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Is There any Possible Association Between Trimethylamine N-Oxide (TMAO) and Cancer? A Review Study

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Abstract

Background: During the transit of digested animal source foods, gut microbiota synthesize metabolites that can affect the body cells. One of these metabolites, i.e. Trimethylamine (TMA) that is an intermediary metabolite, ultimately leads to the production of Trimethylamine N-oxide (TMAO). Several studies have been conducted to show the association between TMAO and different diseases. This article aimed to search literature in order to review published findings about the possible association between TMAO and cancer.

Materials and Methods: In this literature review, a comprehensive electronic search of different databases was done using "Trimethylamine N-oxide" and "cancer" as the main keywords.

Result: Research suggests that TMAO can be related to the increased risk of cancer. The results showed a higher level of serum TMAO in cancer patients, most importantly colorectal cancer (CRC), than in healthy controls. Nevertheless, inflammation, oxidative stress, and DNA damage could be the reasons for the link between TMAO and cancer. Limiting dietary intake of animal products can reduce levels of TMAO.

Conclusion: It is concluded that a higher rate of TMAO production could potentially be associated with the development of different types of cancers, particularly CRC.

Keywords: Trimethylamine N-oxide, Cancer, Colorectal Cancer, Trimethylamine

Introduction

Cancer is a leading cause of death worldwide. There was an estimated rate of 19.3 million new cancer cases, accounting for nearly 10 million deaths in 2020. The overall incidence rate was higher in transitioned countries than in transitioning ones in both sexes [1].

Several factors can be responsible for the incidence of cancer [2-4]. One of the factors that has recently been shown to have a relationship with cancer, along with other diseases, is an organic compound called trimethylamine N-oxide (TMAO) [5, 6]. TMAO is produced by a precursor, i.e. trimethylamine (TMA), being a metabolite of various precursors, mainly choline and carnitine from ingested foods. The increase in TMAO levels can be attributed to two sources. The first source is TMA that is derived from precursor molecules by the action of gut bacteria and subsequent oxidation in the liver. The second one is dietary intake of TMAO-rich foods, such as red meat, eggs, milk, and certain fish products, including salmons [7, 8].

High levels of serum TMAO could be associated with the risk of Cardiovascular Disease (CVD) [9-11]. Research shows that by increasing cholesterol accumulation in macrophages and in foam cells of artery walls, TMAO contributes to atherosclerosis, thereby leading to cardiovascular disease [12]. According to animal studies, elevated levels of TMAO are directly associated with progressive organ fibrosis and dysfunction [13, 14]. The TMAO pathway and its metabolites are possibly involved in the development of two major health problems, including insulin resistance and cancer [15]. There is an association between high TMAO levels with low bacterial diversity and a change in the composition and distribution of bacterial phylotypes. Thus, a change in gut microbiota contributes to oncogenesis and tumor progression, both locally and systemically. Although inflammatory and metabolic cues support this phenomenon, additional mechanisms could attribute to the ability of dysbiosis to promote carcinogenesis [16]. We firstly describe TMAO and its formation pathways in brief. Next, we investigate the possible association that may exist between TMAO and cancer. Finally, we review recent studies on the potential correlation between TMAO and cancer.

Materials and Methods

A comprehensive review of electronic databases, including ISI web of knowledge, Scopus, and PubMed was made using the main keywords of "cancer" and "Trimethylamine N-oxide". Besides, a manual search was done in the references of the articles gathered to improve the precision of the review. There were no restrictions on the date of publication. Randomized trials, case control studies, and prospective cohort studies were included for the purpose of this study. However, we excluded reviews and studies on animals, available articles with incomplete texts, and articles irrelevant to our topic.

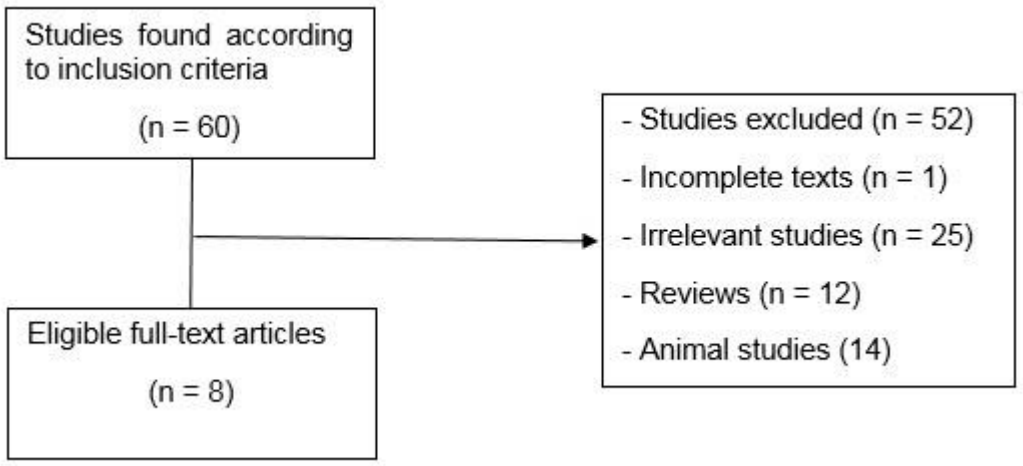

Fig. 1. Study selection

Results

TMAO and its formation pathway: Trimethylamine N-oxide (TMAO) is a compound whose consideration in blood is dependent on the amount of phosphatidylcholine and L-carnitine produced after digestion of animal source foods [6, 17]. The production mechanism of TMAO in humans initiates with the digestion of food sources of two main TMAO precursors called L-carnitine and choline. These precursors are mostly found in animal source foods, such as red meat, milk, eggs, and several types of fish, particularly in salmons [7, 18]. Certain types of gut microbiome convert these molecules to an intermediate precursor for TMAO called trimethylamine (TMA) which is then absorbed by intestinal epithelium. Next it is transported to the liver by the bloodstream so as to be ultimately converted to TMAO by the enzymes of the Flavin Mono Oxygenase (FMO) family, in particular FMO-1 and FMO-3 isoforms [19]. In addition, different compounds found in foods may have a potential impact on the hepatic production of TMAO [20].

The possible association between TMAO and cancer: TMAO has the potential for causing malignant changes to body cells. TMAO has been identified as a metabolite with deleterious effects on exposed cells. Such effects can be exerted by the formation of N-Nitroso compounds, thereby leading to DNA damage [21, 22]. In addition, high consumption of animal source foods can contribute to the formation of TMAO and its precursors. This may increase the risk of cancer in the gastrointestinal (GI) tract, and in particular, colorectal cancer (CRC) [23]. In a retrospective study in 2017, results of 108 patients with

colorectal cancer and 30 healthy controls showed that pretreatment serum levels of TMAO were higher in CRC patients than in the healthy control group. This could be a prognostic marker for CRC [24]. In a case-control study conducted on women in the United States, the plasma TMAO levels were positively associated with CRC risks. In another study, participants in the highest quartile of plasma TMAO concentrations were shown to be at a higher risk of rectal cancer (by 3.4 times) than those in the lowest quartile of plasma TMAO concentrations. This study verified the presence of a positive association between plasma TMAO levels and the risk of colorectal cancer [25].

It could be concluded that TMAO is responsible for CRC. However, several studies reject such linkage, in which TMAO has been shown to have a protective effect on carcinogenesis by correcting folding defects of mutant proteins [26, 27].

TMAO may be responsible for offsetting protective effects of alpha-casein, i.e. a milk protein acting as a tumor suppressor via activation of STAT1 signaling. It can also be a preventive factor against cancer tumor growth and metastasis [28, 29].

Evidence suggests that inflammation could be a causing factor for the link between TMAO and cancer. TMAO has been found to activate the signaling of nuclear factor-κB (NF-κB) [30]. According to a study in Germany, there is a positive association between plasma TMAO concentrations and TNF-α levels. Furthermore, serum levels of TMAO were shown to be associated with TNF-α and IL-6 in diabetic patients with chronic kidney disease. Both TNF-α and IL-6 can induce chronic inflammation, which can be carcinogenic [31] and may explain carcinogenicity of TMAO.

There are associations between high TMAO levels, low bacterial diversity, and a change in the composition and distribution of bacterial phylotypes. Past research shows that a change in the composition of microbiomes could be correlated with the increased risk of CRC, breast cancer [32], and gastric cancers [33].

Oxidative stress is another pathway between TMAO and cancer. Increased levels of TMAO circulation result into superoxide production, i.e. a reactive oxygen species (ROS) linked to oxidative stress [34]. Oxidative stress was revealed to contribute to carcinogenesis [35].

Table 2. Details of included human studies

Author	Year of study	Sample size	Type of study	Research objectives	Results
Guertin et al (23)	2017	644 CRC cases and 644 controls	Case-control study	To investigate the relationship between serum concentrations of TMAO and its precursors (choline, carnitine, and betaine) and incidence of CRC in male smokers	Higher serum choline concentrations (but not TMAO, carnitine, or betaine) were associated with the risk of CRC
Liu et al (24)	2017	108 CRC cases and 30 healthy controls	Case-control study	To determine whether TMAO is a predictor of patients with CRC	Median serum TMAO levels were significantly higher in CRC patients than in healthy controls.
Bae et al (25)	2014	835 CRC cases and 835 controls	Case-control study	To examine the association between plasma choline metabolites and the risk of CRC	Positive associations between plasma TMAO and the CRC risk
Griffin et al (41)	2019	115 healthy people at the risk of CRC	Randomized controlled trial	To determine if the Mediterranean diet would reduce TMAO concentrations	Results suggest that broad dietary pattern interventions over six months may not be sufficient for reducing TMAO levels.
Liu et al (47)	2018	671 PLC cases and 671 controls	Case-control study	To measure TMAO and choline levels of serum and their association with the PLC risk	Higher serum levels of TMAO were associated with an increased PLC risk.
Mondul et al (48)	2015	200 cases (100 aggressive cases) and 200 controls	Cohort study	Prospective analysis of prostate cancer concerning Alpha-Tocopherol and Beta Carotene	Positive associations between TMAO and prostate cancer
Bag et al (49)	2015	18 specimens were confirmed as OSCC and 12 as the control group	Cross -sectional	Metabolomics alterations in oral cancer	Trimethylamine N-oxide is an important metabolic signature for oral cancer.
Xu et al (46)	2015	a comprehensive database of human genes	Experimental framework for human genes	Presenting an unbiased data-driven network-based systems approach to uncovering a potential genetic relationship between TMAO and CRC	Results show that TMAO is genetically associated with CRC.

Discussion

Several studies have addressed an association between high intake of animal source foods, being a potential causative factor for an increase in serum TMAO levels and cancer disease, in particular colorectal cancers (CRC). A genome-wide analysis performed by Xu et al showed that TMAO, produced by dietary intake of red meat, may genetically have a strong relationship with CRC [36, 37]. New findings demonstrate that even diets have an important effect on the composition of microbiomes existing in the gut. Diets can also alter certain types of gut microbiomes to generate TMA from their precursors existing in animal source foods, thereby resulting in higher serum TMAO levels [38]. The colon contains numerous microorganisms, so dietary changes may be responsible for gut dysbiosis and a reason for promoting progress of colorectal carcinogenesis via multiple mechanisms. These mechanisms are comprised of inflammation, activation of carcinogens and tumorigenic pathways, as well as the damaging of host DNA [39]. A study was conducted on germ-free mice. The mice were transfaunated with rice bran-modified microbiota collected from human stool during fecal microbiota transplant. The results showed that TMAO and tartrate, being associated with CRC development, were reduced in murine colon tissues [40].

Nevertheless, these findings may vary under different circumstances. A study was conducted in healthy adults on the consumption of a Mediterranean diet for six months to determine if a high-fiber diet would reduce plasma concentrations of TMAO as an appropriate selection for reducing the risk of colon cancers. Accordingly, Griffin et al suggested that there was no significant correlation between consumption of the Mediterranean diet and plasma TMAO concentrations in healthy adults [41]. Vegetarian diets, by altering composition of gut microbiota, reduced TMAO production [42].

A randomized controlled trial showed that consumption of animal source foods, in particular fish, was associated with a significant increase in circulated TMAO levels in healthy young men [43]. In another study conducted by Kruger et al, it was reported that consumption of animal source foods had a positive correlation with an increase in circulatory TMAO levels [44]. Several studies indicate that consumption of certain animal source foods, in particular fish, is the reason for having a significant increase in TMAO production; however, it could not be concluded that such foods are certainly responsible for increasing the risk of cancer. Besides, fish consumption is associated with the intake of certain health-promoting compounds, with protective effects on cancer.

A meta-analysis with 42 studies demonstrated that fish intake could even be protective against certain types of cancers, in particular gastrointestinal cancers (GIC), by reducing their risk [45]. On the other hand, TMAO may be an important intermediate marker linking dietary meat, fat, and gut microbiota metabolism to the risk of CRC [46]. Serum TMAO concentrations can contribute to the incidence of different types of cancers, such as primary liver cancer (PLC), as shown in a study conducted by Liu et al. In their study, they found an association between higher serum TMAO concentrations and PLC risks [47].

In a cohort study in Finland, a positive correlation was observed between increased levels of plasma TMAO with the risk of aggressive prostate cancer [48]. This result was supported by other studies indicating that patients with oral squamous cell carcinoma have a higher Serum level of TMAO than healthy controls [49].

Inconsistent with other studies, a study found no relationship between TMAO levels and CRC risks [15]. Differences in results could be explained by the inclusion of different covariates in multivariate logistic regression analyses.

Limitations of previous studies were disregarding kidney function as well as consumption of probiotic and gut-blood barrier permeability as the confounder.

In previous articles, we discussed about glucose and glutamine restrictions along with the increase in non-fermentable ketones for cancer treatment [50-53].

It is suggested that TMAO Should be considered in dietary interventions for cancer prevention and treatment purposes. It is worth noting that modulation of the composition of intestinal microbiota by dietary interventions can result in a reduction in production levels of TMA and TMAO.

In general, a considerable body of evidence is needed to suggest whether TMAO production is correlated with the increased risk of certain cancers.

Conclusion

Elevated levels of TMAO production could potentially be associated with developments of different types of cancers, particularly CRC. TMAO can be produced by intestinal bacteria from TMA precursors in ingested foods. Further studies are needed on the relationship between intestinal microbiota and cancer.

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