ORIGINAL ARTICLE

doi.org/10.1590/S0004-2803.230302023-43

Increased risk of colorectal cancer in patients with chronic tophaceous gout: a population-based study

Antoine **BOUSTANY**[1], Romy **RAHHAL**[2], Jad **MITRI**[3], Somtochukwu **ONWUZO**[1], Hadi Khaled Abou **ZEID**[4] and Imad **ASAAD**[1]

[1] Department of Medicine, Cleveland Clinic Foundation, Cleveland, OH, USA. [2] Department of Medicine, Massachusetts General Hospital, Boston, MA, USA. [3] Department of Medicine, St. Elizabeth's Medical Center, MA, USA. [4] Department of Medicine and Medical Sciences, University of Balamand, Koura, Lebanon.

HIGLIGHTS

- The study aims to investigate the risk of developing Colorectal cancer in patients with a history of chronic tophaceous gout.
- A retrospective cohort analysis of adults extracted from a validated multicenter and research platform database from hospitals in the United States was utilized.
- The risk of Colorectal cancer was statistically significantly increased in male gender, smokers, alcoholics, obese, type 2 Diabetic, and chronic tophaceous gout patients.
- The risk of developing Colorectal cancer was significantly higher in patients who have a history of Chronic tophaceous gout while accounting for potential confounding variables.

ABSTRACT – Background – Colorectal cancer is the third most common type of cancer in both men and women and ranks second as the most common cause of cancer death in the United States. Classic risk factors include tobacco smoking, high alcohol consumption, physical inactivity and excess body weight. A prospective study found that an elevated serum uric acid was associated with higher rates of cancer-associated polyps. Interestingly, other studies found an association between elevated levels of serum uric acid and other types of cancer including colorectal cancer. **Objective** – Our study aimed to evaluate whether patients with chronic tophaceous gout had an increased risk of developing colorectal cancer. **Methods –** A validated multicenter and research platform database of more than 360 hospitals from 26 different healthcare systems across the United States was utilized to construct this study. Patients aged 18 years and above were included. Individuals who have had a history of familial adenomatous polyposis, a family history of colon cancer, and those diagnosed with inflammatory bowel disease were excluded from the analysis. The risk of developing colon cancer was calculated using a multivariate regression analysis to account for potential confounders. **Results –** 80,927,194 individuals were screened in the database and 70,177,200 were selected in the final analysis after accounting for inclusion and exclusion criteria. Type 2 diabetics (28.57%), smokers (10.98%), obese individuals (18.71%), alcoholics (3.13%), and patients who have had a diagnosis of chronic tophaceous gout were more common in the colon cancer group compared to those without the malignancy. Using multivariate regression analysis, risk of colon cancer was calculated for male gender (OR: 1.02; 95%CI: 1.01–1.03), smokers (OR: 1.54; 95%CI: 1.52–1.56), alcoholics (OR: 1.40; 95%CI: 1.37–1.43), obese patients (OR: 1.52; 95%CI: 1.50–1.54), type 2 diabetic individuals (OR: 3.53; 95%CI: 3.50–3.57), and those who have had a diagnosis of chronic tophaceous gout (OR: 1.40; 95%CI: 2.48–3.23). **Conclusion –** As expected, patients with colon cancer were found to have a higher prevalence in males, obese, tobacco and alcohol users. We also demonstrated that patients with gout have a significantly higher prevalence of CRC than those who do not before and after adjusting for metabolic risk factors. In fact, uric acid was found to induce production of reactive oxygen species, thus potentially promoting tumorigenesis. It would be interesting to assess the prevalence of colon cancer in patients with gout who have a serum uric acid that is less than 7 mg/dL. This might promote a tighter control of serum uric acid levels in this population in order to decrease the risk of colon cancer.

Keywords – Colorectal cancer; tophaceous gout; colon cancer; gout.

Received: 19 March 2023
Accepted: 20 July 2023

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
Corresponding author:
Hadi Abou Zeid. E-mail:
hadi_abou_zeid@hotmail.com

INTRODUCTION

Colorectal cancer (CRC) is ranked second among the most common causes of cancer death in the United States. It is the third most common type of cancer in men and women, with the incidence in men being higher than in women[1,2]. While some forms of CRC are transmitted through familial clustering or inherited syndromes[3], most CRC cases are sporadic and the age of onset is above 50 years. In fact, 60% of patients with CRC are above 70 years old[4]. For patients with sporadic CRC, some of the risk factors include environmental exposure and lifestyle characteristics such as obesity, physical inactivity, meat consumption (red or processed), tobacco, and alcohol. There has been a recent surge in both the incidence and mortality of sporadic CRC among younger patients. This change is alarming and warrants better screening to optimize primary prevention through patient education and addressing appropriate risk factors[5].

Gout is characterized by high levels of uric acid in the blood, typically higher than the limit of urate solubility. It affects around 3% of the adult population in the United States. Its incidence has been trending upward for the past few decades[6]. Risk factors for gout essentially include hyperuricemia, older age, male sex, obesity, a diet high in animal protein, alcohol, and fructose beverages. Typically, it is most prevalent among older males with metabolic syndromes. There are four stages of gout: asymptomatic hyperuricemia, acute gout attacks, inter-critical period, and chronic tophaceous gout. The disease course progresses as uric acid accumulates in the body, crystallizes, and eventually forms foreign body granulomas (known as gouty tophi) which marks chronic tophaceous gout[7,8].

There is a noticeable overlap in risk factors for gout and colon cancer. Despite the overlap, there has been increased evidence reporting on a potential association between hyperuricemia and colon cancer. For instance, a prospective study in 2014 by Orannapalai et al. reported that a serum uric acid level higher than 7 mg% increased the rate of cancer-associated colorectal polyps[9]. More so, "the Kailuan study" prospectively examined a large cohort of Chinese participants and demonstrated a positive association between gout and colon cancer[10]. The mechanism for the cancerous effect of uric acid is still uncertain. Despite having protective antioxidant effects in some neurological disorders, uric acid also acts as a pro-oxidant, potentially contributing to chronic kidney disease progression, cardiovascular events, hypertension, hyperlipidemia, metabolic syndrome, and diabetes[11]. It is believed that the pro-oxidant effect of uric acid might precipitate carcinogenesis in the colon[12].

The aim of this study is to provide further evidence on the association between chronic tophaceous gout and CRC, with statistical awareness and minimization of concomitant confounding by similarities in risk factors.

METHODS

Database

Explorys Inc., Cleveland, OH, USA is a validated multicenter and research platform database of more than 360 hospitals from 26 different healthcare systems across the United States consisting of data accumulated from 1999 to September 2022. Explorys was developed and has been prospectively maintained by IBM Corporation, Watson Health[13], including electronic health record (EHR) from greater than 60 million unique patients and provide a broad regional distribution of the United States representing approximately 15% of the population. It was utilized to construct a retrospective cohort analysis. A Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) hierarchy[14] was used to select diagnoses, findings, and procedures. Prescription drug orders are mapped into SNOMED and RxNorm[15]. Institutional Review Board (IRB) was not required as source data are de-identified. To protect patient confidentiality, Explorys rounds population counts to the nearest 10 and treats all counts between zero and 10 as equivalent. The study was conducted in accordance to the Declaration of Helsinki (as revised in 2013). Access to the database is granted to participating healthcare systems. Use of the Explorys platform has been validated in multiple fields including gastroenterology[16-21].

Patient selection

Adults over 18 years of age were included in the

study. Patients with a history of familial adenomatous polyposis, a family history of colon cancer, and those diagnosed with inflammatory bowel disease were excluded. A subgroup of patients with a diagnosis of "CRC" was later selected and used in the analysis. The control group was identified as adult patients who did not have a diagnosis of CRC.

Statistical analysis

Patients who developed CRC were compared to those who did not. A multivariate regression analysis was performed to account for potential confounders including male gender, smoking history, alcoholism, obesity, type 2 diabetic individuals, and those who have had diagnosis of chronic tophaceous gout. Age was excluded from the data analysis to bring greater clarity to the association between CRC and the other parameters. A two-sided *P* value <0.05 was considered as statistically significant, and all statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria, 2008).

RESULTS

Descriptive epidemiology

80,927,194 individuals aged over 18 years were screened in the database and 70,177,200 were selected after excluding familial adenomatous polyposis, a family history of colon cancer, and inflammatory bowel disease. The baseline characteristics of our cohort are displayed in TABLE 1.

TABLE 1. Baseline characteristics of patients with colorectal cancer and control.

	Colon cancer (%)	No colon cancer (%)
Type 2 Diabetes Mellitus	67,100 (28.57)	5,531,130 (7.90)
Smoker	25,790 (10.98)	3,733,140 (5.33)
Male	117,630 (50.08)	31,243,450 (44.67)
Obesity	43,940 (18.71)	5,311,980 (7.59)
Alcohol	7,370 (3.13)	1,071,950 (1.53)
Chronic tophaceous gout	190 (0.08)	10,540 (0.01)
Total	234,840	69,942,360

Type 2 diabetic (28.57%), smoking history (10.98%), obesity (18.71%), alcoholism (3.13%), and chronic tophaceous gout (0.08%) were more common in the CRC group compared to those without the malignancy.

Risk and predictors of colon cancer in patients using a multivariate regression analysis

In order to adjust for confounding variables, a multivariate regression analysis was performed (FIGURE 1).

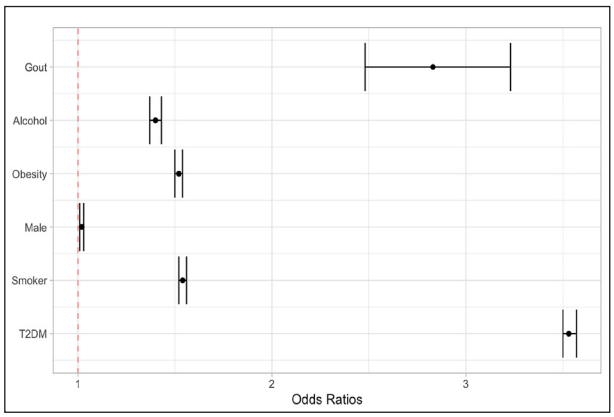

FIGURE 1. Forest plot for risk of developing colorectal cancer.
T2DM: type 2 diabetes mellitus.

The risk of CRC was increased in male gender (OR: 1.02; 95%CI: 1.01–1.03), smokers (OR: 1.54; 95%CI: 1.52–1.56), alcoholics (OR: 1.40; 95%CI: 1.37–1.43), obese patients (OR: 1.52; 95%CI: 1.50–1.54), type 2 diabetic individuals (OR: 3.53; 95%CI: 3.50–3.57), and those diagnosed with chronic tophaceous gout (OR: 1.40; 95%CI: 2.48–3.23) as seen in (FIGURE 1).

DISCUSSION

Gout appears to be independently correlated with having CRC, as displayed in our results after controlling for known CRC risk factors (smoking, alcohol consumption, gender, obesity, and type 2 diabetes). This is the first US population-based study assessing the relationship between those two diseases independently of other mediating factors. Prior studies looked at this association in different demographic populations (Chinese, Taiwanese, and Swedish populations). The findings warrant more prospective research on this topic and could imply encouraging tighter uric acid control in patients at risk of develo-

ping CRC. Moreover, this study can set the grounds for further research that would incorporate uric acid serum levels in future CRC screening tools.

The number of new cases of CRC reached 1,9 million worldwide in 2020 with around 100 000 deaths[22]. According to the latest data from the Center for Diseases Control and Prevention [CDC], the prevalence of CRC was 36.3 per 100 000 cases in the United States[23]. This number is expected to rise with the increased urbanization and the shift in lifestyles that come with it. CRC is more prevalent among males and increases with age, but it is also multifactorial. Personal history of diabetes, inflammatory bowel disease, and colonic polyps are known risk factors for developing CRC. In addition to genetic predisposition and family history of malignancy, 2 to 8% of CRC cases result from inherited syndromes such as hereditary nonpolyposis colorectal cancer (Lynch syndrome), and familial adenomatous polyposis (FAP). Lifestyle components also play an important role in developing CRC and include tobacco smoking, alcohol consumption, visceral obesity, and specific diets: high in red meat diets, low in calcium and vit D and fibers[24]. Interestingly, most of these modifiable risk factors overlap with gout risk factors. In fact, a recent study by Liu et al. examining gout-associated risk factors demonstrated that 65% of gout incidence was related to obesity, hypertension, and alcohol consumption, 2 of which are known risk factors for CRC[25]. Other common risk factors for gout include obesity, high purine intake (found in red meat), and advanced age[26].

Given that this was a large population-based study gathering data from more than 360 hospitals, its findings should be generalizable and should reflect the prevalence of the US population. The prevalence of gout in this population sample (1%) is similar to what is found in the literature[27]. Moreover, CRC risk factors already established in previous literature[26] were consistent with our results further confirming their generalizability.

This study found that patients with gout have a significantly higher prevalence of CRC than those who do not before and after adjusting for metabolic risk factors (8% vs 1%; $P<0.01$). This result implies that gout can be a causative factor of CRC through specific mechanisms rather than being an indicator or mediator of metabolic factors. This result has not been consistently reported in the literature, nor was it clearly examined in the US population. On one hand, a large-scale Swedish study that prospectively followed patients with gout demonstrated a significantly increased risk of many neoplasms, including colorectal cancer[28]. Additionally, a population-based Taiwanese cross-sectional study exhibited the same result[29]. However, in contrast to our analysis, both studies did not account for the common risk factors mentioned above. The results could therefore be explained by the mediating effects of lifestyle habits (alcohol intake, red meat consumption, physical inactivity). On the other hand, another prospective nationwide Taiwanese study that prospectively assessed this association failed to show statistical significance after correcting for age, sex, diabetes, hyperlipidemia, and hypertension[30] which contradicts our findings. It is important to note that one major limitation of that study was its inability to account for some CRC known risk factors such as alcohol consumption, body mass index (BMI), and family history of cancer, all of which were considered in ours: besides controlling for BMI and alcohol intake, patients with a family history of cancer were excluded from the study. While US studies did not explore gout itself, a prior study by Orannapalai et al. did look at uric acid levels and reported that levels above 7 mg/dL were associated with developing cancer-associated polyps (OR=2.51; CI= [1.35–4.65])[9]. This finding is promising and complements our results. More research is still however needed to define specific uric acid level cut-offs mediating this relationship. Serum uric acid control could be incorporated into future screening protocols and in the lifestyle recommendations of patients at risk of CRC.

Gout's independent association with developing CRC could have many plausible explanations. Recent theories indicate that uric acid plays a dual role as an antioxidant and pro-oxidant. While these roles seem paradoxical, the effect of uric acid is highly dependent on its microenvironment: Intracellular uric acid appears to hold pro-oxidant effects while its antioxidant role is prominent in hydrophilic environments[31,32]. Oxidative stress is a known risk factor for carcinogenesis and notably colon cancer[12]. In addition, dysbiosis of the intestinal microbiota appears to be a common mechanism in both CRC initiation

and progression as well as in gout[33,34]. Finally, it is possible that patients with CRC could be using chronic medication (thiazide diuretics) or chemotherapy regimens that could be elevating uric acid levels by either affecting renal reabsorption or causing tumor lysis syndrome, respectively[35,36].

It is worth mentioning that the cross-sectional nature of this database study limited the ability to draw causality associations. While the results indicate that a statistically significant correlation exists between having gout and CRC, it is not possible to prove with the given data which one led to the other. For this reason, prospective studies examining this outcome (developing CRC) will be needed for a more in-depth interpretation. In addition to that, due to the limitations of the database itself, dietary factors could not be taken into account in the multivariate regression model and could have affected the final results. In fact, studies have consistently shown that red meat consumption is a known risk factor for both gout and CRC[20]. Age is an established factor for both gout and CRC. This variable was subtracted from our model for the sole purpose of highlighting the association between the other parameters more clearly.

CONCLUSION

Gout appears to be independently associated with developing CRC. Uric acid's oxidative properties could mediate this relationship. Further prospective studies are needed to better understand this association and elucidate the mechanisms that foster it.

Authors' contribution

Boustany A: conceived and designed the analysis, performed data analysis, methodology. Rahhal R: wrote the manuscript (literature review). Mitri J: wrote the manuscript (introduction, abstract, conclusion). Onwuzo S: data collection. Zeid HKA: Wrote the manuscript (discussion). Asaad I: supervised the project.

Orcid

Antoine Boustany: 0000-0002-4661-1443.
Romy Rahhal: 0000-0001-8861-1911.
Jad Mitri: 0009-0005-7331-1592.
Somtochukwu Onwuzo: 0000-0001-5060-3131.
Hadi Khaled Abou Zeid: 0000-0002-5111-3043.
Imad Asaad: 0000-0002-0648-6625.

Boustany A, Rahhal R, Mitri J, Onwuzo S, Zeid HKA, Asaad I. Risco aumentado de câncer colorretal em pacientes com gota tofácea crônica: um estudo populacional. Arq Gastroenterol. 2023;60(3):339-44.

RESUMO – Contexto – O câncer colorretal é o terceiro tipo mais comum de câncer em homens e mulheres e ocupa o segundo lugar como a causa mais comum de morte por câncer nos EUA. Os fatores de risco clássicos incluem tabagismo, alto consumo de álcool, inatividade física e excesso de peso corporal. Um estudo prospectivo descobriu que um ácido úrico sérico elevado estava associado a taxas mais altas de pólipos associados ao câncer. Curiosamente, outros estudos encontraram uma associação entre níveis elevados de ácido úrico sérico e outros tipos de câncer, incluindo o câncer colorretal. **Objetivo** – Nosso estudo teve como objetivo avaliar se os pacientes com gota tofácea crônica tinham um risco aumentado de desenvolver câncer colorretal. **Métodos** – Utilizou-se um banco de dados validado multicêntrico e de plataforma de pesquisa de mais de 360 hospitais de 26 diferentes sistemas de saúde nos Estados Unidos para a construção deste estudo. Foram incluídos pacientes com 18 anos ou mais. Indivíduos com histórico de polipose adenomatosa familiar, histórico familiar de câncer de cólon e aqueles diagnosticados com doença inflamatória intestinal foram excluídos da análise. O risco de desenvolver câncer de cólon foi calculado usando uma análise de regressão multivariada para contabilizar possíveis confusões. **Resultados** – 80.927.194 indivíduos foram rastreados no banco de dados e 70.177.200 foram selecionados na análise final após considerar critérios de inclusão e exclusão. Diabéticos tipo 2 (28,57%), fumantes (10,98%), indivíduos obesos (18,71%), alcoólatras (3,13%) e pacientes que tiveram diagnóstico de gota tofácea crônica foram mais comuns no grupo de câncer de cólon em comparação com aqueles sem a malignidade. Usando a análise de regressão multivariada, o risco de câncer de cólon foi calculado para o sexo masculino (OR: 1,02; IC95%: 1,01–1,03), fumantes (OR: 1,54; IC95%: 1,52–1,56), alcoólatras (OR: 1,40; IC95%: 1,37–1,43), pacientes obesos (OR: 1,52; IC95%: 1,50–1,54), indivíduos diabéticos tipo 2 (OR: 3,53; IC95%: 3,50–3,57), e aqueles que tiveram diagnóstico de gota tofácea crônica (OR: 1,40; IC95%: 2,48–3,23). **Conclusão** – Como esperado, os pacientes com câncer de cólon foram encontrados com maior prevalência em homens, obesos, usuários de tabaco e álcool. Demonstramos também que os pacientes com gota têm uma prevalência significativamente maior de câncer colorretal do que aqueles que não a têm, antes e após o ajuste para fatores de risco metabólicos. De fato, descobriu-se que o ácido úrico induz a produção de espécies reativas de oxigênio, promovendo assim potencialmente a tumorigênese. Seria interessante avaliar a prevalência de câncer de cólon em pacientes com gota que têm um ácido úrico sérico inferior a 7 mg/dL. Isso poderia promover um controle mais rígido dos níveis de ácido úrico sérico nesta população para diminuir o risco de câncer de cólon.

Palavras-chave – Câncer colorretal; gota tofácea; câncer de cólon; gota.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
2. Cronin KA, Scott S, Firth AU, Sung H, Henley SJ, Sherman RL, et al. Annual report to the nation on the status of cancer, part 1: National cancer statistics. Cancer. 2022;128:4251-84.
3. Burt RW, DiSario JA, Cannon-Albright L. Genetics of colon cancer: impact of inheritance on colon cancer risk. Annu Rev Med. 1995;46:371-9.
4. Millan M, Merino S, Caro A, Feliu F, Escuder J, Francesch T. Treatment of colorectal cancer in the elderly. World J Gastrointest Oncol. 2015;7:204-20. doi:10.4251/wjgo.v7.i10.204
5. Sinicrope FA. Increasing Incidence of Early-Onset Colorectal Cancer. N Engl J Med. 2022;386:1547-58.
6. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum. 2011;63:3136-41.
7. Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet. 2016;388:2039-52.
8. Neogi T. Gout (Heinig, 2006 #7925). Ann Intern Med. 2016;165: Itc1-itc16.
9. Orannapalai N, Attawettayanon W, Kanngern S, Boonpipattanapong T, Sangkhathat S. Predicting the occurrence of cancer-associated colorectal polyp using a metabolic risk score. Mol Clin Oncol. 2014;2:124-8.
10. Li W, Liu T, Siyin ST, Zhang Q, Wang Y, Cao L, et al. The relationship between serum uric acid and colorectal cancer: a prospective cohort study. Scientific reports. 2022;12:16677.
11. Heinig M, Johnson RJ. Role of uric acid in hypertension, renal disease, and metabolic syndrome. Cleve Clin J Med. 2006;73:1059-64.
12. Carini F, Mazzola M, Rappa F, Jurjus A, Geagea AG, Al Kattar S, et al. Colorectal Carcinogenesis: Role of Oxidative Stress and Antioxidants. Anticancer research. 2017;37:4759-66.
13. Health IBM Corporation. The IBM Explorys Platform: liberate your healthcare data. Available from: https://www. ibm.com/downloads/cas/4P0QB9JN
14. SNOMED CT. Accessed July 28, 2023. https://www.nlm.nih.gov/healthit/snomedct/index.html
15. Nelson SJ, Zeng K, Kilbourne J, Powell T, Moore R. Normalized names for clinical drugs: RxNorm at 6 years. J Am Med Inform Assoc. 2011; 18:441-8
16. Boustany A. Epidemiology and risk of colorectal cancer in patients with a history of Helicobacter pylori infection: a population-based study. Ann Gastroenterol. 2023;36:1-5. doi: 10.20524/aog.2023.0783.
17. Boustany A, Mardelli M, Onwuzo S, Zeid HKA, Asaad I, Mardelli M, et al. Increased Risk of Central Retinal Vein Occlusion in Patients with Inflammatory Bowel Disease: A Population-Based Study. J Ophtalmol Open Access. 2022;6. doi:10.17303/jooa.2022.6.105.
18. Onwuzo SS, Hitawala AA, Boustany A, Kumar P, Almomani A, Onwuzo C, et al. Prevalence of non-alcoholic fatty liver disease in patients with nephrotic syndrome: A population-based study. World J Hepatol. 2023;15:265-73. doi:10.4254/wjh.v15.i2.265
19. Onwuzo S, Boustany A, Khaled Abou Zeid H, Hitawala A, Almomani A, Onwuzo C, et al. Prevalence and Risk Factors Associated With Inflammatory Bowel Disease in Patients Using Proton-Pump Inhibitors: A Population-Based Study. Cureus. 2023;15:e34088. doi:10.7759/cureus.34088
20. Boustany A, Onwuzo S, Zeid HKA, Almomani A, Kumar P, Hitawala A, et al. Non-alcoholic steatohepatitis is independently associated with a history of gestational diabetes mellitus. J Gastroenterol Hepatol. 2023;38:984-8. doi:10.1111/jgh.16163.
21. Almomani A, Kumar P, Onwuzo S, Boustany A, Krishtopaytis E, Hitawala A, et al. Epidemiology and prevalence of lean nonalcoholic fatty liver disease and associated cirrhosis, hepatocellular carcinoma, and cardiovascular outcomes in the United States: a population-based study and review of literature. J Gastroenterol Hepatol. 2023;38:269-73. doi:10.1111/jgh.16049
22. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71:209-49.
23. Center for Disease Control and Prevention (CDC). WSQARS (Web based Injury Statistics Quey and Reporting System). 2020. Available from: https://www-cdc-gov.ezproxy.aub.edu.lb/injury/wisqars/overview/key_data.html
24. Sawicki T, Ruszkowska M, Danielewicz A, Niedźwiedzka E, Arłukowicz T, Przybyłowicz KE. A Review of Colorectal Cancer in Terms of Epidemiology, Risk Factors, Development, Symptoms and Diagnosis. Cancers (Basel). 2021;13:2025. doi: 10.3390/cancers13092025.
25. Liu K, Yao Y, Chen W, Mao Y, Ye D, Wen C. Modifiable risk factors and incidence of gout: Estimation of population attributable fraction in the US. Semin Arthritis Rheum. 2022;55:152040.
26. Saag KG, Choi H. Epidemiology, risk factors, and lifestyle modifications for gout. Arthritis Res Ther. 2006;8(Suppl 1):S2. doi: 10.1186/ar1907.
27. Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nat Rev Rheumatol. 2020;16:380-90.
28. Boffetta P, Nordenvall C, Nyrén O, Ye W. A prospective study of gout and cancer. European Eur J Cancer Prev. 2009;18:127-32. doi: 10.1097/CEJ.0b013e328313631a.
29. Kuo CF, Luo SF, See LC, Chou IJ, Fang YF, Yu KH. Increased risk of cancer among gout patients: a nationwide population study. Joint Bone Spine. 2012;79:375-8.
30. Chuang JP, Lee JC, Leu TH, Hidajah AC, Chang YH, Li CY. Association of gout and colorectal cancer in Taiwan: a nationwide population-based cohort study. BMJ Open. 2019;9:e028892.
31. Kang DH, Ha SK. Uric Acid Puzzle: Dual Role as Anti-oxidantand Pro-oxidant. Electrolyte Blood Press. 2014;12:1-6.
32. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci U S A. 1981;78:6858-62.
33. Kim J, Lee HK. Potential Role of the Gut Microbiome in Colorectal Cancer Progression. Front Immunol. 2021;12:807648.
34. Méndez-Salazar EO, Martínez-Nava GA. Uric acid extrarenal excretion: the gut microbiome as an evident yet understated factor in gout development. Rheumatol Int. 2022;42:403-12.
35. Ansari Z, Findakly D, Wang J. A Retrospective Review of Tumor Lysis Syndrome Associated With Colorectal Cancer. Cureus. 2020;12:e8257.
36. Raja R, Kavita F, Amreek F, Shah A, Sayeed KA, Sehar A. Hyperuricemia Associated with Thiazide Diuretics in Hypertensive Adults. Cureus. 2019;11:e5457.