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Review Article

The Role of Food containing Nitrosamine in the Development of Nasopharyngeal Carcinoma: A Literature Review

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Abstract

Nasopharyngeal carcinoma (NPC) is a rare malignancy originating from epithelial cells in the nasopharynx, with an incidence rate of fewer than 1–2 cases per 100,000 people annually but exceeding 20 cases in endemic regions. Its development is influenced by multiple factors, including nitrosamines found in preserved foods, beer, cigarettes, and drinking water. This review explores the role of nitrosamines in food and the mechanism that caused NPC development by analyzing relevant literature from major databases such as Google Scholar, Web of Science, and PubMed. In addition, nitrosamines, such as N-nitrosodimethylamine (NDMA), form through nitrosation, a process involving nitrites and nitrogen oxides interacting with amino compounds. Although the World Health Organization (WHO) sets a daily nitrosamine intake limit of 10 µg/kg body weight, excessive or prolonged exposure may contribute to cancer development. Once metabolized by cytochrome P450, nitrosamines can cause DNA damage, potentially leading to carcinogenesis. However, NPC results from a complex interplay of factors, and nitrosamines alone do not directly cause cancer. Their carcinogenic potential increases when combined with other risk factors. Additionally, chemopreventive agents such as curcumin and vitamin C may help reduce cancer risk.

Keywords:

Nasopharyngeal carcinoma
Nitrosamine
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DNA damage

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1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy originating from epithelial cells in the nasopharynx. The development of this malignancy is influenced by a complex interplay of environmental factors, genetic structures, and Epstein-Barr virus (EBV) infection. NPC is an uncommon malignancy, with an incidence rate of fewer than 1-2 cases per 100,000 population per year (1). Clinical manifestations commonly associated with nasopharyngeal carcinoma include nasal congestion, nasal bleeding, tinnitus, hearing loss, and headaches, among others (2).

Nasopharyngeal carcinoma exhibits a distinct geographical distribution. It is primarily concentrated in East Asia and Southeast Asia (3). Other literature suggests that regions with the highest incidence are found in East Asia, South Asia, and Southeast Asia, with China having the highest national incidence rate (1). The incidence rates in endemic areas also indicate high figures, reaching over 20 cases per 100,000 population, resulting in a heavy public health burden in endemic areas (1,4). It is intriguing to investigate the risk factors contributing to the elevated incidence of NPC in specific areas.

NPC is caused by various factors such as environmental conditions, genetic susceptibility, and EBV infection. Some studies have shown that nitrosamines contribute to the development of NPC in patients. Environmental factors such as alcohol consumption, smoking, and the intake of preserved foods (2,3) are examples of sources containing nitrosamines. In addition, nitrosamines are also contained in marinated/smoked foods, beer, cigarettes, and even drinking water (5,6).

These findings strengthen the likelihood that the presence of nitrosamines in such dietary items may be linked to the increased incidence of cancer. Furthermore, this study further discusses nitrosamines in food and the mechanism that causes NPC.

2. Diet-related to Nitrosamine

Three types of nitrosamines are most commonly found in food. The nitrosamines include N-nitrosodimethylamine (NDMA), N-nitrosopyrrolidine (NPYR), and N-nitrosopiperidine (NPIP) which are most frequently discovered while other types of nitrosamines are discovered in rare cases. NDMA was the most frequently detected nitrosamine and was found in 30% of food samples, with 6% of them having concentrations above 5 µg/kg. On the other hand, NPYR and NPIP were found at concentrations above 0.5 µg/kg in only 3% and 2% of foods, respectively (7). Other studies showed that NDMA was the most common nitrosamine found in food with an average concentration of 2.2 ± 0.3 ng/g followed by NDBA, NPYR, NDEA, NPIP, NMOR, NMEA, and NDPA (8). Details on the concentration of nitrosamines in foodstuffs are summarized in **Table 1**.

Table 1. Concentration of total nitrosamine in various food categories (8)

Food	Concentration of Nitrosamine
Fats, Oils, and Sweets	8.92 µg/Kg
Meats	8.10 µg/Kg
Fish	5.55 µg/Kg
Vegetables	5.35 µg/Kg
Beverages	4.95 µg/L
Condiments	4.26 µg/Kg
Grains	2.05 µg/Kg
Alcoholic Beverages	1.98 µg/L
Dairy products	0.51 µg/Kg

3. Formation Process of Nitrosamine in Food

The addition of nitrite and/or nitrate salts to meat, fish, and poultry is a way of preserving food. Nitrites and nitrates have also been widely used in the preservation of meat products as an effective antimicrobial measure against some pathogenic bacteria. However, nitrite and nitrate can react with proteins in certain products and produce harmful substances called nitrosamines (9,10). Nitrosamines can also be found in the environment and agricultural products. Nitrosamine occurs in waters as a disinfection byproduct produced during chlorination and ozonation of wastewater. Sewage treatment and wastewater discharge from factories can also lead to the occurrence of nitrosamine in water. Hence, nitrosamine can accumulate in agricultural products and aquaculture resulting in the pollution of raw food materials (11,12). Similarly, livestock that consume feed contaminated with nitrosamines may contribute to the accumulation of these carcinogens in meat and dairy products. Furthermore, food packaging materials, particularly those made from rubber or plastic, may introduce nitrosamines into processed foods. Cooking methods, such as frying or smoking, can further enhance nitrosamine formation, compounding the risk (8,12).

Nitrosamines are formed in food through a process called nitrosation. The role of nitrite and nitrogen oxides in nitrosamine formation is through their interaction with secondary and tertiary amino compounds. These are found in foods that contain nitrite or that have been exposed to nitrogen oxides (5). Nitrogen oxides formed during food processing, preservation, and preparation are capable of

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reacting with amino and other compounds and forming nitrosamines. Two major sources of nitrosating agents are the addition of nitrates or nitrites to foods and the heating and/or drying of foods in combustion gas so that nitrogen-containing molecules can be oxidized to nitrogen oxides (7,9).

Some salts like sodium nitrite ($NaNo_2$) are contained in food through some preservation process and converted into nitrous acid (HNO_2) under acidic conditions. Due to the instability of nitrous acid, it decomposes easily into nitrous anhydride (N_2O_3). Nitrous anhydride (N_2O_3) is a compound that reacts with amines and then produces nitrosamine (12). Amines that undergo nitrosation in food products, especially meat, are often secondary amines. Some of which are derived from excessive oxidation of proteins. Other nitrosated amines are derived from cyclization and deamination reactions found in meat (10). The process of nitrosamine formation in food is presented in **Figure 1**.

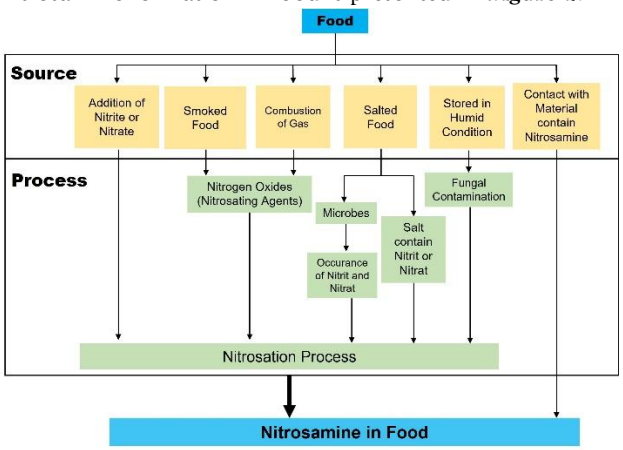

Figure 1. Formation Process of Nitrosamine in Food. The sources of nitrosamine formation in food can be classified into six categories: the direct addition of nitrite or nitrate, smoked foods, food combustion with gases, salted processed foods, foods stored in humid conditions, and foods that come into direct contact with nitrosamines. These foods undergo various processes that ultimately lead to the formation of nitrosamines.

4. Exposure and Carcinogenicity of Nitrosamine

The primary mechanism involves the metabolic activation of nitrosamines by cytochrome P450 enzymes, which convert them into highly reactive compounds. These compounds can induce alkylation of DNA, leading to mutations in critical tumor suppressor genes and oncogenes. Over time, this genetic instability promotes uncontrolled cell growth, inflammation, and eventually tumor formation (13,14). Nitrosamines may also play a role in cancer development through epigenetic changes. These alterations can result in the suppression of tumor suppressor genes or the activation of oncogenic pathways, thereby promoting carcinogenesis (15,16). Furthermore, prolonged exposure to nitrosamines can create a pro-cancerous environment by enhancing oxidative stress and suppressing immune responses. Oxidative stress has been associated with the initiation and progression of cancer, as it can increase DNA mutations, cause DNA damage, disrupt genome stability, and promote uncontrolled cell proliferation (13,17).

Nitrosamine is one of the components contained in salty foods that is involved in the development of NPC. Several studies have shown that processed or salted foods are associated with nitrosamine-mediated NPC (18). There are many types of Nitrosamines contained in food and proven to cause cancer. Some in vivo studies have also shown that foods such as salted fish are carcinogenic in NPC cases. Of the various causes of NPC, NDMA is a nitrosamine that is proven to be the most frequently found in food and causes cancer. More than 300 types of nitrosamines have been identified as carcinogenic in several animal species (7). NDMA was also identified previously in 20 human and non-human species and proven to be a cause of cancer. Especially for nitrosamines in fed rats, the induction of tumors is more common in the nasal cavum (13).

Tobacco use is known to be the largest source of daily nitrosamine intake with 21,800 ± 4,350 ng/day. Meanwhile, nitrosamine from food is the second largest source of nitrosamine exposure. The type of diet model between one another also affects daily nitrosamine intake. In a vegetarian diet, daily nitrosamine intake ranged from 1,800 ± 350 ng/day while in a western diet ranged from 1,900 ± 380 ng/day. In addition, consumption of beer or other malt beverages contributes to daily nitrosamine intake ranging from 1,000 ± 200 ng/day. In addition, nitrosamine can be contained in drinking water although in small portions. Exposure to drinking water contributes to daily nitrosamine intake ranging from 120 ± 24 ng/day (8).

Nitrosamine is becoming a frequently detected environmental contamination material. Hence, several studies indicate some daily intake limits for nitrosamine. Permissible daily exposure (PDE) of NDMA is 0.6 µg/person/day and 6.2 µg/person/day for PDE mutation and PDE cancer, respectively. Meanwhile, NDEA is 0.04 µg/person/day for PDE mutation and 2.2 µg/person/day for PDE cancer (19). According to other literature, the allowable intake (AI) of NDMA is 96.0 ng/day and NDEA is 26.5 ng/day (20). In addition, according to WHO (World Health Organization), the daily limit of total nitrosamine was 10 µg/kg body weight (21).

Many nitrosamines have been identified as carcinogenic. NDMA is proven to have a high level of carcinogenicity.

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According to the IARC classification, NDMA is included in group 2A which means probably Carcinogenic to Humans, the same as NDEA (5,8). Other nitrosamines such as NPIP, NDBA, NPYR, NDEA, and NMEA belong to group 2B and are possibly carcinogenic to humans (8). Table 2 summarizes the carcinogenicity of nitrosamines and the daily intake limit for nitrosamines.

The IARC's recognition underscores the seriousness of nitrosamines as public health threats, particularly given their widespread presence in processed foods, tobacco smoke, and contaminated water sources. Regulatory measures to limit human exposure to nitrosamines through improved food safety standards, stricter control of industrial emissions, and clearer labeling of processed food products. Public awareness campaigns and dietary recommendations can help reduce nitrosamine intake, especially in populations with high NPC incidence. Integrating IARC findings into national and international health guidelines can play a critical role in cancer prevention strategies.

According to the EFSA Panel on Contaminants in the Food Chain, there are priorities for better understanding the risks of nitrosamines (N-NAs) in human exposure. These priorities include studying their absorption, distribution, metabolism, and excretion (ADME), as well as fully characterizing their metabolic activation pathways and DNA adduct formation in humans and animals. Furthermore, additional research is necessary to determine the mutagenic potency of specific N-NAs present in food, particularly those with unclear genotoxic mechanisms. The panel recommends epidemiological studies using molecular and omics approaches to assess the link between N-NAs and cancer while accounting for confounding factors such as medication use, occupational exposure, and smoking. Standardizing sensitive analytical methods for detecting both volatile and non-volatile N-NAs in various foods is crucial. Moreover, expanding data collection beyond processed meats to include raw meats, vegetables, cereals, dairy products, fermented foods, and human milk is essential for a more comprehensive exposure assessment, especially in infants (22).

6. How Nitrosamines Trigger NPC

Nitrosamine is supposed to be stable if under its physiological condition. To make it carcinogenic, nitrosamine requires metabolic activity by cytochrome P450-dependent. Nitrosamine is metabolized by CYP2E1 into molecules that are carcinogenic and expressed mainly in the nasal cavity epithelium of animals including humans (13). This process hydroxylates the carbon adjacent to the N-nitroso group. After that, there is spontaneous elimination of the aldehyde with carbon-nitrogen bond learning resulting in dealkylated primary nitrosamine. This unstable product then forms diazonium, a DNA alkylating agent. Diazonium can act on various cellular nucleophilic sites. DNA alkylation is generally considered to be the cause of cancer initiation by carcinogens (24). Another study also stated that nitrosamine can cause DNA damage directly (25). The process of nitrosamine transformation and activation is shown in Figure 2.

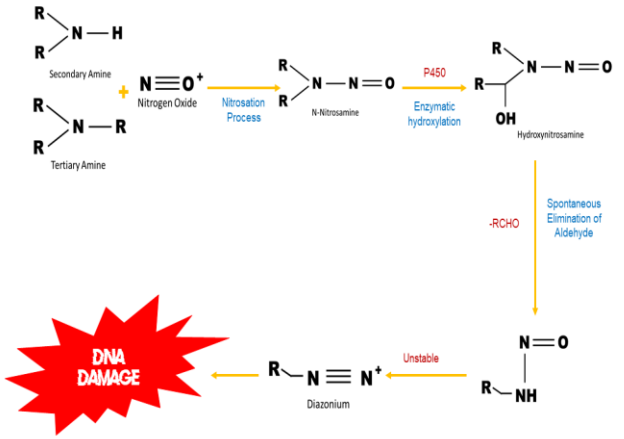

Figure 2. Transformation and activation of nitrosamine thus causing DNA damage (13,24).

Recent studies have also suggested that nitrosamines may contribute to NPC through epigenetic modifications. Exposure to nitrosamines has been associated with DNA methylation changes, histone modifications, and RNA dysregulation, all of which can alter gene expression without directly changing the DNA sequence. These epigenetic alterations can silence tumor suppressor genes or activate oncogenic pathways, further promoting carcinogenesis (15,16). Additionally, chronic inflammation triggered by nitrosamine exposure can create a tumor-friendly microenvironment by increasing oxidative stress and suppressing immune responses (13,17).

Several studies have demonstrated that nitrosamines can be synthesized from endogenous sources, notably by activated macrophages, neutrophils, and naturally occurring bacteria in the body. Endogenous bacteria can propose nitrosamine formation in humans through several enzyme reactions. Recent studies have shown that bacteria, such as Streptococcus spp, Veillonella spp., Staphylococcus aureus, S. epidermidis, and Corynebacterium, play a key role in the proposed nitrosamine formation in humans as they catalyze the formation. The nitrification process in the gut, from NH3 to NO_2^- to nitrosamine, is an important step in the carcinogenic process. The normal function of reduction

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Table 2. Nitrosamine carcinogenicity and its daily intake limit (8,23)

Nitrosamine	Carcinogenicity (IARC Classification)	Daily Intake Limit
N-Nitrosodimethylamine (NDMA)	Group 2A (Probably Carcinogenic to Humans)	PDE: 6.2 µg/day AI: 96.0 ng/day
N-Nitrosodiethylamine (NDEA)	Group 2A (Probably Carcinogenic to Humans)	PDE: 2.2 µg/day AI: 26.5 ng/day
N-Nitrosopiperidine (NPIP)	Group 2B (Possibly Carcinogenic to Humans)	AI: 1300 ng/day
N-Nitrosopyrrolidine (NPYR)	Group 2B (Possibly Carcinogenic to Humans)	ND
N-Nitrosodi-n-butylamine (NDBA)	Group 2B (Possibly Carcinogenic to Humans)	AI: 26.5 ng/day
PDE: Permissible daily exposure; AI: Allowable intake; ND: No data		

(denitrification) which changes to oxidation function (nitrification) plays a major role (26,27). Nitrosamine is synthesized endogenously also through macrophages and neutrophils. Furthermore, macrophages and neutrophils produce nitric oxide radicals, which play a role in cytotoxicity and are believed to contribute to the formation of carcinogenic nitrosamines, DNA deamination, and oxidative damage. (13).

7. Food, Nitrosamine, Cancer, and NPC Relationship

Nasopharyngeal carcinoma (NPC) is influenced by multiple factors. Among them, Epstein-Barr virus (EBV) infection, consumption of salt-preserved foods, and HLA polymorphisms are strongly associated with an increased risk of NPC (16). Of these, EBV infection is the most extensively studied etiological factor in NPC development. Persistent EBV infection and genetic alterations drive the development of nasopharyngeal carcinoma (NPC) by promoting genomic instability and uncontrolled cell proliferation. Key mutations, including the inactivation of tumor suppressor genes and activation of EBV latency genes, enhance tumor progression and clonal expansion. In advanced stages, additional mutations contribute to tumor heterogeneity, recurrence, and metastasis. Additionally, Genetic studies have shown that certain susceptibility genes play a role in increasing the risk of nasopharyngeal carcinoma (NPC). Among these, HLA genes located in the MHC region on chromosome 6p21 are widely recognized as key genetic risk factors for NPC (3).

The relationship between nitrosamine, food, and NPC was also discussed in several previous studies. Based on a meta-analysis of observational studies, salted fish foods and processed foods have an increased risk of NPC, but have different risk characteristics of different intake taps, different stages, and different types. There are significant positive associations between the consumption of processed food and the risk of NPC in both Asians and Caucasians. Many studies also indicate a strong correlation between NPC and dietary habits in Asian regions (18,28). In addition, nitrosamine and high salt consumption may reactivate EBV infection from the latent stage which may increase the risk of NPC (29).There is supporting evidence indicating that individuals who use tobacco products may experience an increased risk of developing cancers in the lung, pancreas, esophagus, and oral cavity due to the presence of nitrosamine (30).

Nitrosamine is a contaminant product that is often found in food. In addition, nitrosamine can be endogenously synthesized. Nitrosamine is also found in daily drinking water. Many studies also show the relationship between nitrosamine and cancer. The question that needs to be asked is why everyone did not get cancer.

First of all, the daily intake of nitrosamine does not exceed the daily limit of nitrosamine according to WHO. However, the excess consumption of nitrosamine in some of its types such as NDMA, and long-term contamination to nitrosamine needs to be further considered in the formation of cancer. On the other hand, nitrosamines cause cancer by causing DNA damage. DNA damage by nitrosamines can be done directly (without the need for metabolic activation) and indirectly (Requires bioactivation in host cells) (25). DNA alteration causes changes in genetic material. However, the body has a DNA repair mechanism that helps prevent the development of cancer cells. If the body successfully repairs DNA, the risk of cancer can be reduced. Nitrosamines are compounds that are classified as carcinogenic agents. On the other hand, there are chemopreventive agents, all agents that prevent cancer. Some studies show that there are chemopreventive agents that protect against nitrosamines. Curcumin, as an antioxidant, was shown to have a protective effect against the oxidizing agent of nitrosamine (31). Nitrosation reactions that occur in the body can also be inhibited by vitamin C and other antioxidants. Vitamin C has also been shown to increase cell viability, reduce ROS production, and protect against genotoxic effects (32). This protective

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effect is obtained from the ability of vitamin C to inhibit cell apoptosis and interact with the enzyme system of Nitrosamine thus inhibiting the production of genotoxic intermediates. Vitamin E and selenium minimize and prevent the reaction of nitrite/nitrate with amines thereby reducing the risk of cancer (33). Other foods that can reduce nitrosamine concentrations include: green tea, garlic, chinese onion, carrot, rice soup, sweet potato, and arrowhead (26). In addition, nitrosamine also does not act as a single cancer-causing component considering that NPC can be caused by various complex factors. It is possible that a little nitrosamine consumption could trigger cancer if followed by other problems, and vice versa.

8. Conclusion

Nitrosamines are a key factor contributing to nasopharyngeal carcinoma (NPC). Nitrosamines are found in preserved and smoked foods, beer, cigarettes and even drinking water. Daily intake of nitrosamines is generally within the limits recommended by the WHO. However, excessive consumption of certain types of nitrosamines, such as NDMA, and prolonged exposure should be monitored, as they may play a role in carcinogenesis. Nitrosamines are formed in food by nitrosation, which involves the interaction of nitrite and nitrogen oxides with secondary and tertiary amino compounds. Nitrogen oxides produced during food processing can react with amino compounds to form nitrosamines. Nitrosamines induce cancer by causing DNA damage, either directly (without metabolic activation) or indirectly (requiring bioactivation in the host cell). However, the body has a DNA repair mechanism that helps to prevent the formation of cancer cells. There are also chemopreventive agents - compounds that have an inhibitory effect on the development of cancer. Some studies suggest the existence of chemopreventive agents that offer protection against the adverse effects of nitrosamines.

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Conflict of interest
The authors declare that they have no competing interest.

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Ethical statement
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