EJMI

DOI: 10.14744/ejmi.2022.19023
EJMI 2022;6(2):141–146

Review

Uric Acid & Cancer

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Abstract

Uric acid (UA) (C5H4N4O3), is a heterocyclic compound with a molecular weight of 168.11 Da and, it's the last product of purine metabolism in humans. The relationship in-between UA and cancer is complex as UA has both anti-oxidant and pro-oxidant functions. Due to its anti-oxidant function, it was proposed as a protector for cancer growth. Also the products of xanthine oxidoreductase (XOR) activity; reactive oxygen species (ROS), and UA induced immuno-inflammatory reaction and oxidative stress were proposed to have roles in carcinogenesis. In fact, ROS may activate the inflammation mediated cell proliferation, angiogenesis and metastasis related signal pathways and so may have a possible carcinogenic potential. So, UA may promote inflammation mediated oncogenesis by both ROS production and cell transcription and cytokine synthesis. Higher levels of UA seem to be closely related to oncogenesis, though more specifically designed extended studies are needed on the subject.

Keywords: Cancer, oncogenesis, uric acid

Cite This Article: *Yilmaz H, Barutca S. Uric Acid & Cancer. EJMI 2022;6(2):141–146.*

Uric acid (UA) (C5H4N4O3), is a heterocyclic compound with a molecular weight of 168.11 Da, and it is the last product of purine metabolism in humans.[1] Antoni van Leeuwenhoek has firstly described UA crystals in gout tophus in 1679.[2] Normal UA levels in serum are 2.6-5.7 mg/dL (155-339 µmol/L) in premenopausal women and 3.5-7.0 mg/dL (208-416 µmol/L) in postmenopausal women and men.[3] It is taken by diet exogenously or it is formed as a result of adenine/guanine-based purine metabolism.[4] Nucleotidase enzymes produce adenosine/guanosine by influencing on adenosine monophosphate (AMP) and guanosine monophosphate (GMP) and removing phosphate part.[5] Adenosine is converted to inosine by adenosine deaminase and inosine converted to hypoxanthine by purine nucleoside phosphorylase. Guanosine is converted to guanine by purine nucleoside phosphatase and guanine is converted to xanthine by guanine deaminase.[5] Hypoxanthine is converted to xanthine by xanthine oxidase and xanthine is converted to UA by xanthine oxidase.[5] Although purine degradation pathway contains many enzymes, xanthine oxidoreductase (XOR) is the critical and rate-limiting enzyme in purine metabolism.[1] This enzyme has two different structures that can transform into each other, xanthine oxidase and xanthine dehydrogenase.[6] Although XOR activity is present in many tissues, endogenous UA synthesis occurs mostly in liver, intestines, kidneys, muscles, breast tissue and vascular endothelium.[7] Though amount of exogenous purine taken by diet varies, it exists abundantly in red meat such as offal (liver, kidney, etc.), fatty poultry, fatty dairy products, sea products and alcohol.[8] Purine catabolism is stopped at UA stage due to lack of a functional uricase gene and thus lack of active uricase enzyme in human.[9] Because it couldn't move freely throughout cellular membranes, specific carriers provide transportation of UA throughout plasma membranes. Although there are UA carriers in many cell types, those carriers are found abun-

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Submitted Date: October 12, 2021 **Accepted Date:** January 16, 2022 **Available Online Date:** March 21, 2022

dantly in kidney and intestine due to being main route of excretion of UA. Excretion occurs approximately 70% via kidneys, 30% via gastrointestinal system (GIS).[6]

Antioxidant role of UA is its best known and extensively recognized function,[10] when UA level in circulation is between normal ranges. UA forms 50% of total antioxidant capacity of biological fluids in human.[11] It is known that uric acid prevents protein nitrification, lipid and protein peroxidation caused by peroxynitrite and acts as an antioxidant.[12] As an antioxidant, UA functions to eliminate reactive oxygen species (ROS) which show carcinogenic effect by increasing mutation ratios and oncogenic potentials of cells.[13] As a result of this effect, it has been suggested that it is associated with decreased cancer risk by preventing neoplastic transformation.[14]

Hyperuricemia is defined as being average UA serum level above 6.8 mg/dL (404 μM).[15] Degradation of nucleic acids also increases together with increased cell turnover in many pathological processes such as hemolysis, tumor progression or tumor lysis syndrome and may cause large amounts of purine, and therefore this increases demand for purine elimination and UA formation.[16] It has been determined that UA has pro-oxidative effects in intracellular environment in case of hyperuricemia while UA has antioxidant feature in extracellular environment.[17] Also evidences supporting influence of UA on immuno-inflammatory system through potential relation between carcinogenesis and mortality by increasing XOR and ROS production have been increasing gradually.[18] In this review, it has been aimed to summarize role of hyperuricemia in cancer development and mechanisms between UA and carcinogenesis.

Cancer, Reactive Oxygen Species and Uric Acid

Increase of oxidative stress occurs with increase of cytotoxic superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) by XOR enzyme, primarily by ROS.[19] UA formed by XOR as a result of purine metabolism causes increase of mitochondrial ROS production as a result of pyrin domain-containing 3 (NLRP3) inflammasome stimulation.[20] Although ROS has a physiological task in cellular signal conduction, its pathological effects are seen in many conditions including inflammation, aging, cancer, diabetes, cardiac diseases and metabolic syndrome.[5] The relation between cancer and ROS has been known for long years. It is thought that ROS plays dual role in arrangement of tumor cell signal pathway.[21] Firstly ROS forms a carcinogen potential by activating signal pathways related to cell proliferation, angiogenesis and metastasis through inflammation in line with the mechanisms described below.[22,23] Cyclins synthesized at specific phases of cell cycle activate inactive cyclin-dependent kinase (CDK) molecules. ROS down-regulates cyclins by activating Jun N-terminal kinase (JNK) and p38 mitogen activated protein kinase (MAPK) signal pathway. Together with reduction of cyclins, CDKs couldn't be activated and neoplastic transformation develops.[24] Increasing ROS also induces tumor development through matrix metalloproteinases (MMP) in tumor microenvironment.[25,26] It also accelerates angiogenesis by increasing production of angiogenic factors such as vascular endothelial growth factor (VEGF) and nitric oxide (NO).[27] Moreover, ROS stimulates epithelial-mesenchymal transformation (EMT) by activating pathways of MAPK family and forms a premetastatic niche at distant organs.[28] However, it can increase adhesion of tumor cells by inducing phosphorylation of integrin responsible from adhesion and focal adhesion kinase (FAK).[29] Distinct from all those events, increased ROS level may also stimulate cell aging by inducing cell apoptosis as a second effect.[30]

It is well known that chronic inflammation developed in a microenvironment induces development of neoplasia and tumor progression.[31] Similarly, also role of inflammation of UA-origin has been demonstrated in cancer development.[31,32] As described above, UA may trigger oncogenesis indirectly via ROS production. In hyperuricemia state, UA feeds body fluids and undergoes to a phase change by nucleation into monosodium urate (MSU) crystals.[33] MSU particles released from dying cells are phagocytized by neutrophils and macrophages.[34,35] When MSU particles are phagocytized, "NOD-like receptor family" is stimulated and they convert interleukin-1 (IL-1) to its proinflammatory and active form IL-1β in order to activate NLRP3 inflammasomes.[36] Activated NLRP3 inflammasomes put cyclin-D1 into the circuit and binds to IL-1β receptor; thus, it activates Nuclear Factor Kappa B (NF-κB) which initiates JNK signal causing proliferation, invasion and cancer development.[37] As a result, UA may change transcription program of a cell and arranges inflammation responses by modulating cytokine production.[38] Also, UA triggers inflammation by collecting monocytes in the circulation by leading to increase of serum chemokine ligand 2 (CCL2) which is a chemo-attractant playing a role in chronic low-grade inflammation.[39]

Uric Acid in Cancer Etiology

Subject of serum UA levels and risk of cancer development has been mentioned in various studies. In AMORIS study, UA levels have been associated with risks in general and for some specific cancers in 493.281 cancer patients. While statistically significant correlations have been found between UA level and increased incidence for colorectal, hepatobiliary, renal and non-melanoma skin cancers in males; a significant relation has been found between reduced UA

level and increased incidence of lung cancer. In women, while significant correlations have been found between UA level and increased incidence for head and neck cancers; significant correlations have been found between reduced UA levels and increased incidence of breast, hematological and lymphatic cancers.[40]

In EPIC-Heidelberg study, while incidence of breast cancer and overall cancer mortality have decreased with increased levels of both albumin and UA, this correlation hasn't been determined in lung, prostate and colon cancer.[41] Also, any direct correlation couldn't be found between UA levels and overall cancer mortality in this study.[41]

Kolonel et al.[42] hasn't been able to demonstrate any significant correlation between UA levels and total cancer risk (lung, stomach, colon, rectum, bladder or hematopoietic system cancers, while they have found a significant correlation between increased UA levels and risk of prostate cancer in 1544 Japanese male cancer patients.

In some studies, hyperuricemia has been found to be associated with increase in cancer incidence and poor survival.[43] According to five independent studies and a meta-analysis including 632.472 patients, higher UA levels have been found to be associated with increased overall incidence of cancer.[13] In that meta-analysis, it has been also shown that high UA levels were significantly associated with cancer incidence in males. Higher UA levels appear to be associated especially with increased cancer incidence and mortality risk.[13]

It has been demonstrated that high UA levels were also associated with frequency of occurrence of urological cancers. It has been found that gout patients have risk of prostate, bladder and renal cancers, respectively.[44] A study conducted on 28.613 elderly women in Austria has shown that higher UA levels before diagnosis has been associated with increase of overall cancer risk and cancer mortality in women.[45]

Uric Acid in Clinical Process of Cancer

In a study in which hyperuricemia mouse model was used, it has been shown that hyperuricemia disturbed T cell proliferation by influencing functionality of CD8+T cells *in vivo* and decreased efficiency of immunotherapy agents as well as leading to increased death rate and poorer prognosis in cancer.[46]

It has been found that it was responsible from increased cell cycle and tumor lysis syndrome and increased UA levels in some cancers, consequently it was associated with cancer progression and decreased survival.[47]

It has been found that plasma UA levels were lower after CRT for patients whose chemo-radiotherapy (CRT) treatment was efficient in patients with nasopharynx cancer.[48] In squamous cell esophagus cancer, it has been pointed out that patients with higher preoperative UA level had significantly shorter survival times and this situation was an independent prognostic factor in those underwent R0 esophagectomy.[49] For colorectal cancer (KRK), it has made us thought that UA levels increased gradually from stage I up to stage IV and it could also help evaluation of treatment response as well as prognosis of KRK patients.[23]

In patients with stage I-III renal cell carcinoma, it has been reported that a postoperative ≥10% increase in UA level was predictive for overall survival and survival without recurrence.[50]

In a study conducted, it has been pointed out that high UA level is an important prognostic marker for lymphatic metastasis in KRK patients.[51] It has also been determined in non-small-cell lung cancer that more brain metastasis was seen in patients with higher UA levels.[52] Also, it has been determined that time until brain metastasis and overall survival time were shorter.[52]

In a study conducted by Strasak et al.,[53] it has been demonstrated that higher UA levels were associated with increase of risk of total cancer mortality independently. However, it has been shown in many studies that higher UA levels were an independent risk factor for cancer related mortality.[54] In a study conducted on hypertensive Chinese patients, an independent and positive correlation has been determined between higher UA levels and GIS cancer and risk of cancer mortality.[55] It has been observed in patients with pancreas cancer that higher UA levels were an independent prognostic factor for overall survival.[56] In a meta-analysis performed, association with cancer mortality has been revealed in female individuals having higher UA levels.[13] At the same time, it has been found that there was an association between higher UA levels and increased mortality of GIS cancer.[13]

On the other hand, it has been found in some other studies that hyperuricemia was associated with better results in cancer patients.[57] Taghizadeh et al.[58] has reported that increasing UA levels were associated with a reduction in risk of cancer mortality. Kuo et al.[59] has put forward that lower UA levels were associated with increase of risk of cancer-related mortality compared to higher UA levels.

Result

In this review, studies included in medical literature about possible influence of hyperuricemia on development of various cancers, their clinical course and mortality after summarizing UA metabolism. Because serum UA level reflects the balance between UA synthesis and excretion,

increase of production and/or decrease of excretion may cause hyperuricemia. Both inflammation caused by urate crystals and ROS production might be thought as a main mechanism stimulation development of cancer cells together with hyperuricemia.

Higher quality additional researches are needed in order to provide certain determination of relation between higher serum UA and development of cancer, especially associated with gender and certain cancer types. However, currently published epidemiological studies about relation between UA levels and cancer-related incidence and mortality have provided different findings possibly due to different study design, patient groups, sample size and statistical power. But it is thought that there is a correlation between higher UA level and increased incidence of cancer, disease progression and poor survival.

Disclosures

Ethics Committee Approval: Ethics committee approval was not requested for this study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.B.; Design – H.Y.; Supervision – S.B.; Materials – H.Y.; Data collection &/or processing – H.Y.; Analysis and/or interpretation – S.B.; Literature search – H.Y.; Writing – H.Y.; Critical review – S.B.

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