent cells in different tissues. Nat Rev Mol Cell Biol 2024. [Epub ahead of print]
15. López-Otín C, Pietrocola F, Roiz-Valle D, et al. Meta-hallmarks of aging and cancer. Cell Metab 2023;35:12-35.
16. Savvidis C, Koutsilieris M. Circadian rhythm disruption in cancer biology. Mol Med 2012;18: 1249-60.
17. Li D, Yu Q, Wu R, et al. Interactions between oxidative stress and senescence in cancer: Mechanisms, therapeutic implications, and future perspectives. Redox Biol 2024;73:103208.
18. Farfariello V, Gordienko DV, Mesilmany L, et al. TRPC3 shapes the ER-mitochondria Ca^{2+} transfer characterizing tumour-promoting senescence. Nat Commun 2022;13:956.
19. Lee IK, Song H, Kim H, et al. RORα regulates cholesterol metabolism of CD8+ T cells for anticancer immunity. Cancers (Basel) 2020;12:1733.
20. Hong C, Schubert M, Tijhuis AE, et al. cGAS-STING drives the IL-6-dependent survival of chromosomally instable cancers. Nature 2022;607: 366-73.
21. Hou J, Yun Y, Cui C, et al. Ginsenoside Rh2 mitigates doxorubicin-induced cardiotoxicity by inhibiting apoptotic and inflammatory damage and weakening pathological remodelling in breast cancer-bearing mice. Cell Prolif 2022;55:e13246.
22. Reuter S, Gupta SC, Chaturvedi MM, et al. Oxidative stress, inflammation, and cancer: how are they linked. Free Radic Biol Med 2010;49:1603-16.
23. Wang J, Wei J, Inuzuka H. Aging and cancer hallmarks as therapeutic targets. Acta Materia Medica 2023;2:281-4.
24. Vickridge E, Faraco CCF, Nepveu A. Base excision repair accessory factors in senescence avoidance and resistance to treatments. Cancer Drug Resist 2022; 5:703-20.
25. Kettner NM, Katchy CA, Fu L. Circadian gene variants in cancer. Ann Med 2014;46:208-20.
26. Sato S, Solanas G, Peixoto FO, et al. Circadian reprogramming in the liver identifies metabolic pathways of aging. Cell 2017;170:664-77.e11.
27. Hatanaka F, Ocampo A, Izpisua Belmonte JC. Keeping the rhythm while changing the lyrics: Circadian biology in aging. Cell 2017;170:599-600.
28. Masri S, Sassone-Corsi P. Sirtuins and the circadian clock: bridging chromatin and metabolism. Sci Signal 2014;7:re6.
29. Feng D, Shi X, Zhang F, et al. Energy metabolism-related gene prognostic index predicts biochemical recurrence for patients with prostate cancer undergoing radical prostatectomy. Front Immunol 2022;13:839362.
30. Jia Z, Ren Z, Ye D, et al. Immune-ageing evaluation of peripheral T and NK lymphocyte subsets in Chinese healthy adults. Phenomics 2023;3:360-74.
31. Gao H, Nepovimova E, Heger Z, et al. Role of hypoxia in cellular senescence. Pharmacol Res 2023; 194:106841.
32. Liu F, Yuan L, Li L, et al. S-sulfhydration of SIRT3 combats BMSC senescence and ameliorates osteoporosis via stabilizing heterochromatic and mitochondrial homeostasis. Pharmacol Res 2023;192:106788.
33. Peng H, Yao F, Zhao J, et al. Unraveling mitochondria-targeting reactive oxygen species modulation and their implementations in cancer therapy by nanomaterials. Exploration (Beijing) 2023;3:20220115.
34. Ma J, Dong S, Lu H, et al. The hydrogen storage nanomaterial MgH2 improves irradiation-induced male fertility impairment by suppressing oxidative stress. Biomater Res 2022;26:20.
35. Liu RF, Hu L, Wu JN, et al. Changes in tumor suppressors and inflammatory responses during hydrogen peroxide-induced senescence in rat fibroblasts. Free Radic Res 2022;56:77-89.
36. Hou J, Yun Y, Xue J, et al. Doxorubicin-induced normal breast epithelial cellular aging and its related breast cancer growth through mitochondrial

autophagy and oxidative stress mitigated by ginsenoside Rh2. Phytother Res 2020;34:1659-69.
37. Wilking M, Ndiaye M, Mukhtar H, et al. Circadian rhythm connections to oxidative stress: implications for human health. Antioxid Redox Signal 2013;19:192-208.
38. Krishnan N, Davis AJ, Giebultowicz JM. Circadian regulation of response to oxidative stress in Drosophila melanogaster. Biochem Biophys Res Commun 2008;374:299-303.
39. Kolanjiappan K, Manoharan S. Diurnal rhythmicity of thiobarbituric acid reactive substances and antioxidants in experimental mammary carcinogenesis. Exp Oncol 2005;27:298-302.
40. Li D, Yu Q, Wu R, et al. Chronobiology of the tumor microenvironment: Implications for therapeutic strategies and circadian-based interventions. Aging Dis 2024. [Epub ahead of print]
41. Katamune C, Koyanagi S, Hashikawa KI, et al. Mutation of the gene encoding the circadian clock component PERIOD2 in oncogenic cells confers chemoresistance by up-regulating the *Aldh3a1* gene. J Biol Chem 2019;294:547-58.
42. Zetner D, Andersen LP, Rosenberg J. Melatonin as protection against radiation injury: A systematic review. Drug Res (Stuttg) 2016;66:281-96.

Cite this article as: Feng D, Xiao Y, Wang J, Wu R, Tuo Z, Yoo KH, Wei W, Wusiman D, Wang Z, Li D, Yang Y, Cho WC, Ke M. Unraveling links between aging, circadian rhythm and cancer: Insights from evidence-based analysis. Chin J Cancer Res 2024;36(3):341-350. doi: 10.21147/j.issn.1000-9604.2024.03.09

Supplementary materials

Research category

Pubmed

1. ("Aging"[Mesh]) OR (((Senescence[Title/Abstract]) OR (Biological Aging[Title/Abstract])) OR (Aging, Biological [Title/Abstract]))
2. ("Neoplasms"[Mesh]) OR (((Tumor[Title/Abstract]) OR (Neoplasm[Title/Abstract]) OR (Tumors[Title/Abstract]) OR (Neoplasia[Title/Abstract]) OR (Neoplasias[Title/Abstract]) OR (Cancer[Title/Abstract]) OR (Cancers[Title/Abstract]) OR (Malignant Neoplasm[Title/Abstract]) OR (Malignancy[Title/Abstract]) OR (Malignancies[Title/Abstract]) OR (Malignant Neoplasms[Title/Abstract]) OR (Neoplasm, Malignant[Title/Abstract]) OR (Neoplasms, Malignant[Title/Abstract]) OR (Benign Neoplasms[Title/Abstract]) OR (Benign Neoplasm[Title/Abstract]) OR (Neoplasms, Benign[Title/Abstract]) OR (Neoplasm, Benign[Title/Abstract])))
3. ("Circadian Rhythm"[Mesh]) OR ((((((((((((((((((((Circadian Rhythms[Title/Abstract]) OR (Rhythm, Circadian[Title/Abstract])) OR (Rhythms, Circadian[Title/Abstract])) OR (Twenty-Four Hour Rhythm[Title/Abstract])) OR (Rhythm, Twenty-Four Hour[Title/Abstract])) OR (Rhythms, Twenty-Four Hour[Title/Abstract])) OR (Twenty Four Hour Rhythm[Title/Abstract])) OR (Twenty-Four Hour Rhythms[Title/Abstract])) OR (Nyctohemeral Rhythm[Title/Abstract])) OR (Nyctohemeral Rhythms[Title/Abstract])) OR (Rhythm, Nyctohemeral[Title/Abstract])) OR (Rhythms, Nyctohemeral[Title/Abstract])) OR (Nycthemeral Rhythm[Title/Abstract])) OR (Nycthemeral Rhythms[Title/Abstract])) OR (Rhythm, Nycthemeral[Title/Abstract])) OR (Rhythms, Nycthemeral[Title/Abstract])) OR (Diurnal Rhythm[Title/Abstract])) OR (Diurnal Rhythms[Title/Abstract])) OR (Rhythm, Diurnal[Title/Abstract])) OR (Rhythms, Diurnal[Title/Abstract]))
4. 1 and 2 and 3. 142 records

Web of Science

1. (TS=Senescence) OR (TS=Senility) OR (TS=Aging) OR (TS=Age*) OR (TS=Dotage) OR (TS=Apolexis)
2. (TS=Tumor*) OR (TS=Neoplas*) OR (TS=Cancer*)
3. (TS=Circadian Rhythm*) OR (TS=Nyctohemeral rhythm*) OR (TS=Diurnal rhythm*) OR (TS=Day-night rhythm*) OR (TS=Twenty Four Hour rhythm*)
4. 1 and 2 and 3, language was set as English, 917 records.