Gastroenterology and Hepatology From Bed to Bench.
2024 **RIGLD**, Research Institute for Gastroenterology and Liver Diseases

REVIEW ARTICLE

p-ISSN: 2008-2258 e-ISSN: 2008-4234

The link between gluten intake and the risk of cancers

Sajjad Bakhtiari[1], Nastaran Asri[2], Sepehr Maleki[3], Saba Rahimi[1], Amirreza Jabbari[4], Alireza Ahmadzadeh[5], Somayeh Jahani-Sherafat[6], Masoumeh Farahani[7], Ehsan Nazemalhosseini Mojarad[1], Mohammad Rostami-Nejad[2]

[1]Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Celiac Disease and Gluten Related Disorders Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Department of Computer Science, University of Tabriz, Tabriz, Iran
[4]Department of Laboratory Diagnostics, Faculty of Health Sciences, University of Pecs, Hungary
[5]Proteomics Research Center, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[6]Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[7]Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ABSTRACT

Gluten is a complex mixture of hundreds of related proteins, with the two major groups being gliadin and glutenin. Gliadin primarily affects the viscosity of dough, while glutenin contributes to its strength. Nowadays, there is evidence suggesting an increase in gluten exposure due to advancements in cereal technology. Consumption of gluten can lead to development of gluten-related disorders (GRDs) in susceptible individuals. Some GRDs have been strongly associated with an increased risk of developing certain types of cancer. Colorectal cancer and lymphoma are among the most commonly reported malignancies associated with GRDs. Dietary factors, including gluten intake, have been recognized as significant modifiable risk factors for the development of digestive system cancers. The present study aimed to collect current information on the effect of gluten on the incidence of cancer in the general population and among GRDs patients. Protein-Protein Interaction (PPI) Network analysis of common genes between celiac disease (CD) and cancer was also conducted.

Keywords: Gluten-related disorders, Celiac disease, Cancer, Network.

(Please cite as: **Bakhtiari S, Asri N, Maleki S, Rahimi S, Jabbari A, Ahmadzadeh A, Jahani-Sherafat S, Farahani M, Nazemalhosseini Mojarad E, Rostami-Nejad M. The link between gluten intake and the risk of cancers. Gastroenterol Hepatol Bed Bench 2024;17(2):132-139. https://doi.org/10.22037/ghfbb.v17i2.2945).**

Introduction

Gluten, the complex protein network found in wheat flour, is composed of various components and exhibits a diverse range of sizes (1). Its composition is influenced by factors such as genotype, cultivation conditions, and technological processes (1). Gluten is commonly obtained by washing a dough made from wheat flour and water with excess water or a dilute salt solution, leaving behind the protein mass remnant (2). Gluten consists of two major protein groups known as gliadin and glutenin. These proteins reveal a unique ability to interact and form a cohesive network within the dough matrix. The intermolecular bonding between gliadin and glutenin contributes to the elasticity and viscoelastic properties of gluten, enabling it to trap gases produced during fermentation and subsequently leaven the dough. This integral structural framework is responsible for conferring desirable textural attributes to bread products, such as lightness and fluffiness (3). Gliadin mainly affects the dough's viscosity, while glutenin often contributes to its strength (1).

Received: 21 November 2023 *Accepted*: 03 February 2024
Reprint or Correspondence: **Mohammad Rostami-Nejad,** PhD, *Celiac Disease and Gluten Related Disorders Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*
E-mail: m.rostamii@gmail.com
ORCID ID: 0000-0003-2495-1831

Electrophoresis of gliadin at low pH indicated four bands, which were called α-gliadin, β-gliadin, γ-gliadin, and ω-gliadin. However, comparing their amino acid sequence showed that α- and β-gliadin often form a group called α-type gliadin. Due to the glutenin polymer's size, it was impossible to separate it by conventional electrophoresis. However, their separation by SDS-PAGE revealed two band groups: HMW and LMW. The LMW group is subdivided into a main B-type group and two minor C-type and D-type groups (4).

The current understanding of gluten consumption in the general population is limited due to insufficient information on the gluten content of food products. Estimations of gluten intake primarily rely on calculating the protein content in cereals containing gluten and utilizing available recipe information, making these estimates approximate. Nonetheless, existing reports indicate that daily gluten intake in Western populations may range from 5 to 20 grams per day. Findings from a Danish study further revealed an average intake of 10.4 grams per day among adults aged 20-75 years. Among gluten-containing foods, bread made from wheat serves as the primary source of gluten, with each slice containing approximately 4 grams. Notably, evidence suggests an increase in gluten exposure alongside advancements in cereal technology (5).

Gluten-related disorders (GRDs) refer to the term for the diseases instigated by consumption of gluten (6). Numerous variants of alpha, gamma, and omega gliadin sequences, along with glutenin, have been identified as potential contributors to the pathogenesis of GRDs. Notably, research indicates that an extensive array of gluten peptides, numbering in the hundreds, possess the capability to elicit T-cell-mediated immune responses (7). Note that the prevalence of GRDs has experienced a surge in recent times, largely attributable to shifts in dietary practices and the Westernization of consumption patterns. These disorders are classified into three distinct categories: 1) autoimmune conditions, encompassing celiac disease (CD), gluten ataxia (GA), and dermatitis herpetiformis (DH); 2) allergic conditions, exemplified by wheat allergy (WA); and 3) non-autoimmune/non-allergic conditions, such as non-celiac gluten sensitivity (NCGS) (8). Adhering to a gluten-free diet (GFD) is crucial for effectively managing the symptoms and manifestations of celiac disease as well as other gluten-related medical conditions (9).

According to reports, there is a strong association between some of GRDs and increased risk of developing certain types of cancer (10). Moreover, dietary factors have been widely recognized as significant modifiable risk factors for the development of digestive system cancers (11, 12). Thus, there has been a surge of interest in investigating the association between gluten consumption and gastrointestinal (GI) cancers. Indeed, understanding the potential preventative or susceptible role of gluten in this context holds significant importance. Accordingly, the present study aims to collect the current information pertaining to this particular correlation.

Gluten and the risk of colorectal cancer

Colorectal cancer, colloquially referred to as CRC, claims the third highest incidence rate among cancer types and stands as the fourth most prominent contributor to cancer-related mortality. Annually, an estimated cohort of one to two million individuals receive colorectal cancer diagnosis, yielding a global death toll of 700,000. Furthermore, CRC constitutes the second most prevalent cancer in females (9.2%) and the third in males (10%) when analyzing gender-specific data (13). As with other types of cancer, mutations in specific genes can trigger the development of CRC. These genetic aberrations can transpire within oncogenes, tumor suppressor genes, and genes associated with DNA repair mechanisms, ultimately fostering the development of colorectal carcinomas (14). Personal characteristics and habits, including age, medical history of chronic conditions, and lifestyle choices, exert influential roles in CRC development (15). The gut microbiota has a significant role in this process, and any imbalance in its composition, called dysbiosis, can engender colon cancer via prevalent inflammatory processes (16).

Specific dietary factors have been found to affect the likelihood of developing CRC. In pursuit of diminishing cancer risk, nutritional guidelines advocate the adoption of a plant-based regimen abundant in whole grains, while simultaneously limiting consumption of refined grains and sugary comestibles (15, 16). Indeed, a plausible hypothesis posits that dietary inclusion of whole grains engenders a reduction in the probability of CRC incidence. Numerous mechanisms underlie this potential risk reduction,

including enhanced stool bulk consequent to whole grain intake, which facilitates dilution of detrimental substances within the colon (17). Furthermore, the transit time of stool throughout the colon can be expedited through whole grain consumption, thereby minimizing exposure to toxic agents. Notably, the consumption of whole grains may elicit a beneficial impact on the gut microbiome, distinguished by augmented presence of bacteria capable of generating short-chain fatty acids (SCFAs), as well as the concomitant reduction in pro-inflammatory bacterial species. The multi-faceted composition of whole grains encompasses antioxidants which offer protection against oxidative harm targeting colon epithelial cells. Additionally, the presence of fermentable carbohydrates in whole grains enables their breakdown by gut microbial species, thereby conferring potential health benefits (18, 19).

Caroline Y.um et al. investigated the association between grain plus gluten intake and CRC risk in the Cancer Prevention Study (CPS)-II Nutrition Cohort, a large prospective study of US adults. In 1999, 50,118 men and 62,031 women participated in this study, filling out food frequency questionnaires evaluating their grain intake. Participants were asked to specify the common portion size for each whole and refined grain food, such as one slice of bread or 1 cup of cold breakfast cereal. They were then asked about their average consumption frequency of this amount over the past year. The protein amount in wheat, barley, and rye food items was multiplied by a conversion factor of 0.75 to determine the gluten content in whole and refined grain products. This conversion factor was based on the Osborne plant protein classification system and reflects the proportion of protein making up gluten. The study employed Cox proportional hazards regression to determine the multivariable-adjusted hazards ratio (HR) and 95% confidence interval (CI) of their risk of developing CRC. This study revealed that men who consume more gluten containing whole grains have a lower risk of developing colorectal cancer, especially in the rectum. This association was not found in women (20). The 2017 WCRF/AICR Continuous Update Project indicated probable evidence that consuming whole grains can reduce the risk of CRC. Based on studies, it was estimated that consuming 90 g of whole grains daily can lower the risk of CRC by 17% (21). The study suggests that gluten has a more substantial impact on the area of the colon that is closer to the small intestine, where protein digestion takes place (20, 21).

The potential beneficial effects of grains, particularly gluten as an important component, on CRC, are attributed to their ability to reduce DNA damage in colon cells caused by oxidative stress, promote the formation of tight junction proteins to preserve the intestinal barrier, and inhibit the growth of tumor cells through fermentation by gut microbes (22-24). In a study conducted by Caroline et al., the relationship between whole grain consumption, including its main components such as dietary fiber and gluten, and the composition of gut microbes was examined. This particular study, known as the Food and Microbiome Longitudinal investigation (FAMiLI), involved 779 participants. The participants were asked to complete a questionnaire covering various aspects including demographics, lifestyle, and dietary habits. Additionally, they provided either oral or stool samples for analysis. A 137-item food frequency questionnaire (FFQ) was utilized to assess participants' diets. Gluten content was determined using specific calculations, where the bacterial 16SV4 rRNA gene found in the participants' baseline stool samples was amplified and sequenced. The results revealed that the consumption of whole grains had an impact on the overall composition of the intestinal microbiota throughout the study. This study reinforces the notion that consuming gluten-containing whole grains is linked to a decreased risk of CRC, primarily due to the association with a more favorable gut microbial profile (23).

While gluten has been recognized for its protective properties against CRC development, research suggests that in genetically susceptible individuals with abnormal immune responses to gluten, consumption of this protein is associated with elevated cancer risk. Specifically, these individuals exhibit aberrant T-cell responses in the presence of gluten, which can contribute to the heightened likelihood of developing cancer (25, 26). According to a recent investigation conducted by Wang et al. (24), the correlation between gluten consumption and the risk of developing digestive system cancer, including the gastrointestinal tract and accessory organs, was examined in U.S. adults using validated food frequency questionnaires (FFQs) and population-based cohort studies. These cancers

accounted for a substantial proportion of new cancer cases (30%) and cancer-related deaths (39%). The results of the study indicated that there is no evidence supporting a connection between long-term gluten consumption and the development of digestive system cancers in U.S. adults who do not have gluten-related disorders. Thus, based on their findings, it is improbable that the reduction of dietary gluten intake would be an effective preventive measure against digestive system cancers in the general population (27).

The findings of this study align with the research conducted by Behrendt et al. (25), examining the relationship between gluten consumption and overall mortality as well as mortality from specific causes in adults without gluten-related disorders. Behrendt et al. (28) reported that there is no significant association between gluten intake and cancer mortality. Hu et al. (29) conducted a cellular study with the aim of investigating the potential advantages of utilizing gluten derivatives as food additives. The hydrolysis of corn proteins was employed to release bioactive peptides, which have been recognized for their ability to augment the value of food products. The resultant hydrolysate fraction was subjected to evaluation to determine its anticancer potential using a liver cancer HepG2 cell model system. The findings unveiled the potential inhibitory effect of the corn peptide fraction on the growth of HepG2 cells without inducing toxicity. As a result, they concluded that both crude hydrolysates and peptide fractions derived from corn gluten meal seem to be promising as safe and natural antioxidants, thereby holding the potential to enhance the quality and extend the shelf life of food products.

On the contrary, the authors conducted a multivariate analysis incorporating backward stepwise logistic regression. The objective was to account for potential confounding factors while examining the impact of increased sensitivity to gluten in the mucosal lining of the colon. The researchers found that an exaggerated immune response within the colon, triggered by heightened gluten sensitivity, could lead to the proliferation of T lymphocytes and subsequent tumor development. Remarkably, individuals with CD, characterized by gluten enteropathy, exhibited a higher susceptibility to CRC compared to other well-established risk factors including smoking, obesity, alcohol abuse, and type 2 diabetes mellitus (25). This observation underscores the heightened risk of CRC associated specifically with CD. Additionally, research conducted by Lasa et al. (30) suggests that celiac patients are more likely to develop CRC. However, a study by Volta et al. (31) found that a rise in CRC incidence was only evident in those aged 60 and above. In a study conducted by Holmes and colleagues, it was indicated that patients who followed the GFD for a longer duration were at a lower risk compared to those who followed it for a short time or consumed gluten or a regular diet. Specifically, patients who strictly adhered to the gluten-free diet for five or more years did not have a significantly higher overall risk of cancer. These findings suggest that excluding gluten from the diet could potentially have a promising impact on preventing cancer in individuals with CD (32, 33). Further, according to Leonard et al. (34), the increased risk of malignancy was observed among patients with DH, and patients who followed a GFD had a lower risk of developing malignancy than those who followed a normal diet (34). Furthermore, some studies have shown no increase in the frequency of colonic neoplasia among patients with CD (11).

Gluten and the risk of lymphoma

Lymphomas are one of the common cancers of our immune system, divided into Hodgkin's lymphoma and non-Hodgkin's lymphoma (35, 36). The occurrence and characteristics of lymphoma differ based on factors such as age, gender, ethnicity, and location. This implies that various parameters such as infectious agents, environmental factors, and individual lifestyle choices could play a role in the development of lymphoma, alongside a person's genetic composition (37). There is insufficient information regarding the effects of gluten on developing lymphoma in general population, but it is believed that consuming a gluten-containing diet may activate immune and inflammatory signals, potentially leading to the onset or progression of lymphomas in susceptible individuals (38). In order to examine the relationship between a GFD and lymphoma, Lewis et al. conducted a study involving 206 patients with DH who were being monitored over time. The results indicated that only those patients who did not adhere to a GFD or had been on it for less than five years reported cases of lymphoma, despite their DH being under control. The study further revealed that patients who strictly followed

a gluten-free diet for more than five years had a lower risk of developing lymphoma compared to the general population. It is possible that the short duration of the diet did not fully counteract any potential cancer-causing factors that could have been present for a longer period. Another possibility is that the lymphoma may have already been present prior to adopting the GFD. These findings suggest that following a gluten-free diet could be protective against lymphoma, and it is advisable to encourage patients with DH to adhere to this dietary approach (39).

Silano et al. (40) aimed to explore the potential protective role of a gluten-free diet in preventing enteropathy-associated T-cell lymphoma (EATL) in patients with CD. The researchers followed 1,757 celiac patients over a period of 31,801 person-years and collected data on gluten intake plus the incidence of EATL. In order to evaluate the impact of gluten consumption on the likelihood of developing EATL, researchers used the X2 test. The results of the test indicated that there is a connection between consuming gluten in the diet and the risk of developing intestinal lymphoma, regardless of the frequency of consumption. According to their results, celiac patients who consumed dietary gluten had a significant risk of developing intestinal lymphoma. These findings highlight the

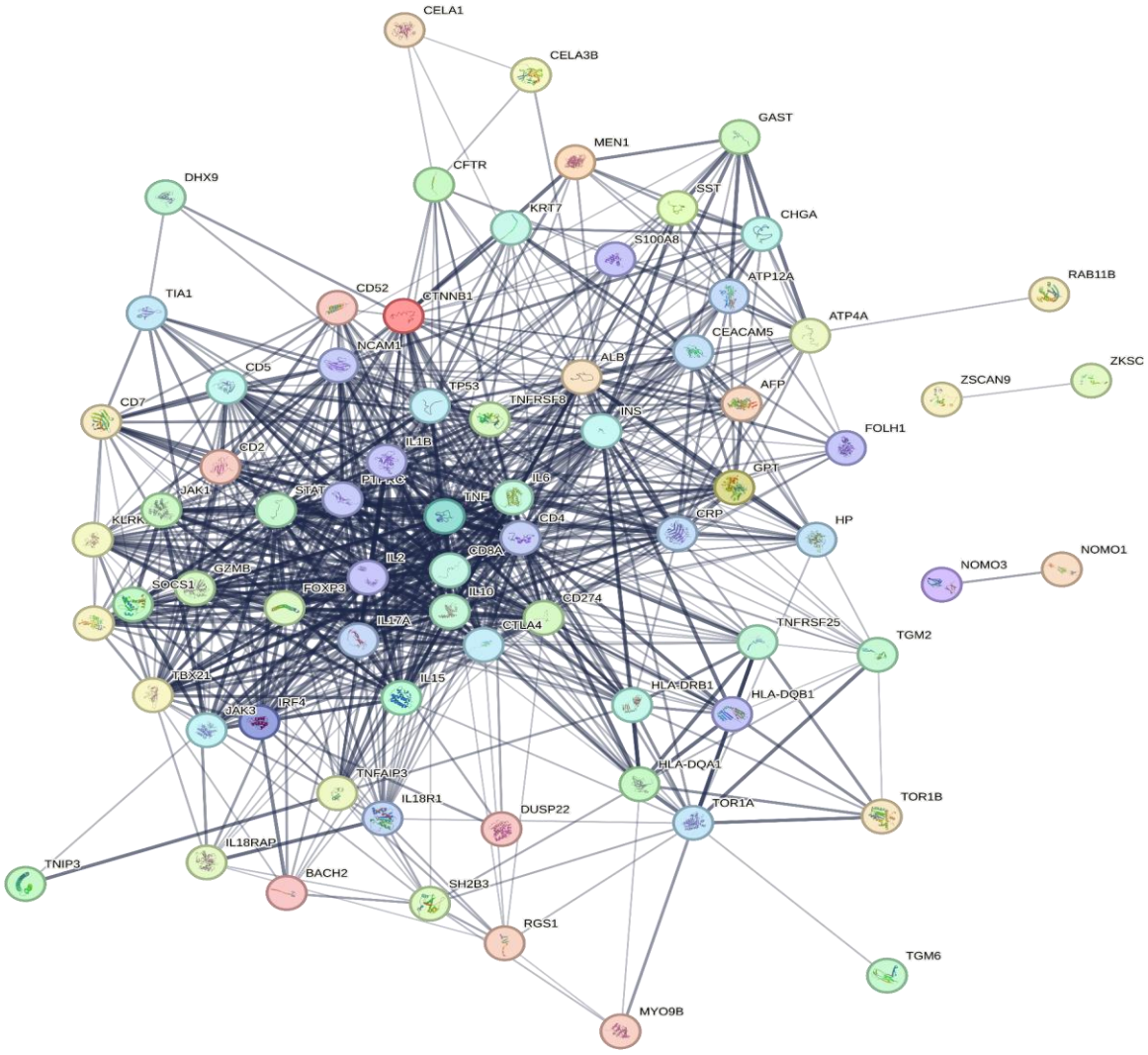

Figure 1. Protein-protein interaction network of CD and Cancer-related genes. The thickness of the lines connecting genes or proteins in the network indicates the strength or confidence of the supporting evidence for their interaction. There is no particular meaning of the node color itself.

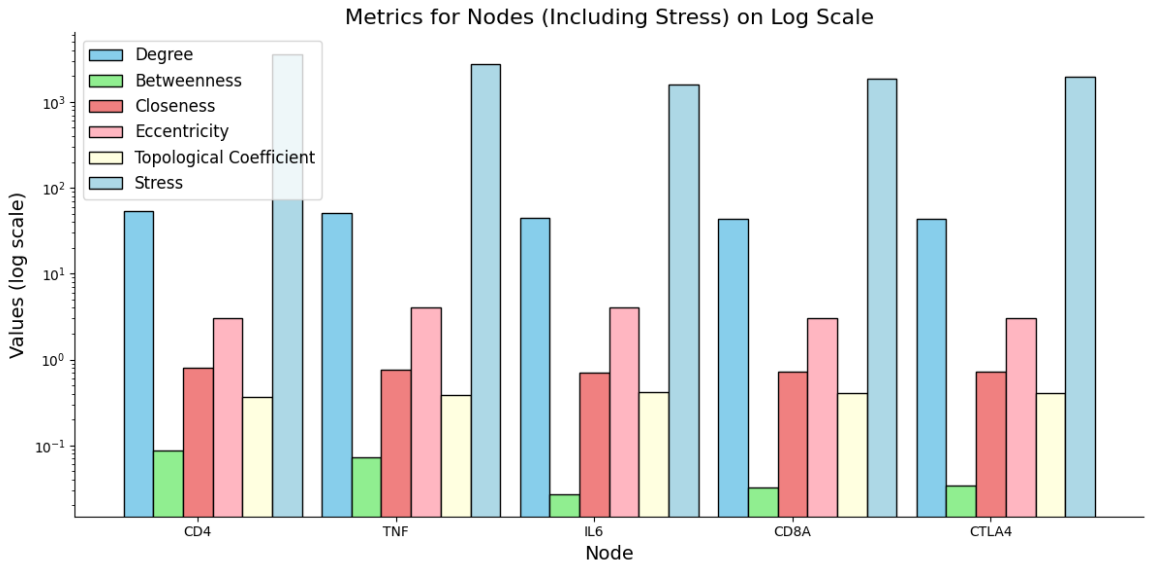

Figure 2. Comparative Network Node Metrics

Table 1. The five crucial nodes related to CD and Cancer

Display Name	Degree	Betweenness Centrality	Closeness Centrality	Stress	Eccentricity	Topological Coefficient
CD4	54	0.088	0.804	3586	3	0.367
TNF	51	0.073	0.752	2776	4	0.388
IL6	45	0.026	0.707	1596	4	0.421
CD8A	44	0.032	0.721	1886	3	0.411
CTLA4	44	0.034	0.721	1958	3	0.408

importance of a strict gluten-free diet as a protective measure against the development of enteropathy-associated T-cell lymphoma in individuals with CD.

Gluten and its effects on chromosome abnormalities

Abnormalities within the structure of chromosomes are common in cancerous genomes, ranging from minor changes to major alterations (41). This chromosomal instability contributes to the diversity within tumors and drives adaptive changes during tumor evolution (42). Chromosome aberrations can be found in various types of cancers, including lung, colon, and breast cancer (43). A study by Kolacek and colleagues (44) suggests that chromosome instability is not an inherent genetic flaw but rather a defect caused by external factors. In their research, they examined the effects of GFD on chromosome aberrations in 17 children with CD who followed the diet for at least 24 months (average of 33 months). They also included 15 healthy children in their study. The frequency of chromosome aberrations was initially determined at the patients' initial presentation and was found to be significantly elevated. Through statistical analysis using the Mann-Whitney U and Wilcoxon matched-pairs signed-ranks tests, the researchers observed that the consumption of GFD led to a decline in chromosome aberrations in the patients' peripheral blood lymphocytes. As a result, the study concluded that excluding gluten from the diet has a positive effect on reducing chromosome instability in lymphocytes of patients with cancer, offering a potential explanation for how dietary changes can help protect against the development of malignancies.

The links between CD and increased risk of oropharyngeal as well as esophageal cancers and liver abnormality were also reported and the positive effect of GFD on reducing the risks of cancers of the mouth, pharynx, and esophagus has also been observed previously (45, 46).

Protein-Protein Interaction (PPI) network analysis of common genes between CD and cancer

We retrieved curated gene-disease relations for celiac disease (CD) and cancer from the DisGeNET v2.0 server and created a protein-protein interaction (PPI) network using Cytoscape version 3.10.1 in conjunction with StringApp version 2.0.1. Our results indicated that CD4 is the standout hub gene in this network, with a degree of 54, suggesting numerous connections. CD4 also demonstrates high closeness and betweenness centrality, indicating efficient communication and important network roles. TNF, with a degree of 51, is another key player in the network. Although IL6, CD8A, and CTLA4 show lower connectivity, they still play significant roles. These findings highlight the central positions of CD4 and TNF in facilitating crucial biological processes related to cancer and immune contexts.

A thorough analysis of network metrics for five key genes (CD4, TNF, IL6, CD8A, and CTLA4) was performed using Python programming language version 3.10.12, along with the Pandas, Numpy and Matplotlib libraries. This combination of software and tools enabled comprehensive analysis and visualization of the network's node metrics, contributing to a more comprehensive understanding of the biological interactions under investigation. The examined metrics provided important information about the roles and significance of these genes within a biological network. Notably, CD4 and TNF revealed the highest degrees and betweenness centralities, indicating their central positions in connecting other genes and facilitating the flow of information. CD4 also had the highest closeness centrality, highlighting its efficient communication with other genes. Additionally, IL6 displayed a significant topological coefficient, suggesting a greater degree of interconnectedness among its neighboring genes. These findings enhance our understanding of the network properties of these genes, offering valuable insights into their functional importance and potential roles in cancer as well as celiac disease-related pathways (Table 1; Figure 1 and 2).

Conclusion

Based on currently available evidence, eliminating gluten from the diet is effective in controlling the symptoms and inflammation caused by gluten-related disorders (especially CD) and preventing them from developing cancer. In contrast, gluten consumption in non-GRD populations has been shown to be involved in cancer prevention. However, more research is needed to learn the exact role of gluten as a cancer prevention factor, especially in people with a family history of these cancers.

Conflict of interests

There is no conflict of interest for authors of this article.

Ethnical ID: IR.SBMU.REC.1403.008

References

1. Khoshbaten M, Rostami Nejad M, Farzady L, Sharifi N, Hashemi SH, Rostami K. Fertility disorder associated with celiac disease in males and females: fact or fiction? J Obstet Gynaecol Res. 2011;37:1308-12.

2. Rostami Nejad M, Rostami K, Yamaoka Y, Mashayekhi R, Molaei M, Dabiri H, et al. Clinical and histological presentation of Helicobacter pylori and gluten related gastroenteropathy. Arch Iran Med. 2011;14:115-8.

3. Lafiandra D, Shewry PR. Wheat Glutenin polymers 2. The role of wheat glutenin subunits in polymer formation and dough quality. J Cereal Sci 2022;106:103487.

4. Shewry PR, Tatham AS, Forde J, Kreis M, Miflin BJ. The classification and nomenclature of wheat gluten proteins: a reassessment. J Cereal Sci 1986;4:97-106.

5. Biesiekierski JR. What is gluten? J Gastroenterol Hepatol 2017;32:78-81.

6. Asri N, Rostami-Nejad M. Chapter 4 - Gluten-related disorders definition. In: Rostami-Nejad M, editor. Gluten-Related Disorders: Academic Press; 2022. p. 49-57.

7. Arentz–Hansen H, Mcadam SN, Molberg Ø, Fleckenstein B, Lundin KE, Jørgensen TJ, et al. Celiac lesion T cells recognize epitopes that cluster in regions of gliadins rich in proline residues. Gastroenterology 2002;123:803-9.

8. Tovoli F, Masi C, Guidetti E, Negrini G, Paterini P, Bolondi L. Clinical and diagnostic aspects of gluten related disorders. World J Clin Cases 2015;3:275.

9. Aljada B, Zohni A, El-Matary W. The gluten-free diet for celiac disease and beyond. Nutrients 2021;13:3993.

10. Kalra N, Mukerjee A, Sinha S, Muralidhar V, Serin Y, Tiwari A, et al. Current updates on the association between celiac disease and cancer, and the effects of the gluten-free diet for modifying the risk (Review). Int J Funct Nutr 2022;3:2.

11. Han Y, Chen W, Li P, Ye J. Association between coeliac disease and risk of any malignancy and gastrointestinal malignancy: a meta-analysis. Medicine 2015;94:1612.

12. Wang Y, Cao Y, Lebwohl B, Song M, Sun Q, Green PHR, et al. Gluten intake and risk of digestive system cancers in 3 large prospective cohort studies. Clin Gastroenterol Hepatol 2022;20:1986-96.

13. Mármol I, Sánchez-de-Diego C, Pradilla Dieste A, Cerrada E, Rodriguez Yoldi MJ. Colorectal carcinoma: a general overview

and future perspectives in colorectal cancer. Int J Mol Sci 2017;18:197.

14. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61:759-67.

15. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington DC: AICR, 2007.

16. World Cancer Research Fund/American Institute for Cancer Research. Diet, nutrition, physical activity, and cancer: a global perspective. Continuous Update Project Expert Report 2018. Available at dietandcancerreport.org.

17. Slavin J. Why whole grains are protective: biological mechanisms. Proc Nutr Soc 2003;62:129-34.

18. Martínez I, Lattimer JM, Hubach KL, Case JA, Yang J, Weber CG, et al. Gut microbiome composition is linked to whole grain-induced immunological improvements. ISME J 2013;7:269-80.

19. Slavin JL. Mechanisms for the impact of whole grain foods on cancer risk. J Am Coll Nutr 2000;19:300-7.

20. Um CY, Campbell PT, Carter B, Wang Y, Gapstur SM, McCullough ML. Association between grains, gluten and the risk of colorectal cancer in the Cancer Prevention Study-II Nutrition Cohort. Eur J Nutr 2020;59:1739-49.

21. Kyrø C, Skeie G, Loft S, Landberg R, Christensen J, Lund E, et al. Intake of whole grains from different cereal and food sources and incidence of colorectal cancer in the Scandinavian HELGA cohort. Cancer Causes Control 2013;24:1363-74.

22. Peng L, Li Z-R, Green RS, Holzman IR, Lin J. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. J Nutr 2009;139:1619-25.

23. Um CY, Peters BA, Choi HS, Oberstein P, Beggs DB, Usyk M, et al. Grain, gluten, and dietary fiber intake influence gut microbial diversity: data from the food and microbiome longitudinal investigation. Cancer Res Commun 2023;3:43-53.

24. Kõiv V, Tenson T. Gluten-degrading bacteria: availability and applications. Appl Microbiol Biotechnol 2021;105:3045-59.

25. Onwuzo S, Boustany A, Saleh M, Gupta R, Onwuzo C, Monteiro JM, et al. Increased risk of colorectal cancer in patients with celiac disease: a population-based study. Cureus 2023;15.

26. Nanayakkara M, Lania G, Maglio M, Discepolo V, Sarno M, Gaito A, et al. An undigested gliadin peptide activates innate immunity and proliferative signaling in enterocytes: the role in celiac disease. Am J Clin Nutr 2013;98:1123-35.

27. Wang Y, Cao Y, Lebwohl B, Song M, Sun Q, Green PH, et al. Gluten intake and risk of digestive system cancers in 3 large prospective cohort studies. Clin Gastroenterol Hepatol 2022;20:1986-96.

28. Behrendt I, Fasshauer M, Eichner G. Gluten intake and all-cause and cause-specific mortality: prospective findings from the UK biobank. J Nutr 2021;151:591-7.

29. Hu R, Xu J, Qi G, Wang W, Sun XS, Li Y. Antioxidative hydrolysates from corn gluten meal may effectively reduce lipid oxidation and inhibit HepG2 cancer cell growth. J Agric Food Res 2022;7:100252.

30. Lasa J, Rausch A, Bracho LF, Altamirano J, Speisky D, de Dávila MTG, et al. Colorectal adenoma risk is increased among recently diagnosed adult celiac disease patients. Gastroenterol Res Pract 2018;2018:6150145.

31. Volta U, Vincentini O, Quintarelli F, Felli C, Silano M. Low risk of colon cancer in patients with celiac disease. Scand J Gastroenterol 2014;49:564-8.

32. Holmes G, Stokes P, Sorahan T, Prior P, Waterhouse J, Cooke W. Coeliac disease, gluten-free diet, and malignancy. Gut 1976;17:612-9.

33. Holmes G, Prior P, Lane M, Pope D, Allan R. Malignancy in coeliac disease-effect of a gluten free diet. Gut 1989;30:333-8.

34. Leonard J, Tucker W, Fry J, Coulter C, Boylston A, McMinn R, et al. Increased incidence of malignancy in dermatitis herpetiformis. Br Med J 1983;286:16-8.

35. de Leval L, Jaffe ES. Lymphoma classification. Cancer J 2020;26:176-85.

36. Matasar MJ, Zelenetz AD. Overview of lymphoma diagnosis and management. Radiol Clin North Am 2008;46:175-98.

37. Kalra N, Mukerjee A, Sinha S, Muralidhar V, Serin Y, Tiwari A, et al. Current updates on the association between celiac disease and cancer, and the effects of the gluten-free diet for modifying the risk. Int J Funct Nutr 2022;3:1-10.

38. Marafini I, Monteleone G, Stolfi C. Association between celiac disease and cancer. Int J Mol Sci 2020;21:4155.

39. Lewis H, Renaula T, Garioch J, Leonard J, Fry J, Collin P, et al. Protective effect of gluten-free diet against development of lymphoma in dermatitis herpetiformis. Br J Dermatol 1996;135:363-7.

40. Silano M, Volta U, Vincenzi AD, Dessì M, Vincenzi MD. Effect of a gluten-free diet on the risk of enteropathy-associated T-cell lymphoma in celiac disease. Dig Dis Sci 2008;53:972-6.

41. Kou F, Wu L, Ren X, Yang L. Chromosome abnormalities: new insights into their clinical significance in cancer. Mol Ther Oncolytics 2020;17:562-70.

42. Bakhoum SF, Landau DA. Chromosomal Instability as a Driver of Tumor Heterogeneity and Evolution. Cold Spring Harb Perspect Med 2017;7.

43. Solomon E, Borrow J, Goddard AD. Chromosome aberrations and cancer. Science 1991;254:1153-60.

44. Kolacek S, Jadrešin O, Petkovic I, Mišak Z, Sonicki Z, Booth IW. Gluten-free diet has a beneficial effect on chromosome instability in lymphocytes of children with coeliac disease. J Pediatr Gastroenterol Nutr 2004;38:177-80.

45. Holmes GK, Prior P, Lane MR, Pope D, Allan RN. Malignancy in coeliac disease--effect of a gluten free diet. Gut 1989;30:333-8.

46. Villavicencio Kim J, Wu GY. Celiac Disease and Elevated Liver Enzymes: A Review. J Clin Transl Hepatol 2021;9:116-24.