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Original Research Article

Systems Biology and Epidemiology in Cancer Medicine

Cancer Systems Biology and Epidemiology: Target Identification, Combination Therapy, and Personalized Treatment in Cancer Medicine.

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Abstract: Cancer signaling networks are complex, involving gene regulation, signaling, and cell metabolism. Alterations in these networks caused by different mutations can lead to malignancy. We aim to evaluate these networks' computational models that allow us to understand their complex behavior better. This study aims to validate the correlation between cancer signaling pathways' complexity (clustering coefficient) and cancer epidemiological data sets, including cancer incidence, death rate, and lifetime risk. These results support the hypothesis that network complexity directly indicates cancer risk. Understanding the differential behavior of regulatory networks during health, disease, and in response to drugs is crucial for enhancing drug development efforts, identifying new targets, delineating off-target effects, predicting disease, developing combinatorial drug regimens, and developing personalized treatments targeted at the molecular level.

Keywords: Cancer Epidemiology; clustering coefficient; Betweenness centrality; Combinatorial Drug Therapy; Personalized Medicine; Network biology

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1. INTRODUCTION

Cancer continues to be a major global health threat, significantly impacting individuals, families, and healthcare systems worldwide[1]. In 2020, cancer was responsible for an estimated 9.9 million deaths globally, making it the second leading cause of death after cardiovascular diseases[2]. While the overall cancer mortality rate has been declining in recent years, the incidence of cancer is still on the rise due to factors such as population growth, aging, and changes in lifestyle and environmental factors[3]. The World Health Organization (WHO) estimates that cancer incidence will continue to increase by approximately 50% by 2040[4]. Moreover, the burden of cancer is not distributed evenly around the world, with low- and middle-income countries facing the highest cancer mortality rates. According to WHO, over 70% of cancer deaths occur in these countries, where access to cancer prevention, diagnosis, and treatment is often limited[5]. Efforts are ongoing to reduce the impact of cancer through various measures, including cancer prevention, early detection, and improved treatments. Surgery, radiation therapy, and chemotherapy have been the cornerstone of cancer treatment for many years and have played a crucial role in improving survival rates and reducing symptoms for many cancer patients[6]. However, while these therapies can be effective, they also have side effects that impact a patient's quality of life. Moreover, despite significant progress in cancer research, mortality rates for many major types of cancer have remained largely unchanged over the past few decades[7]. It underscores the need for innovative new cancer treatment approaches, including targeted therapies that selectively attack cancer cells while leaving healthy cells unharmed[8].One promising area of research in this field is molecularly targeted therapy, which aims to identify and target specific molecular pathways involved in the growth and spread of cancer cells[9]. By targeting these pathways, researchers hope to develop more effective and less toxic treatments for various cancers[10].Recent advances in genomics and other molecular technologies have made it possible to identify a growing number of potential targets for molecularly targeted therapies, and several such therapies have already been approved for use in cancer patients. These include drugs that target specific genes or proteins that are known to be involved in cancer development, as well as immunotherapies that stimulate the immune system to attack cancer cells[11].In addition, many researchers are also exploring the use of combination therapies that combine targeted therapies or traditional therapies like surgery and radiation[12]. These combination therapies can potentially enhance the effectiveness of cancer treatments while minimizing the risk of adverse effects[13].Overall, while traditional cancer therapies like surgery, radiation, and chemotherapy remain important tools in the fight against cancer, the growing emphasis on molecularly targeted therapies and combination therapies is a promising development that offers new hope to patients and their families[14]. With ongoing research and innovation, we may continue to make significant strides in treating cancer in the future.In recent years, molecularly targeted therapy has emerged as a newer and more precise approach to cancer treatment[15]. Unlike standard methods such as surgery, radiation, and chemotherapy, targeted therapy inhibits crucial cancer signaling pathways while causing minimal damage to normal cells[16]. Small-molecule drugs like Gleevec® (imatinibmesylate), Iressa® (gefitinib), and Sutent® (sunitinib) have shown success in inhibiting specific tyrosine kinases and receptors involved in cancer cell growth[17].Another class of substances used in targeted therapy is antibody drugs, such as Avastin® (bevacizumab) and Erbitux® (Cetuximab), which are designed to seek out and lock onto specific molecules involved in cancer cell growth to facilitate their destruction[18]. While these drugs may not affect the body's normal functions to the extent of standard chemotherapy, they can still cause side effects[19]. For example, angiogenesis inhibitors like Nexavar® (sorafenib), Sutent® (sunitinib), and Votrient® (pazopanib) interfere with the formation of new blood vessels, which can lead to problems with bruising and bleeding of blood vessels[20].Despite the potential side effects, targeted therapy has shown promising results in treating certain types of cancer. For example, in 2020, the FDA approved a targeted therapy drug called Retevmo® (selpercatinib) for treating certain lung and thyroid cancers[21]. In addition, a study published in Nature in 2021 found that targeted therapy with a combination of drugs, including a VEGFR inhibitor, could effectively treat a subset of patients with advanced renal cell carcinoma.Overall, targeted therapy represents a growing part of many cancer treatment regimens, with ongoing research focused on developing new and more effective drugs for cancer treatment[22].Cancer is a complex systems biology disease involving dysregulation of multiple signaling pathways[23]. The development and progression of cancer involve complex interactions between various cancer signaling pathways, which translate external signals into biological responses such as cell growth, differentiation, or apoptosis[24]. Dysregulation of these signaling pathways can lead to the acquisition of growth factor independence by cancer cells[25].Understanding the cancer signaling pathways and their role during carcinogenesis and cancer progression is critical in developing targeted therapies. For example, immunotherapy drugs like pembrolizumab, nivolumab, and ipilimumab target the immune checkpoint proteins that prevent T cells from recognizing and attacking cancer cells[26].Recent studies have identified new cancer signaling pathways and potential targets for treatment[27]. For instance, recent research has focused on the potential therapeutic benefits of targeting the Hippo signaling pathway, which regulates cell growth and proliferation. The Hippo pathway is dysregulated in many types of cancer, including breast, liver, and lung cancer, and targeting this pathway may provide a new avenue for cancer treatment. Understanding these pathways is critical for developing more effective cancer therapies, including targeted therapies like immunotherapy, and identifying new pathways and targets for treatment[28].This study aimed to explore the relationship between cancer signaling network complexity and cancer epidemiological data sets. The present study analyzed molecular pathways for various cancer sites and computed network metrics, such as betweenness centrality and clustering coefficient. The study's findings suggest a correlation between the clustering coefficient metric, which indicates the complexity of the network, and cancer epidemiological data sets. It was observed that cancer networks with higher levels of complexity were linked with an elevated risk of cancer.

2. MATERIALS AND METHODS

2.1 Dataset collection

To correlate the investigation between molecular cancer pathways and epidemiological data, the study focused on cancers for which detailed molecular pathways are available in public pathway databases such as BioCyc, Reactome,

BioGRID, BioCarta, KEGG, human signaling network, Pathway Interaction Database, and Biological-Networks. These databases contain literature-based, computationally predicted metabolic pathways or data from other databases such as NCBI, Ensembl, and UniProt. Only cancers with available pathway datasets in these public databases were selected for the study. In addition, the study accessed the Surveillance Epidemiology and End Results (SEER) Program database to obtain cancer statistics, a resource for epidemiological data compiled by the National Cancer Institute. The cancer incidence, mortality, and lifetime risk data were gathered only for the cancer sites selected for the study.

2.2 Network Assessment and Analysis

The software cytoscape3.0.1 did network assessment and network metrics analysis. The clustering coefficient (a measure of complexity) and betweenness centrality (a measure of the extent that a node lies on the paths between other nodes) are statistical parameters used in correlation analysis with epidemiological data sets[29].The expression gives the betweenness centrality of a node $\boldsymbol{v}$:

$$g(v) = \sum_{s \neq v \neq t} \frac{\sigma_{st}(v)}{\sigma_{st}}$$

Where σ_{st} is the total number of shortest paths from node s to node t, and $\sigma_{st}(v)$ is the number of those paths that pass through v[30].The clustering coefficient is a local property that quantifies the likelihood that the neighboring nodes of a given node are interconnected.

It is determined as **Ci = 2n/[ki(ki - 1)],**

Where *ki*the node degree of the node *I* [30]

3. STATISTICAL ANALYSIS

The cancer epidemiology data sets, network statistics, and literature searches were subjected to correlation analysis, with a significance level of $p<0.05$ being used to determine statistical significance.

4. RESULTS

This research aims to investigate the relationship between the statistical metrics of a network and cancer epidemiology. The study has revealed a crucial finding: the clustering coefficient is strongly linked to cancer incidence, mortality rate, and lifetime risk of developing cancer. Furthermore, the results demonstrate that networks with higher clustering coefficients tend to be associated with greater incidence and mortality rates and an increased lifetime risk of cancer. A prime example of this relationship can be seen in small-cell lung cancer, which has the highest clustering coefficient among cancers and displays the highest incidence and mortality rates and a heightened lifetime risk of developing cancer (Table 1). This research has unveiled a significant association between network properties and cancer epidemiology, emphasizing the importance of considering network topology when exploring the dynamics of cancer spread and potential treatment strategies. The statistical analysis conducted in this study involved the calculation of correlation coefficients (r) and P values to assess the relationship between epidemiological parameters and clustering coefficients. The results are tabulated in Table 2. Additionally, the relationship between cancer incidence, death rate, and lifetime risk of cancer with a clustering coefficient was visualized using scatter plots. The scatter plot of cancer incidence against the clustering coefficient, as depicted in Figure 1, revealed that only one data point lay outside the 95% confidence band. It suggests the correlation between cancer incidence and the clustering coefficient is strong and significant. Similarly, the scatter plot of death rate versus clustering coefficient, illustrated in Figure 2, indicated that only two data points fell outside the 95% confidence band. Again, this finding supports the notion that a notable correlation exists between the death rate and the clustering coefficient. On the other hand, the scatter plot of lifetime risk versus clustering coefficient, as shown in Figure 3, indicated that all data points fell within the 95% confidence band. It suggests a robust and consistent correlation between lifetime risk and the clustering coefficient. These statistical findings indicate a high correlation between epidemiological parameters and the clustering coefficient, which cannot be attributed to random sampling. These results reinforce that the clustering coefficient is an important factor in cancer epidemiology and may help inform future cancer prevention and treatment strategies. The death rate of cancer patients is known to be impacted by multiple factors, including the quality of treatment provided and the economic status of the patients. In contrast, cancer incidence and lifetime risk are believed to be less influenced by these factors. The study confirms these findings, as the data indicates that the standard of treatment and economic status have a weaker influence on cancer incidence and lifetime risk but a more significant impact on death rates. Furthermore, the study has revealed that cancer incidence and lifetime risk exhibit a stronger correlation with network complexity when compared to the death rate. This finding emphasizes the importance of considering the network properties of cancer when exploring the underlying mechanisms that influence the development and spread of the disease. In essence, this research supports the idea that a patient's access to quality healthcare and economic status can impact their risk of dying from cancer but may have less of an impact on their likelihood of developing the disease. Additionally, the study highlights the importance of network complexity in understanding the dynamics of cancer, particularly the incidence and lifetime risk. The cancer metabolic pathways in the pathway database are based on scientific literature. As a result, there is a possibility that the extent to which a

particular type of cancer is studied may be influencing the topology and complexity of the networks that are generated. To address this possibility, the researchers conducted a thorough literature review by performing a set of PubMed and Google Scholar searches that corresponded to each cancer site of interest. The total number of citations obtained from these searches was then compared to the clustering coefficient values in Table 3. This analysis aimed to determine whether a correlation exists between the number of citations and clustering coefficient values, which could indicate a potential bias in the results.

Table 1: Cancer Epidemiological data sets

Type of cancer	Cancer incidence*	Death rate**	Lifetime Risk***	Cluster Coefficient
Lung cancer	52	35	6	0.274
Colorectal cancer	37.7	13.1	4.1	0.222
Endometrial cancer	27.8	5.1	3.1	0.2
Bladder cancer	18.7	4.2	2.3	0.199
Renal cell carcinoma	17.3	3.5	1.8	0.195
Pancreatic cancer	13.3	11.1	1.7	0.215
Glioma	6.3	4.4	0.6	0.189
Melanoma of skin	21.5	2.1	2.1	0.191
AML	4.1	2.7	0.5	0.144

Table-1. Cancer Epidemiological data sets (Cancer incidence, Death rate in cancer, and lifetime risk of cancer) and network statistics (cluster coefficient) for each of the 10 cancer sites in this study. *Cancer incidence per 100,000 men and women per year; **Death per 100,000 men and women per year; *** Lifetime Risk is the probability of developing cancer during one's lifespan. Lifetime risk may also be discussed regarding the probability of developing or dying from cancer. Based on cancer rate up to 2020.

Table 2: Correlation analysis between Network statistics (cluster coefficient of cancer network pathway) and Cancer Epidemiological data sets (Cancer incidence, Death rate in cancer, and lifetime risk of cancer)

Correlation Between	Correlation coefficient (r)	R squared	P value	Is the correlation significant?
Cancer Incidence & Cluster Coefficient	0.868	0.754	0.0024	Yes
Death rate &ClusterCofficient	0.884	0.782	0.0015	Yes
Lifetime Risk & Cluster Coefficient	0.886	0.786	0.0014	Yes

Table-2. Correlation analysis between Network statistic (cluster coefficient of cancer network pathway) and Cancer Epidemiological data sets (Cancer incidence, Death rate in cancer and life time risk of cancer).

Table 3: Total number of citations in Pubmed & Google Scholar Search

Type of cancer	Number of citations	
	PubMed	Google Scholar
Lung cancer	415,794	37,00,000
Colorectal cancer	288,516	21,80,000
Endometrial cancer	44,725	9,67,000
Bladder cancer	93,760	30,70,000
Renal cell carcinoma	62,508	21,50,000
Pancreatic cancer	132,415	26,70,000
Glioma	118,243	10,80,000
Melanoma of skin	60,785	15,50,000
AML	89,089	13,20,000

Table-3.Search terms corresponding to each of the cancer sites in the study were used to perform searches on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Google Scholar (http://*www.google.com/scholar*)using the default (nonadvanced) search type. The total number of citation results returned by each search was recorded. The searches were performed on February 17, 2023.

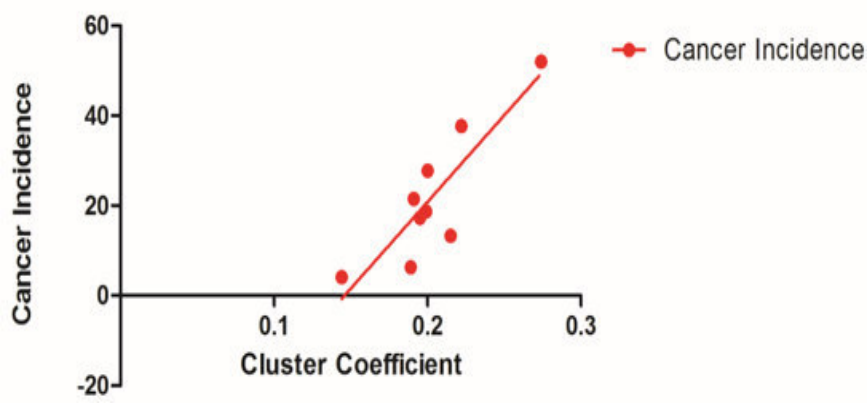

Fig 1: Scatter plot showing the correlation between cancer incidence rate and cluster coefficient Data points are shown for cancer sites in the study.

The x-axis is the incidence rate for the cancer site, and the y-axis is the clustering coefficient for the cancer site. The line is a linear regression fit, with a Correlation coefficient (r) = 0.868.

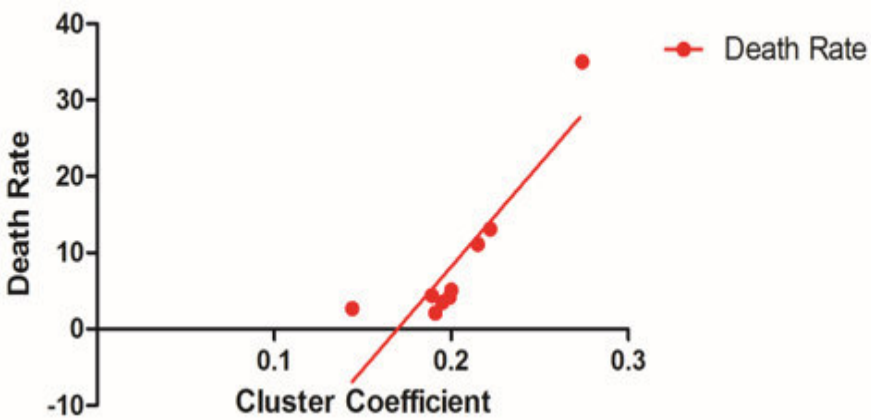

Fig 2: Scatter plot showing the correlation between death rate for cancer and cluster coefficient. Data points are shown for cancer sites in the study.

The x-axis is the death rate for the cancer site, and the y-axis is the clustering coefficient for the cancer site. The line is a linear regression fit, with a Correlation coefficient (r) = 0.884.

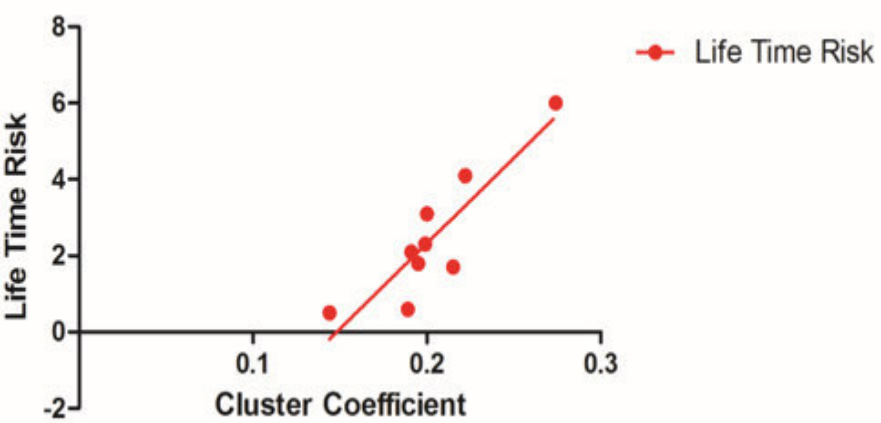

Fig 3: Scatter plot showing the correlation between lifetime risk of cancer and cluster coefficient. Data points are shown for cancer sites in the study.

The x-axis is the lifetime risk for the cancer site, and the y-axis is the clustering coefficient for the cancer site. The line is a linear regression fit, with a Correlation coefficient (r) = 0.886.

5. DISCUSSION

This analysis revealed no significant correlation between the total number of citations and the clustering coefficient values. This finding supports the notion that the extent to which a particular type of cancer has been studied is not biasing the results. In other words, the study suggests that the topologies and complexities of the analyzed metabolic networks are likely representative of the underlying biology of the respective cancer types rather than being influenced by the degree to which these cancer types have been studied in the literature. It is an important consideration when interpreting the study results, as it reinforces the idea that the network properties of cancer can provide valuable insights into the disease, which may be used to inform future research and treatment strategies. Understanding the topological characteristics of a network can provide important insights into identifying critical components that could serve as potential drug targets. By targeting these components, nonessential genes can be inhibited, while disrupting information flow between functional modules may lead to therapeutic effects with minimal toxicity[31].One topological measure that can be useful in identifying such components is betweenness centrality, which indicates the relative importance of a particular node in the overall network connectivity. Nodes with high between-ness centrality may be attractive targets for drug discovery, as targeting these nodes could significantly impact the overall network structure and function. By leveraging the insights provided by topological analysis, researchers may be able to identify new drug targets that could be used to develop effective therapies for cancer and other diseases. The betweenness centrality, in particular, can help guide drug discovery efforts by identifying key network components that may be amenable to therapeutic intervention. As such, the study of network topology and the identification of critical network components is a promising area of research that could lead to significant advances in medicine [32]. KRAS and GBR2 are among the most frequently occurring nodes in the network, which is consistent with the findings reported by Breitkreutz et al. in 2012[33]. KRAS, also known as V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog or K-ras, is a member of the Ras family of oncogenes. Mutations in the RAS genes are found in approximately 30% of human tumors, and K-ras is the most commonly mutated member of the family in adenocarcinomas of the lung[34].Given its high frequency of mutation and its importance in cancer, alterations in KRAS activity can significantly affect information processing within the protein-protein interaction network[34]. Identifying KRAS as a key node in the network highlights the potential importance of this oncogene in cancer development and progression. By targeting KRAS or other key nodes in the network, it may be possible to develop new therapies that can disrupt cancer progression and improve patient outcomes. The findings of this study add to the growing body of research on the role of KRAS and other key nodes in cancer development and progression. By better understanding the molecular mechanisms underlying cancer, researchers can develop new and more effective therapies that can improve patient outcomes and ultimately lead to a better understanding of this complex and devastating disease[35].Grb2 is an adapter protein that plays a crucial role in various cellular processes and is a vital mediator in several oncogenic signaling pathways. Its expression is elevated during carcinogenesis, leading to enhanced signaling through the MAPK pathway[36]. In addition, studies have shown that Grb2 promotes keratinocyte growth factor (KGF)-induced motility in cancer cell lines, indicating its potential as a therapeutic target for cancer therapy to prevent local invasion and metastasis of solid tumors[37]. Identifying key proteins in the molecular pathway network of cancer based on their betweenness centrality can be a powerful tool for developing new drug targets. By focusing on these critical nodes in the network, it may be possible to develop more effective therapies that can specifically target the molecular pathways involved in cancer development and progression. This approach provides a solid foundation for developing chemoprevention strategies that can help prevent the onset of cancer or slow its progression. Overall, identifying Grb2 as a potential therapeutic target for cancer therapy highlights the importance of understanding the molecular mechanisms underlying cancer development and progression. By targeting key proteins in the molecular pathway network, researchers can develop new and more effective treatments that can improve patient outcomes and ultimately lead to a better understanding of this complex disease [38]. Breitkreutz et al. (2012) found a correlation between the complexity of cancer molecular signaling networks and the 5-year survival probability of cancer patients[29b]. The 5-year survival probability is greatly affected by various factors such as economic status, standard of treatment, and advancements in cancer therapy. However, the present study focuses on the statistical analysis of cancer incidence and lifetime risk of cancer, as these parameters are less affected by this factors[39]. The study results reveal a strong correlation between the network complexity and these epidemiological parameters. The development and progression of cancer is a complex process that involves multiple signaling pathways, making it challenging to achieve desired therapeutic outcomes with a single drug[16, 40]. Therefore, there is a growing interest in the potential of combination therapies to improve cancer treatment. Combinatorial targeted chemotherapy involves using multiple drugs that target specific molecules or pathways involved in cancer development and progression to improve treatment efficacy and reduce the risk of drug resistance[41]. Combination therapies have shown promising results in preclinical and clinical studies and are an active area of research in oncology[42].Systems biology has the potential to play a critical role in identifying the most effective therapeutic targets, which can aid in discovering optimal drug combinations[42b]. Combinatorial drugs consist of multiple active components that act synergistically on various nodes of the cancer signaling network, increasing their therapeutic potential several-fold compared to single-drug targeted therapy[43]. Combinatorial therapy also helps compensate for the toxicity and improve the bioavailability of active compounds. By targeting multiple nodes of the cancer signaling network, this approach may prevent the development of resistance by cancer cells to drug therapies. Additionally, this method can be useful in developing combinatorial therapies for other diseases, such as diabetes, tuberculosis, Alzheimer's, and cardiovascular disease[44].Systems biology is a field of study that seeks to describe and comprehend the workings of complex biological systems. This approach is important because it accommodates individual human complexity and its effects on health and disease. We can move beyond the traditional "one-size-fits-all" treatment strategy and identify treatments specific to each patient[45] by employing a systematic approach. The advancements in tools and technologies in systems biology analyses have provided great opportunities to explore the emerging field of personalized medicine. This

approach holds significant promise for treating various diseases, including cancer, by allowing us to identify the most effective diagnosis and treatment for each patient. Additionally, personalized medicine has the potential to make therapeutic methods more cost-effective by reducing the need for ineffective treatments and minimizing the risk of side effects. Overall, systems biology is a powerful tool in the pursuit of personalized medicine, which has the potential to revolutionize the way we approach medical treatments[45a, 46]. Understanding how regulatory networks behave under different conditions, such as during health, disease, and drug response, can greatly improve drug development efforts. This knowledge can aid in identifying new drug targets, determining off-target effects, predicting diseases, developing combinatorial drug therapies, and providing personalized treatment options. Moreover, it could enhance drug discovery by generating testable hypotheses directly from network components and structure. By integrating information from multiple levels of biological complexity and drug-protein or drug-ligand interaction networks, regulatory networks provide a template for systems modeling drug discovery. This approach has the potential to revolutionize the drug development process by enabling the identification of more effective therapies with fewer side effects, leading to improved patient outcomes.

6. CONCLUSION

Based on the analysis of results, it has been demonstrated that there is a strong correlation between the complexity of the cancer signaling network pathway (as measured by the clustering coefficient) and various epidemiological data sets related to cancer (such as cancer incidence, death rate, and lifetime risk of cancer). This finding provides strong evidence that the complexity of network matrices can directly indicate cancer risk. Understanding the complex behavior of cancer signaling networks is crucial for providing a foundation for developing effective therapeutic strategies for cancer and other life-threatening diseases. Furthermore, by identifying the most critical nodes in these networks, researchers can develop targeted drug therapies that address specific molecular pathways dysregulated in cancer cells. It can help to improve patient outcomes and ultimately reduce the burden of cancer on society.

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8. AUTHORS CONTRIBUTION STATEMENT

Dr. Chitra Rani Chauhan and Desh Nidhi Singh designed the study and collected and analyzed the data. All authors discussed the methodology and results and equally contributed to the final manuscript.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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