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Food mutagen and lung cancer

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Abstract

This article reviews the role of food mutagens in mutagenesis and carcinogenesis for lung cancer; it also discusses how to evaluate the effects of food mutagens. The relationship between nitrosamine, polycyclic aromatic hydrocarbons, alcohol intake and lung cancer has been the subject of several studies. Many epidemiological studies have identified several risk and protection factors for lung cancer [1, 2, 3], and some have proved that changes in the exposure to these factors may have an influence on incidence and mortality due to this kind of pathology. Diet and nutritional factors are one of several major causes of carcinogenesis. Carcinogenic processes themselves are known to involve multi steps process (initiation, promotion, progression) and influenced by various factors. Human beings are often being exposed to carcinogenic factors during their life, whether they realize it or not. These factors are divided into endogenous (genetics, immunologic disturbances, endocrine imbalance) and exogenous factors (environment, physical, biologic, or chemical agents, nutrition and lifestyle) [4]. The field of investigation of the role of nutrition in the cancer process is very broad. It is becoming clearer as research continues that nutrition plays a major role in cancer [5]. Dietary constituents reduce the risk, in some cases by decreasing the effects of food mutagens, or through carcinogenic detoxification, or protection of DNA from electrophilic carcinogen. Further more, nutritionally related cancer ultimately developed from an imbalance of carcinogenesis and anticarcinogenesis process [6]. Consumption of certain foods containing Nitrosodimethylamine (NDMA) was associated with a higher risk of developing lung cancer. This was particularly evident with the consumption of salted meat. This food item has been associated with an increased risk of oropharyngeal and laryngeal cancer in humans [7, 8]. We tried to illustrate new scientific knowledge regarding food related factors by picturing and integrating new genotoxicological findings for food-borne mutagens/carcinogens and detailing contributions of modulation in lung cancer.

Key Words: Carcinogenesis, Lung Cancer, Diet, Nutrition, Nitrosamine, Polycyclic Aromatic Hydrocarbons, Alcohol,

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Introduction

Lung cancer research is and will be one of the forefront and hotspot subjects of clinical medical sciences. The 7 major industrial

countries (G7: USA, Japan, Germany, Italy, UK, France, and Canada) with USA leading the top, held the top 7 spots of total world production in the field of lung cancer research, along with the domination pattern in the publication in most scientific fields [1].

Lung cancer is the leading cause of cancer-related mortality worldwide [9]. Each year, tens of millions of people are diagnosed with cancer around the world, and more than half of the patients eventually die from it [2, 3]. The cancer rates could further increase by 50% to 15 million new cases in the year 2020, according to the World Cancer Report [1]. Several lines of evidence indicate that diet and nutrition can contribute to human cancer risk [6].

This article reviews the role of food mutagens in mutagenesis and carcinogenesis for lung cancer; it also discusses how to evaluate the effects of food mutagens. There are data to indicate that food mutagens and carcinogens affect specific organs rather than affecting every organ in the body. Separate foods contain many substances that are likely to reduce cancer risks, such as antioxidants or some types of fibres. These are not reviewed herein, but it should be recognized that nutritionally related cancers occur through an imbalance of carcinogenesis and anticarcinogenesis.

Cigarette smoking is the principal and an indisputable risk factor for lung cancer; however, numerous studies have shown that diet may also be of etiologic importance. Red meat (beef, pork, lamb, and goat from domesticated animals) and processed meat (meats preserved by smoking, curing, or salting, or by addition of chemical preservatives) have been hypothesized to play a role in carcinogenesis, owing to their high levels of saturated fat and heme iron content, and potent mutagens produced during high temperature cooking and meat processing or preservation.

The role of these compounds in human carcinogenesis has yet to be confirmed, but recent epidemiological studies suggest that dietary intake of fried, well-done meat may be related to lung cancer [10]. Apart from being present on the meat surface, heterocyclic amines have been identified in smoke condensates from frying of beef, pork, and fish, and their formation is similarly temperature and time dependent. Higher levels are produced during frying and grilling than other cooking methods [11].

Several lines of evidence indicate that diet and dietary behaviors can contribute to human cancer risk. One way that this occurs is through the ingestion of food mutagens. Sporadic cancers result from gene-environment interactions where the environment includes endogenous and exogenous exposures. In this article, we define environment as dietary exposures in the context of gene-environment interactions. Food mutagens cause different types of DNA damage: nucleotide alterations and gross chromosomal aberrations. Most mutagens begin their action at the DNA level by forming carcinogen-DNA adducts, which result from the covalent binding of a carcinogen or part of a carcinogen to a nucleotide [6, 12].

This article reviews the role of food mutagens in mutagenesis and carcinogenesis and how their effects are modified by heritable traits; it also discusses how to identify and evaluate the effects of food mutagens. There are data to indicate that food mutagens and carcinogens affect specific organs rather than affecting every organ in the body. Separately foods contain many substances that likely reduce cancer risk, such as antioxidants or some types of fibers. These are not reviewed herein, but it should be recognized that nutritionally

related cancers occur through an imbalance of carcinogenesis and anticarcinogenesis.

Methods

A review of the literature concerning lung cancer was performed. This review focuses on evidence indicating that diet and nutrition can contribute to human lung cancer risks. The causes of cancers are understood to be mainly cigarette smoking, dietary factors, and infection/chronic inflammation, each of these accounting for up to one third of the total. Iatrogenic factors, accidents, pollution, food additives and sunlight exposure are among the other etiological agents [12].

The heterocyclic amines produced during the cooking of meat are carcinogenesis. Other compounds in food such as aflatoxin B1, polycyclic aromatic hydrocarbons, N-nitrosamines and alcohol are suspected as mutagen [6, 13]. Dietary constituents reduce the risk, in some cases by decreasing the effects of food mutagens, or through carcinogenic detoxification, or protection of DNA from electrophilic carcinogen. Futhermore, nutritionally related cancer ultimately developed from an imbalance of carcinogenesis and anticarcinogenesis process [6].

Diet and nutritional factors are one of several major causes of carcinogenesis. Carcinogenic processes themselves are known to involve multi steps process (initiation, promotion, progression) and influenced by various factors. Food mutagen is working through genotoxic and non-genotoxic pathway in carcinogenesis. Genotoxic pathway works on the level of DNA causing DNA damage. Moreover, non-genotoxic pathway affects the cell through tumour promoters such as inflammation, immunosupression, free radical and so on. More exposure to both pathways, more risks of carcinogenesis [14].

In 1960, Zak *et al*., [15] reported the occurrence of lung carcinomas in rats treated with Nitrosodimethylamine. This observation was consistently replicated in other experiments and as a result, NDMA has been considered carcinogenic in all animal species tested. In fact, NDMA induces benign and malignant tumours after its administration by various routes (including ingestion) in various organs, mainly the kidney, liver, and respiratory tract [16].

Because NDMA is present in several foods and beverages, its role in human carcinogenesis has been considered measurable, and several authors have reported an increased risk of stomach, oesophageal, pharyngeal, laryngeal, and lung cancer associated with a high intake of NDMA [17-19]. In a Study from Uruguay provides additional evidence of an independent effect of dietary NDMA in the risk of lung cancer. They made a food frequency questionnaire was comprehensive and included foods and beverages that allowed a rather precise estimation of NDMA intake in the diet. Furthermore, the estimates of NDMA were fully adjusted for potential confounders like body mass index, total energy intake, and pack-years of cigarette smoking.

The inclusion of terms for 13-carotene, total carotenoid intake, total fat, saturated fat, cholesterol, vitamin C, and total alcohol intake left the estimates for NDMA unchanged. In particular, they attempted to minimize residual confounding from tobacco use, including a term for pack-years as a continuous variable, terms for smoking status, and assigning a value of 0 pack-years for non-smokers. Also, stratification by smoking status was not suggestive of residual confounding [20].

The relationship between nitrosamine intake and human cancer has been the subject of

several case-control studies. According to them, NDMA intake is a risk factor for gastric, oesophageal, laryngeal, and oropharyngeal cancer [17, 19]. Excess calorie intake has been known to contribute to increase risk of several cancers, e.g. breast, colon, and prostate cancer. Digestion, absorption, metabolism, and excretion of fat deposits require oxidative metabolism, which create free radicals capable of causing DNA damage [21].

Goodman *et al*., [19] reported an increased risk of lung cancer associated with NDMA intake. It has been suggested that N-nitroso compounds are more effective as carcinogens in animals when taken per os and given in small quantities over time. This situation is similar to that observed in a human lifetime [18].

Consumption of certain foods containing NDMA was associated with a higher risk of developing lung cancer. This was particularly evident with the consumption of salted meat. This food item has been associated with an increased risk of oropharyngeal and laryngeal cancer in humans [7, 8].

Also, drinkers of beer were at increased risk of developing lung cancer, replicating previous findings [22, 23]. In summary, NDMA intake was associated with an increased risk of lung cancer. Also salted meat and beer proved to be risk factors for this disease [20].

Food Mutagen: Molecular Biology

N-Nitrosamines

Both nitrate and nitrite are capable to form nitrosamines, a large group of compounds with common carcinogenic mechanism. Humans are exposed to N-nitroso compounds in diet from a variety of cured meats and fish products. Sodium nitrite has been used as food addictive for preservation and as colouring substance in meat. N-nitrosamines may also derived from nicotine of tobacco smoking [24, 25].

Cancer of the lung, liver, kidney, mammary gland, stomach, pancreas, bladder, and oesophagus has been observed and these sites are also considered to be the targeted organs [26].

The common carcinogenic mechanism of N-nitrosamines is associated with formation of N-nitrosodimethylamine, which undergoes enzymatic hydroxylation and subsequent hydrolysis to aldehyde and monoalkylnytrosamide that rearranges and releases a carbocation that is reactive toward DNA bases. The hydroxylation is catalyzed mainly by CYP2E1 [6].

Polycyclic Aromatic Hydrocarbons

Polycyclic Aromatic Hydrocarbons (PAH) compounds are formed during incomplete combustion of organic matter. Smoked foods, e.g. ham, sausages, and fish may contain PAH, resulting from incomplete combustion in food processing. These compounds are also commonly found in tobacco smoking. In laboratory animal studies, diets with PAH consistently induce foregut tumours and can also induce lung tumours. In humans, there is some evidences for association of dietary PAH exposure with colon cancer. Animal and human studies suggest that dietary PAH is distributed to organ besides the locally exposed tissues, so it is plausible to consider that dietary PAH may contribute to lung or breast cancer risks [6].

Benzo(a)pyrene is the best-characterized PAH compound available from the diet. Carcinogenesis mechanism is conducted through BaP adduct formation, after being activated by CYP1A and CYP1B enzymes. BaP adduct is associated with site-specific hotspot mutations in the p53 tumour suppressor gene. The mutations are observed in lung cancer of smokers [6].

Table. 1

Carcinogen	Activating enzyme with genetic polymorphisms
N-Nitrosamines	CYP2E1
Polycyclic Aromatic Hydrocarbons	CYP1A, CYP1B
Alcohol	CYP2E1

Alcohol

Epidemiological data have identified chronic alcohol consumption as a significant risk factor for upper alimentary tract cancer, including cancer of the lung, oropharynx, larynx, oesophagus, and of the liver. The increased risk in the large intestine and in the breast is much smaller. However, although the risk is lower, carcinogenesis can be enhanced with relatively low daily doses of ethanol [23, 27].

The exact mechanisms by which chronic alcohol ingestion stimulates carcinogenesis are not known. Experimental studies in animals support the concept that ethanol is not carcinogen but under certain experimental conditions is a co-carcinogen and/or tumour promoter. The metabolism of ethanol leads to the generation of acetaldehyde (AA) and free radicals. Evidence has accumulated that acetaldehyde is predominantly responsible for alcohol associated carcinogenesis.

Acetaldehyde is carcinogenic and mutagenic, binds to DNA and proteins, destructs folate and results in secondary hyperproliferation. It has also been shown that AA interferes with the DNA repair process, where it directly inhibits O6methyl-guanyltransferase, an enzyme important for the repair of adducts caused by alkylating agents. Moreover, individuals with polymorphism tend to accumulate acetaldehyde products, resulting in increased cancer risk. Other mechanism is through the induction of cytochrome P-4502E1 (CYP2E1) that is associated with increased free radicals generation and activation of procarcinogens compounds contained in the alcoholic beverages to their ultimate carcinogens [27].

Conclusions

With this article, we tried to illustrate new scientific knowledge regarding food related factors by picturing and integrating new genotoxicological findings for food-borne mutagens/carcinogens and detailing contributions of modulation in lung cancer. The findings of this review may be of interest for medical staff who are currently undertaking studies and for those who will be performing research and studying about lung cancer.

The relationship between nitrosamine, polycyclic aromatic hydrocarbons, alcohol intake and lung cancer has been the subject of several studies. Also, salted meat proves to be risk factors for this disease, excess calorie intake has been known to contribute to increase risks of several cancers. Digestion, absorption, metabolism, and excretion of fat deposits require oxidative metabolism, which create free radicals capable of causing DNA damage.

Carcinogenic processes themselves are known to involve multi steps process (initiation, promotion, progression) and influenced by various factors. Food mutagen is working through genotoxic and non-genotoxic pathway in carcinogenesis.

Genotoxic pathway works on the level of DNA causing DNA damage.

Based on data from the American Institute for Cancer Research and World Cancer Research Fund, it is estimated that around 30-40

percent of all cancers could be prevented by healthy life-style and a good diet pattern [5]. Hence, a good knowledge of diet, nutrition, and life-style are important to reduce lung cancer risk and risks of cancer in general in the society.

Further studies, particularly those that incorporate molecular markers relevant to metabolic pathways or genetic changes specific to food mutagens, are needed to help which is the best way to cook the food and at which temperatures. This article has focused on the most commonly studied food mutagens and lung cancer, but many others exist in food as do agents that reduce lung cancer risk. The integrated consideration of all of these remains problematic because of the complex nature of the exposure and the documentation of dietary habits, and each of our research methods has strengths and limitations.

Author's Contributions

Author G. Strano, and C. West, equally contributed to this article.

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Conflict of Interests

The authors' declare that there are no conflicts of interests.

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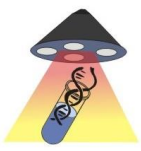

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