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Review Article

Red meat consumption: A comprehensive overview of the mechanistic evidence for the effects of oncogenes

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Abstract

Epidemiological studies have recently shown a very high correlation between consumption of red meat and meat products, the most important source of protein for humans, and cancer. The molecular basis of the red meat-cancer relationship is still poorly understood. The study of heme iron and N-nitroso metabolites, derived from the digestion of red meat, as possible inducers of oxidative stress and DNA damage, which is a major culprit of carcinogenic compounds and mutagenesis, has been pioneering. However, some other factors, like the time of cooking, temperature of cooking, and the direct or indirect contact of meat with flame during preparation, can also help in the formation and release of carcinogenic substances. This review aims to discuss the current evidence on the mechanistic associations between red meat intake and the activation of oncogenes that are central to tumorigenesis, and to generate new ideas for future studies. The synthesis and analysis of the existing evidence are a valuable resource for researchers and healthcare professionals trying to understand the complex interrelationships between dietary patterns, oncogenes, and the development of various cancers.

Keywords: Cancer, Oncogenes, Meat, Molecular mechanisms.

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Proteins are one of the main components of food ingredients, and their supply by food products is vital for health and well-being. They are also responsible for the growth and repair of cells, and after water, proteins are the most abundant substance in the body. Many different types of protein sources are readily available. These sources differ in terms of protein quality and anabolic effect, as well as amino acid content and absorption kinetics. These sources include dairy products, such as milk, eggs, and cheese, as well as meat products, and plant-based sources, including legumes and grains (1-3).

Meat is considered one of the most complete foods due to its high content of valuable proteins that contain essential amino acids for the body, as well as minerals such as iron and zinc, various vitamins, and sufficient energy (4). In addition, meat (including beef, lamb, and veal) contains significant amounts of minerals and vitamins such as phosphorus, selenium, niacin, pantothenic acid, vitamin B6, and vitamin B12 (5, 6). Alongside all of the mentioned benefits of meat compounds, according to the statements of the International Agency for Research on Cancer, it has been determined that the consumption of processed red meat products in large quantities can probably be carcinogenic to humans (7-9).

Based on studies in recent years, it has been claimed that eating 50 grams of processed meat more than the recommended value may increase the risk of cancer by approximately 18%, and the greatest amount of this relationship can be caused by the processing of meat, such as cooking factors, adding too much salt, smoking, etc (9-11).

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Understanding the basic mechanistic pathway involved in the processing of red meat helps us to identify the important causes of the interaction between the high consumption of processed meat products and the high probability of contracting various types of cancer, such as colon, breast, prostate, colorectal, and pancreatic cancer (4, 12). To cover this knowledge gap, we investigated and updated the existing literature, providing an overview of all published literature, focusing on clinical and observational studies in this realm.

Many studies have already explored the relationship between red meat consumption and cancer. The innovation of the current study lies in providing a comprehensive and integrated perspective on the mechanistic evidence concerning the effects of oncogenes on red meat consumption, with a specific focus on the differences arising from processing and cooking methods. While previous studies have often concentrated on specific aspects of this relationship, this review aims to offer a precise roadmap of the molecular mechanisms involved by synthesizing and analyzing dispersed data. Our goal is to bridge the knowledge gap in understanding the intricate interplay between diet, genetics, and oncogenic processes, enabling us to provide more accurate and targeted dietary recommendations for cancer risk reduction.

Methods

A literature search was conducted using MEDLINE, Embase, PubMed, Scopus, Google Scholar, and the Cochrane Library to identify all comparative studies published between 2000 and 2024, restricted to those available in English.

Carcinogenic compounds or oncogenes

The study of cancer was always regarded as a complicated affair; the finding of oncogenes was regarded as a watershed event in this regard. It was assumed that in the early years of the 1900s, environmental factors formed the major causes of cancers. However, in the 1970s, a great paradigm shift arose whereby the work of Bishop and Varmus, Nobel laureates, and others showed that some cancers arose from genetic mutations. Hence, certain carcinogenic states are housed in our very DNA. It could now be understood that not all carcinogens are extrinsic; some are genetic-like modifications of naturally occurring genes (4, 13).

Oncogenes are essentially mutated forms of normal genes referred to as proto-oncogenes. Proto-oncogenes are genes that provide information for the synthesis of proteins involved in normal cellular activities like cell cycle progression, prevention of apoptosis, and DNA repair, which are all important in cellular and tissue development. Therefore, once a proto-oncogene is disrupted by mutation, it can become constitutively active or overexpressed, leading to unregulated cellular proliferation. Such mutations transform proto-oncogenes into oncogenes that drive the uncontrolled growth characteristic of cancers (10).

Oncogene research has opened avenues for the development of many targeted therapies for cancer treatment. Targeted therapies attempt to inhibit signals that arise from aberrant signal transduction pathways activated by oncogenes. Oncogene-targeted therapeutics continue to be developed, offering great hopes for the advancement of cancer therapeutics (10, 14).

In conclusion, oncogenes are very important factors in the etiology of many, but not all, cancers as impaired activators of cellular proliferation. This entire journey of oncogene discovery and targeted therapy application constitutes a most important saga in contemporary medicine. The more we diligently investigate the molecular intricacies of oncogenes, the greater the chances of developing better-defined and more effective therapies to change the course of many cancers from lethal diseases to highly for treatment options. The worldwide search for oncogenes continues as both a meta-story of human ingenuity and a thirst for knowledge, giving hope to countless cancer victims around the globe (4).

Carcinogenic compounds or oncogenes of processed meats

All the published studies up to October 2023 point toward the presence of carcinogenic compounds in processed meats, namely, Polycyclic Aromatic Hydrocarbons (PAHs), Nitrosamines, and highly mutagenic Heterocyclic Aromatic Amines (HAAs) (14, 15). Studies suggest that the major determinant of the presence of these carcinogenic substances is heat and the specific cooking technique used. In laboratory studies, high-temperature cooking is associated with high levels of PAHs and HAAs, both of which cause cancer. Prior work has suggested that reducing cooking temperatures and changing cooking methods were successful in lowering the amount of these hazardous compounds. However, there is evidence that the mere observance of lower cooking temperatures is not sufficient in preventing the formation of these chemicals, and substitute approaches were evaluated (4, 16).

Polycyclic Aromatic Hydrocarbons are compounds with a minimum of two fused benzene rings. Sources include combusting fossil fuels, natural causes such as wildfires, astrobiological phenomena, engineered means, and processed food-meat sources (17-19). Nitrosamines are carcinogenic compounds with the following chemical structure: R2N=O. R usually implies an alkyl group. These compounds arise following metabolic interaction of nitrite preservatives with amines in the acid medium of the gut for nitrosamine production, which are strong carcinogenic agents in some fermented foods and tobacco products. Recent studies show that nitrosamines cause mutations of genes and interfere with normal cell-division. Some of these compounds are N-Nitrosonornicotine, N-Nitrosodimethylamine, N-Nitrosoanabasine, and N-Nitrosoanatabine (5, 20, 21).

Because of their toxicological and carcinogenic properties, and the interest over the past few decades regarding an increase in the global consumption of meat products like sausages, nitrosamines have been considered a serious focus of interest in meat processing. Heterocyclic Aromatic Amines also belong to the other set of carcinogens that have been identified in meat products. These compounds are configured as 2 to 5 aromatic rings with one or more nitrogen atoms and an exocyclic amino group. Studies have shown that heterocyclic aromatic amine synthesis increases at a temperature close to 150 °C, becoming especially remarkable at 200 °C, when the highest concentration of these mutagenic compounds is attained (5, 15, 22-25).

Thermally processed red meat is a source of carcinogenic compounds

The association of high consumption of red meats with risks like cancers of the colorectal, pancreatic, or prostate may arguably be laid at certain high temperatures of cooking or their methods (grilling, frying, or roasting), bringing chemicals into being, which may be termed carcinogenic, such as heterocyclic aromatic amines and polycyclic aromatic hydrocarbons. Such chemicals are formed through protein or fat reactions. Public health may argue for creating general awareness on the risk, but paired with the promotion of "low-risk" cooking techniques alongside pertinent dietary adjustments that lower cancer risks and improve health (7, 26, 27).

Polycyclic aromatic hydrocarbons (PAHs)

Most of the chemicals identified in this carcinogenic pathway of processed meat consumption fall under a broad category called polycyclic aromatic hydrocarbons (PAHs) (figure 1). In the year 2001, it was determined that PAHs constitute the ninth most hazardous chemical for human health. Although now proclaimed as a priority pollutant under the European Union and labeled as the ninth-most evil, exposure to these hazardous chemicals has experienced an upward growth, particularly in lower- and middle-income countries (28, 29). In general, sources of PAHs can be divided into anthropogenic (pyrogenic and petrogenic) and natural (diagenetic) sources. Anthropogenic sources emit PAHs by combustion of fossil fuels, which includes motor vehicles, power generation, and wood burning for cooking, incineration of municipal and industrial waste, and the use of coal tar, coke, asphalt, crude oil, creosote, and roofing tar. Other pertinent sources include industrial discharges into the environment, sewage treatment plants, and hazardous waste burning, sources of human exposure include any releases from coal gasification and smoke (28, 30, 31).

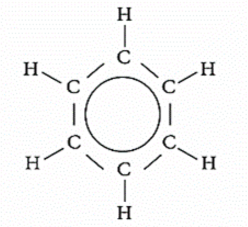

Figure 1. Chemical form of polycyclic aromatic hydrocarbons

Dietary intake of PAHs features one of the major concerns in human cancer risk assessment since it links to a potential exposure pathway of environmental contaminants (32). Mostly, it has been established that many PAHs are teratogenic, mutagenic, and genotoxic and accumulate in the soft tissues of animals. Some of these compounds can act synergistically; in fact, most of these PAHs cause cancer mainly through binding with DNA and thereby producing deleterious effects culminating in tumor development (28, 30, 33).

Evidence indicates that polycyclic aromatic hydrocarbons (PAHs) are linked to multiple cancers, and specific studies associate these compounds with increased gastric cancer risk (28). Diet-led ingestion of benzo(a)pyrene was found to raise the chance of developing colorectal adenomas (34). It has also been proposed that smoke-derived exposure to PAHs might be relevant for considering lung cancer (35). Due to the important nature of this issue, laboratories under the auspices of the International Agency for Research on Cancer had studied PAHs as carcinogenic agents from cooked meat products (32). Processed meats include sausages, bacon, and cured meats, which contain PAHs from the processing methods employed. Those PAHs occur in the products by smoking, cooking, and drying, or by exposing the meat to high temperatures and combustion by-products (17).

The mechanism of PAH formation in grilled and smoked food involves at least three mechanisms, although the exact pathways remain unknown (32). Mechanism 1 is defined as the thermal decomposition of organic materials, including fats, carbohydrates, and proteins, at temperatures of more than 200 degrees Celsius. The best conditions for the formation of PAHs exist in a temperature range of 500 to 900 degrees Celsius, with a maximum concentration of PAHs coming from fat pyrolysis. Mechanism 2 concerns the release of lipids that come into direct contact with flames at high temperatures. This environment favors the generation of volatile PAHs, which then deposit onto the surface of the meat as the smoke ascends. Mechanism 3 has to do with the incomplete combustion of charcoal, resulting in PAHs that stick to the surface of food (32). In all these mechanisms, the PAHs are produced by the interaction of the fats and juices of meat with flames or hot surfaces, which deposit these compounds on meat. For example, juices of organic origin released from meat (or fish) when grilled drip onto charcoal, where they are subjected to pyrolysis, and the resulting PAHs are produced. Also, during grilling, fat dripping down onto the charcoal could ignite flames, which spray smoke onto the food, further inducing PAHs generation, while increasing the temperature close to its surface around ground zero (32).

Molecular and cellular parts of polycyclic aromatic hydrocarbons

At the molecular and cellular levels, polycyclic aromatic hydrocarbons exert their effects through several mechanisms, including metabolic activation, which generates reactive intermediates capable of binding to DNA and inducing mutation. Moreover, PAH-induced oxidative stress, inflammation, and disturbance of cellular signaling cascades negatively impact cellular or human health (19). The understanding of the biological functions of PAHs absorbed into systemic circulation has significantly advanced in recent times. The pathways by which PAHs are absorbed into systemic circulation include: Firstly, they penetrate the mucous layer lining the bronchi and are then absorbed into the pulmonary system. It can also be absorbed through the gastrointestinal tract, especially for fat-soluble substances. Lastly, PAHs can be absorbed through passive diffusion through the stratum corneum and transdermally (10, 28, 36, 37).

Once in the bloodstream, PAHs, carried through the circulation to numerous tissues, are passively diffused from the bloodstream into the lung tissues, facilitated by partitioning into lipid and aqueous layers of the cells. Once inside the gastrointestinal tract, PAHs are rendered soluble in lipids and taken to the circulation through the lymphatic vessels, in particular via the thoracic duct (28, 37-41). Metabolism of PAHs with corresponding formation of a large number of metabolites, including epoxides, dihydrodiols, phenols, quinones, and derivatives, occurs mainly in the liver, lungs, intestinal mucosa, and some other tissues in the presence of cytochrome P-450 and related enzymes (28).

Polycyclic aromatic hydrocarbons in processed meats

The toxic contents of several food categories have been studied, especially when cooking food by grilling or by smoking. According to Amukame et al. (2015), the concentrations retrieved for individual PAHs could reach up to 200 µg/kg in smoked fish and meats. Similarly, Jahurol et al. (2013) reported the levels of the combination of three specified PAHs from various grilled food items, fluoranthene, benzo(b)fluoranthene, and benz[a]pyrene, reaching a peak concentration of 66.28 ng/g from beef, 42.31 ng/g from chicken, 40.69 ng/g from charcoal-grilled fish, 30.76 ng/g from lamb satay, and 17.86 ng/g from grilled chicken (42).

Farhadian et al. also reported further studies concerning the level of PAH in grilled meat and fish collected from this study were between 0-130 ng/g, with BaP from 0.2 up to 50 ng/g. Again, the investigation has declared trapped PAH content level, up to gross quantity PAH of 164 ppb, and over 30 ppb concentration for BaP in some open flame-cooked products like grilled meat. Concentration of BaP was elevated during some studies across Estonia for a wide range of smoked products, including home-made ham, smoked meat, smoked chicken, and smoked sausage at 30.6 µg/kg, 31.2 µg/kg, 15.0 µg/kg, and 20.0 µg/kg, respectively. In contrast, very low levels of PAHs were found in grilled chicken, between 3.51 and 7.14 ng/g, indicating that considerable reductions in PAHs in meat products can probably be achieved by employing other cooking methods such as grilling, baking, and stewing, but at low temperatures and for short times (32).

Factors affecting the concentration of polycyclic aromatic hydrocarbons in meat

Concentration of PAHs in grilled meat depends on multiple factors like meat type, fat content, cooking mode, temperature, time of cooking, type of heat source, and distance from heat source, all studied above and duly listed below:

1. Type of meat: Different types of meat, such as chicken and beef, differ in fat contents, marbling characteristics, and levels of myoglobin, all of which are likely to be factors in the amount of polycyclic aromatic hydrocarbons (PAHs) generated by cooking. Studies indicate that PAH concentrations in grilled beef samples exceed PAH concentrations in grilled chicken samples (32).

2. Fat content of food: Fat content in foods affects PAHs predominantly in terms of thermal degradation, polymerization, and heat treatments (43). Fat, per se, is the most generic precursor to PAH formation, according to Porcaro et al., while fat in processed foods positively correlates with PAH composition in these foods. Therefore, very high-fat meat will ultimately produce elevated PAH levels relative to low-fat foods, resulting in lower PAH levels (44).

3. Cooking methods: Cooking methods, especially direct exposure to combustion gases during grilling and smoking, contaminate food (6). Marks et al. noted that the cooking method was principally responsible for the higher or lower concentrations of PAHs, wherein oven-baked products displayed much lower levels than wood-grilled ones (18).

4. Cooking temperature: High-temperature cooking enhances the formation of PAHs at high levels, especially under grilling. Carbon and hydrogen molecules serving as basis molecules best suitable for PAH production occur at temperature conditions of 500 to 700°C. With pyrolysis, PAHs decompose into smaller, unstable precursor molecules, which then pyrosynthesize into larger, stable PAHs. They may also be formed at temperatures under 100-150° (28).

5. Cooking time/cooking level: As Porcaro et al. suggest, the time of cooking is regarded as one of the important determinants for the levels of PAHs in food. It is directly correlated to cooking time, as higher cooking time results in more PAH concentration. Likewise, increasing time or the degree of cooking leads to higher concentrations of heterocyclic amines. These compounds share similar metabolic pathways to PAHs (45).

6. The type of fuel used or the type of heat sources: The type of fuel is one factor that affects the generation of PAH and fuels, that is, electric, gas, wood, and coal. As Porcaro et al. reported, when carbon is combusted, it produces PAH in a lower amount than wood combustion. Also, they noticed that grilling meat on a charcoal oven produces more PAH than roasting meat in an electric oven (45).

7. Proximity and direct contact with the heat source: For instance, the distance denotes the closeness of the heat source to the food being prepared. According to Porcaro et al., at increased distance, food type shows reduced concentrations of polycyclic aromatic hydrocarbons (PAHs). Charcoal grilling is a very high-temperature cooking method, which may be direct or indirect. Minimize the dripping of fat on the heat source. Direct exposure can be lessened for grilling meat on an open flame to minimize PAH formation in charcoal grilling (45).

Absorption of polycyclic aromatic hydrocarbons in the human body

Several studies have, however, identified three significant avenues through which human uptake of polycyclic aromatic hydrocarbons (PAHs) occurs. These include the respiratory tract, into which the PAHs enter via suspended particles; the direct skin contact route; and the gastrointestinal system when food and/or liquids are ingested (23, 28, 46-48). Entrance inhalation rates for PAHs result from characteristics of the particles on which they have been adsorbed. Commonly, inhaled PAHs are associated with particulate matter. Most of the investigations under this assertion indicated that the rate of absorption increased with decreasing particle size. This was further shown by an in vitro experiment done by Gerde and Scholander that proposed the rate-limiting step for the transport of those particles to the bronchial epithelium depended on PAH release from the particles that carry them (28, 49-51). In addition, for absorption via the gastrointestinal tract, it has to be dissolved in solutions of the intestinal tract, after which it diffuses through cellular membranes into the blood. Hence, the two most critical factors of gastrointestinal absorption are water solubility and lipophilicity of the substances (28).

Metabolism of polycyclic aromatic hydrocarbons in the human body

Once inhaled as PAH, the organism receives initiation of metabolic conversion processes, which can generate relatively powerful metabolic activity in the metabolism of PAH. The metabolism of the PAHs thus includes their work with cytochromes P450s (CYPs) and epoxide hydrolase (EH). Phase I and Phase II reactions include many kinds of aldo-ketone reductases, cytochromes P-450s, catechol-O-methyltransferases, peroxidases, glutathione-S-transferases (GSTs), acetyltransferases, and sulfotransferases (SULTs), which are induced by PAHs (28, 52, 53). Phase I Metabolism structurally modifies the compound into a more polar entity. For example, pyrene is oxidized to 1-hydroxylysine. These changes increase the electrophilicity and reactivity of the molecular compound. Phase II generally involves the conjunction of polar functional groups, which increases the molecular mass and above its solubility in water. Hence, 1-hydroxypyrene underwent further conjugation with glucuronic acid to produce 1-hydroxypyrene glucuronide (28).

Digestion of polycyclic aromatic hydrocarbons in the human body

Digestion is a process that breaks down proteins from meat into smaller building blocks known as amino acids. During this process, some additional carcinogenic compounds may also be generated through amino acid reactions with heterocyclic amines to create entirely different products. Recently, research from the Journal of Agricultural and Food Chemistry has discovered that with digestion, the total carcinogenic content in heat-treated meat spikes significantly. Supposing the analysis is based only on initial heterocyclic amine formation, it means that the cooked meat's potential cancer risks can be significantly underestimated (35). It may be inferred that the increase in total carcinogens after digestion must call for considering the effect of digestion while assessing health risks posed by the consumption of heat-treated meats. Citizen science has already begun building a pretty convincing case regarding the consumption of certain processed meats, hot dogs, sausages, and deli meats, and the increased likelihood of developing cancer. The group placed processed meats as "carcinogenic to humans" under the name of the World Health Organization, citing it as a main cause of colorectal cancer. Learning how digestion affects the carcinogenicity of the heat-processed meat will enable people to make better dietary choices that can lower their risk for cancer (33).

Prevention and control of the consumption of polycyclic aromatic hydrocarbons

Accurate consumer encouragement, i.e., baking, boiling, or steaming rather than grilling, smoking, or coal-heating, is useful in the action of reducing exposure to polycyclic aromatic hydrocarbons (PAHs) present in processed meats. Also, a reduction in the consumption of processed meats and an increase in the consumption of various fruits, vegetables, and other sources of lean protein have been shown to work toward reducing overall PAH exposure (40). Understanding well how PAH act concerning processed meats will help make better dietary choices and reduce the health consequences that they may cause when consumed. Healthy cooking practices and consuming a variety of foods will go a long way toward reducing exposure to PAHs and increasing wellness (54).

Nitrosamines

For several years, processed meat consumption has been a health concern owing to the compounds called nitrosamines. These are chemical-forming agents identified as having been produced during the processing and cooking of meats; they are associated with a variety of health The purpose of this review is to examine the nature and generation mechanisms in processed meats and health hazards of their ingestion and prevention measures against their exposure (55). Basically, nitrosamines are chemicals that fall under carcinogens, meaning that they can cause cancer (figure 2). Formation of nitrosamines is defined as an amination reaction with nitrite or nitrate and can occur on different amine compounds or form through the addition of some tetraploid ammonium compounds, urea, carbonate, and guanine. Related to this, it should be noted that microorganisms of the natural environment can produce nitrosamines by facilitating the nitrosation process or by converting nitrite into secondary amines (5, 56, 57). While synthetic or natural sodium nitrate is concerned only with several processing methods, in general, sodium nitrate constitutes the best-preserved additive used at levels near an analytical concentration of 500 ppm in meats and related processed products. Only under specific conditions, for example, the acidic environment of the stomach, can both synthetic and natural sodium nitrate found in processed meat be converted into nitrosamines (5, 56, 58).

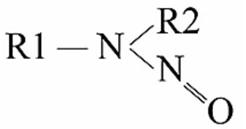

Figure 2. Chemical form of nitrosamines

Apart from meat and its products, such as sausages, nitrosamines have also been found in many other things outside these two categories, among which are tobacco, beer, cheese, seafood, herbicides, and industrial products such as stabilizers and cosmetics. Notably, also, valsartan and tetracycline, as pharmaceuticals, have been shown to contain nitrosamines (5, 59). Nitrosamines are categorized into two types: volatile and non-volatile. The most researched volatile nitrosamines in foods include nitrosodimethylamine and nitrosopyrrolidine. There is a serious scarcity of data on non-volatile nitrosamines and other N-nitroso compounds concentrations in food items because of the restrictions of the current analytical approaches. Volatile nitrosamines have been detected in various cooked meats, especially fried bacon, as well as in beer, certain cheeses, nonfat dry milk, and occasionally in fish (60).

Restrictions on the use of nitrosamines

Regulatory frameworks regulating permissible levels of volatile nitrosamines in food products vary from one country to another. The Canadian Food Inspection Agency set a maximum allowable concentration of nitrosamines of 15 g/kg. In Chile, the limit for nitrosodimethylamine on meat products is limited to 30 g/kg. In the United States, the maximum level of volatile nitrogen amides allowed in beef products is 10 kg-1. The permissible limit of nitrate and nitrite residues in Iran for meat and meat products is pegged at 60 ppm (5, 61).

Relationship between human diet and levels of nitrosamines

In view of the evident public health implications, the interfacing of human diets and nitrosamines requires sound scientific investigations. Nitrosamines are chemical entities that might exist in any food item, especially if subjected to cooking, smoking, or processing. They relate positively to increasing cancer risks, which then advocates for an evaluation of the consumption of diets on these compounds (58).Another widely accepted fact is that nearly all the foods taken by humans will almost have N-nitrosamines, concerning which cancer classification has been conducted. Initially, the inclusion of nitrites as preservatives in meat products was regarded as the prime source of occurrence in such trace amounts. Later on, references suggested that all methods of food processing and packaging could probably add to these compounds, along with other carcinogenic contaminants as found in food (62). As such, the general nitrosating agent in foods is nitrogen anhydride produced from nitrite in acidic aqueous media, where the physical characteristics of the food as well as its ingredients influence nitrosamine production. Some additives, such as ascorbic acid and sulfur dioxide, have been proven to reduce nitrosamines in food products. Interestingly, it has been found that direct fire drying really stimulates the formation of nitrosodimethylamine in various foods, as nitrogen oxides in the drying air can react with the amines in the food to yield nitrosamines (60). How one can handle nitrosamines very much aggrandizes dietary habits. Some nutrients, such as cruciferous vegetables (such as broccoli, cabbage, and Brussels sprouts), contain compounds that detoxify or excrete nitrosamines, whereas a deficiency in those nutrients could lead to greater retention (5). It is reported that human beings inside have been taking volatile constituent nitrosamines at a tolerance margin of 5 to 10 grams per kilogram body weight, seeing as the food intake per person on average daily turns about 1 microgram (5, 55, 60).

The Formation of nitrosamines in processed meats

Introduction of nitrosamines into a very important food group, meat and meat products, occurred due to inadequate cooking and processing methods. Therefore, it becomes possible to assess the nutritional quality of meat and meat products that are prepared under different thermal methods, using nitrosamines (5, 45). Nitrosamines are by-products of treating meat with nitrites, which are used to preserve meat by preventing bacterial growth while retaining its red or pink color. nitrosamines are formed through reactions between naturally occurring amines from meat proteins and nitrites. Temperature-demand increases nitrosamine formation, increasing the probability of development with respect to high-temperature cooking methods, such as frying or grilling meat (60). Some conditions under which meat products are stored would determine the concentrations of nitrosamines. Cooking techniques and temperatures, residual nitrite concentrations, amounts of available precursors for nitrosamines, presence of inhibitors of nitrosamines such as alpha-tocopherol and ascorbic acid, which inhibit the formation of nitrosamines in different types of food products, and storage conditions are important factors that characterize this condition (5, 63).

Concentration of nitrosamines in meat products

Nitrosamines are becoming too common in meat products. Its formation is similar to processing such meats containing nitrates and nitrites under specific conditions. However, nitrosamine concentration in these products could vary due to one or more factors, such as those mentioned below. Different processing methods, like baking, smoking, and cooking by different means, produce nitrosamines. Moreover, above all, the availability of nitrates and nitrites as additives or naturally occurring substances in the meat can also greatly influence nitrosamine levels (20).

Stricter regulations and better monitoring methodologies in the meat industry targeting nitrosamine levels in meat products would include such forms of monitoring for additives concerning nitrosamine formation from their use, different forms of culinary and storage methods (15). Nitrosamines pose a serious health hazard in processed meats, particularly concerning cancer initiation. Education concerning the health effects is relevant to the consumer, while the same is also needed by the food industry and regulatory agencies in research and the implementation of actions to reduce such compounds in products. Consumers can also promote healthy well-being through informed choice of diet, pushing for clearer labeling on food, and safer processing methods (4).

Absorption and mechanism of nitrosamines in the human body

Molecular oxygen is a cofactor in the microsomal NADPH-dependent metabolism of NDMA and NDEA, forming an unstable intermediate that naturally breaks down and yields a strong alkylator. Its reactions are such that it would most probably not exert considerable effects on organs other than the one in which it was generated. A perusal of mechanisms would give most emphasis to alkylation of biological macromolecules, particularly DNA, since this is an extremely relevant mechanism in tumorigenesis attributable to these carcinogens. The maximum ability to turn these nitrosamines into alkylating agents appears to be that of the liver; however, activation to this form may likewise take place in other organs like the esophagus, lungs, and kidneys. Since these organs have lower capabilities than the liver in removing 06-alkylguanine from DNA, they would more likely suffer alkylation than the liver. However, nitrosodimethylamine is rapidly absorbed into portal circulation and transported to the liver after oral ingestion or production from nitrosating processes in the gastrointestinal tract. This mode of administration of small amounts ensures that the carcinogen is maximally metabolized in the liver, while organs such as the lungs barely respond to it. The extremely fast metabolism and clearance of the carcinogen by the liver have two major implications in this case. The first would be that the peripheral blood might have concentrations of nitrosodimethylamine much lower than would be expected according to dietary intake. Any physiological factors that inhibit metabolic activation in the liver would promote increased metabolism of carcinogenic substrates in other tissues and increase the risk of cancer developing at those sites (64, 65).

Digestion of nitrosamines in the human body

Nitrosamines go through a series of processes from being ingested into the human body to being digested. They end up being absorbed through inhalation or transformation, usually after the consumption of smoked or cured meats, a few dairy products, or even beer. After entering, these elements go into the stomach, where acidic conditions induce the formation of nitrosamines from the nitrites and amines in the consumed food, or may be absorbed directly from processed foods. The formed nitrosamines would permeate the gastric mucosa. After this, hepatic metabolizing enzymes begin acting on them, the most well-known of which is cytochrome P450, vasculature and reactive intermediates, which can damage DNA and proteins (4).

The human body has a cleansing mechanism for nitrosamines. Glutathione, a very active antioxidant, conjugates with nitrosamines and reduces their harmful effects. All the byproducts from nitrosamine metabolism are excreted from the body through urine or stool after metabolism and detoxification if necessary. Notably, the metabolism and effect of these nitrosamines differ with the structures of the nitrosamines, the different metabolic rates of individuals, and their general health conditions (59). Digestion forms ingestion, gastric processing, metabolism, detoxification, and excretion, as far as nitrosamines go in humans. A thorough understanding of these processes is necessary to assess the prospective health risks that could be influenced by the arms to the capillaries of humans with nitrosamines (22).

Strategies to reduce exposure to nitrosamines

1. Restriction in consumption: The most efficacious measure of reducing the effect of nitrosamines derived from processed meats is consumption reduction. The American Society of Tumor Surgery thus recommends limiting processed meat consumption (22).

2. Food choices: It is also necessary to try to add to those processed meats, fruits, and vegetables containing antioxidants, which are believed to reduce the influence of nitrosamines (22).

3. Cooking methods: High-temperature cooking increases the occurrence of nitrosamines, while lower temperature cooking with no direct access to flame or hot metal surfaces helps reduce nitrosamines (22).

4. Natural preservatives: Some companies are researching natural preservatives, such as celery powder containing naturally occurring nitrates that they plan to include in the formulation. It remains unclear whether such replacements yield lower nitrosamine levels (22).

Heterocyclic aromatic amines (HAAs)

Heterocyclic aromatic amines (HAAs) (figure 3), a class of compounds with structures in which cyclic arrangements have at least two different elemental atoms placed in their ring, are of particular concern due to their putative carcinogenic nature since they are formed when protein-rich foods are subjected to heating and processing techniques imparting flavors to food. HAAs were first discovered by Professor Sugimura, with more than 30 different types of these compounds already isolated and identified from a variety of cooked protein-rich foods. Aromatic heterocyclic amines (HAAs) and related compounds are formed during the prolonged cooking of protein-rich foods such as pork, chicken, fish, and beef. Present in cooked meats, meat extracts, coffee, flavorings, alcoholic drinks, and meat oils, these substances also come from environmental sources, including surface waters, air, industrial and biological fluids, cigarette smoke, and the kitchen surroundings (15, 26, 66, 67).

Types of heterocyclic aromatic amines

According to the temperature of their synthesis, heterocyclic aromatic amines are classified into two groups: polar, termed thermic for 100-250 °C, characteristic of baking, grilling, and frying protein-rich foods, and nonpolar, mixed at high temperature. Experiments measured the effect of the Maillard reaction in developing polar molecules from alpha-amino acids, reducing sugars [glucose, fructose, ribose], and creatine, naturally found in meat. In such reactions, the amino group of amino acids acts upon the carbonyl group of sugars. The formation of HAAs is based on two mechanisms: the free radical pathway and the carbonyl pathway. The former has to do with the Maillard reaction, whereby free radicals like pyridine as well as pyrazine radicals will be involved in such events as reactive carbonyl conversion. Potent nonpolar HAAs are pyrolytic, generated due to heating at high temperatures from thermal degradation of tryptophan and glutamic acid.

It is in the high temperatures of radical reactions that such fragments can react, offering pathways to condensation into heterocyclic structures (25, 26, 66, 68).

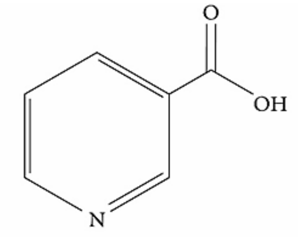

Figure 3. Chemical form of heterocyclic aromatic amines

Formation of heterocyclic aromatic amines

By amines present in heterocyclic compounds, we mean those which have been classified as carcinogenic and mutagenic substances found on the surfaces of protein-rich foods like fish and meat. Such substances arise from Maillard reactions, which occur during the cooking of food by roasting and frying. Among polar and non-polar heterocyclic aromatic amines, Harman and Norharman are synthesized at lower temperatures. It is proposed that free radical species significantly contribute to the formation of IQx (2-amino-3-methyl-3H-imidazo [4, 5-f] quinoxaline) and IQx (2-amino-3-methyl-3H-imidazo [4, 5-f] quinolone). (26) Production of PhIP is causing the presence of reducing sugars, creatinine, and phenylalanine. At first, phenylacetaldehyde is produced from phenylalanine by the degradation processes via the Strecker reaction. Then, in the complete formation of phenylacetaldehyde from aldol reaction with creatinine and an additional aldol product, PhIP is formed through aldol condensation via a condensation reaction (69).

Limitations of the use of heterocyclic aromatic amines

The US National Toxicology Program supports a strong connection between eating cooked meat products and having an HAA intake over 17 ng/kg body weight. Survey data showed that by far the largest contributor to this accumulation in the body is consumption of meat, which ranges from 0-15 mg on a day-to-day basis, depending on the eating habits (24).

Relationship between human diet and heterocyclic aromatic amines

The formation of heterocyclic aromatic amines (HAAs) in food depends on many factors, such as the type of food and nature of raw material, cooking temperature and duration, equipment and methods used, processing techniques, storage time of fresh meat, presence of precursor compounds, etc. Moreover, some enzymes and certain conditions, such as bacterial presence and the digestive system, have all been proven to affect the secretion of HAAs during digestion (15, 24, 26, 70). Thus, the factors that are responsible for HAA formation in food can be distinctly classified into three primary types: cooking or processing techniques, additives that encourage or discourage HAA generation, and specific types and recipes of the food that are to be prepared. Three alternative approaches might be used for reducing the generation of HAAs during food processing and preparation, which are varying the conditions or methods of cooking; adding natural product extracts, antioxidants, or other compounds; and deliberately choosing food ingredients used (26).

The formation of heterocyclic aromatic amines in processed meats

Heterocyclic amines (HAAs) are produced during the chemical treatment of meats. The reaction to produce HAAs begins when muscle tissue is exposed to extreme temperatures higher than 150 °C (300 °F), inducing reactions among the natural amino acids, creatine, and sugars present in the meat. The named compounds owe their nomenclature to the Maillard reaction due to the interaction between amino acids and reducing sugars at the extremes of temperatures, producing an array of many compounds, including HAA. (24) Every kind of meat, mode of cooking, and temperature at which cooking is carried out will differ in HAA production. During HAAs, meats like beef, pork, and chicken make more HAA than fish and other kinds of processed meats that contain less muscle. Methods of cooking, such as grilling or frying in a pan with high heat application, greatly enhance the amounts of HAA. Long cooking periods with direct flame contact will also increase the amounts of HAA (15).

Metabolism of heterocyclic aromatic amines in the body

The metabolism of heterocyclic aromatic amines is a two-phase process, beginning with biotransformation (Phase I) and followed by conjugation (Phase II). During Phase I, the cytochrome P450 (CYP) enzyme system activates heterocyclic aromatic amines by adding a polar functional group. By contrast, Phase II enzymes, such as sulfotransferases (SULT), N-acetyltransferase (NAT), and UDP-glucuronosyltransferase (UGT), will manufacture the activated metabolite with a large molecular weight and reduced reactivity. Phase II may also generate reactive metabolites when such enzymes interact with DNA or proteins, thereby forming DNA adducts. DNA adducts can interfere with replication and misreplicate, which could lead to mutation and, hence, cancer. Meanwhile, metabolic detoxification has been simultaneously carried out by the liver. Microsomal activation requires the oxidation of hydroxyl derivatives with the support of cytochrome P450 isoenzymes. Hydrolytic reactions ultimately yield sulfate and glucuronide esters, with direct N-glucuronidation possible for the exocyclic amino group of heterocyclic aromatic amines. Following detoxification, polar metabolites are excreted from the body through the urinary route (8, 66).

Digestion of heterocyclic aromatic amines in the human body

HAAs are metabolized and have a complex biochemical pathway that brings health implications for humans. So once the food containing HAAs is ingested, it is first metabolically activated and eventually exerts some kind of mutagenic effect. The gastric phase of digestion commences within the stomach and ends in the small intestine with the absorption of HAAs into the circulation. Generally, cytochrome P450 enzymes mediate the HAAs' metabolism to hydroxylate metabolites. After this initial step, phase I metabolic detoxification occurs in the liver through biochemical processes such as oxidation, reduction, and hydrolysis. These reactions yield metabolites, some of which may be toxic or carcinogenic (15).

Carcinogenic effects of heterocyclic aromatic amines

HAAs can induce tumors in the liver, prostate, lungs, mammary glands, and colorectum among rats and nonhuman mammals (26, 69). In humans and other primates, HAAs also cause carcinogenicity in various organ systems. For example, Cross et al. demonstrated that elevated MeIQx and PhIP-mammalian HAAs abundant in cooked meat were significantly associated with the risk of esophageal cancer (43). Furthermore, Malfatti et al. warned that the consumption of heat-treated meat might elevate the likelihood of pancreatic cancer; the mutagenic HAAs can cause alterations of pancreatic cell DNA (71). In addition, Stack et al. provided direct evidence for the association of colon cancer with over-consumption of thermally processed beef (72).

Modification of curing methods to reduce the formation of heterocyclic amines

Penultimate temperature of the cooking surface, which serves the uniform setting of internal temperatures, affects the formation of heterocyclic amines. Indeed, at the cooking surface temperature of 250 °C, meat would attain 70 °C in 7 minutes, while at 160 °C, it would take 9 minutes. The latency is attributed to slow transfer of heat inside the meat; thus, lower cooking surface temperature may help to reduce the formation of HCAs, which does not much extend cooking times (26). For counteracting HCAs, the most preferable method of cooking in the case of pan-fried beef is to turn it every minute during the actual cooking, as opposed to turning it every 5 minutes at medium heat until reaching the internal temperature of 70 °C. This ensures HCA production is minimized without fail while proper cooking is done to the final temperature threshold of 70 °C, which is enough to kill any bacteria in meat that may pose a risk to humans (26). Tiny changes in the recipe of various meat-based dishes may also be advisable to reduce HCA formation. Adding inhibitors or inactive ingredients can alter the levels of precursors, exhibiting inhibitory activity. There have also been reported methods that could reduce the mutagenicity of some HCAs found in minced meats by adding soy flour, antioxidants, glucose, and lactose, which were shown to reduce mutagenic activity (68). Heat transfer during frying of meat is complex: salt solution assists in transferring soluble, water-activated precursors for HCA formation in foods with moisture content. Water-soluble binding agents in minced meat, such as salt, soy protein, or starch, impede the outward transfer of such precursors from the internal to the surface, thus causing a reduction in HCA formation. Persson and others observed that salt and sodium tripolyphosphate largely discourage such permeability. In addition, enzymatic treatment with keratinase aided further detoxification by minimizing keratin availability in meat, which inhibited HCAs as a consequence (24).

The limit of meat consumption

The guidelines regarding meat consumption may differ according to health, tastes, and environment. The experts in health, such as cancer organizations, recommend limiting red and processed meats due to the risk they pose for cancer and heart-related ailments like obesity and high blood pressure. Consulting a nutritionist to determine what is suitable for your health and regularly replacing meat with plant-based protein sources can provide nutritional benefits while also supporting a more sustainable lifestyle. This demonstrates that there are viable alternatives to meat-based diets (4). Alternatives to processed meat include lean cuts of fresh meat, poultry, fish, and plant proteins like beans, lentils, and tofu. Cooking methods- Frying, baking, boiling, steaming, and other dry heat methods- are promoted with strong caution toward carcinogen formation in meat preparation. Dietary changes would minimize exposures to harmful substances and their contribution to predictable cancers and other disease risks (43).

Bioactive compounds

Research on a few various bioactive natural compounds suggests they have anti-cancer activities by preventing the creation of carcinogenic substances during preparation or cooking. Fruits like berries are naturally rich in polyphenols, and these compounds scavenge free radicals; hence, oxidative damage to DNA from carcinogens can be reduced. Similarly, cruciferous vegetables like broccoli and cabbage have glucosinolates, which convert during cooking to isothiocyanates with known chemopreventive properties. Another example is turmeric, much lauded for its anti-cancer action, with curcumin giving that activity via its interaction with numerous molecular pathways associated with tumor initiation and progression (10, 29).

Concepts and future direction

Incorporating bioactive substances into heat-treated meat means reducing the formation of carcinogenic agents and generally reducing the anticipated health consequences of red meat consumption. However, putting this into practice has some caveats. The major hurdle is going to have a concentration of the bioactive materials needed while ensuring that acceptable sensory properties are maintained, viz., taste and texture. Further research should move toward innovating new methodologies to tackle such major hurdles and to improve the target effectiveness of bioactive compounds in the inhibition of carcinogen formation. New methods of cooking or nanotech encapsulation and delivery of such compounds into meat products without compromising the functional properties may be the future aspects of such endeavors (1).

Bioactive compounds derived from fruits, vegetables, and spices have been shown to significantly inhibit carcinogen formation during the heat processing of meat. Incorporating these compounds into meat products presents promising opportunities for mitigating the health risks associated with red meat consumption. However, further research is needed to address challenges related to the practical application and effectiveness of this strategy. Successful advancement in this area could yield substantial public health benefits by reducing the impact of red meat consumption on cancer risk and lowering the overall societal burden of cancer (66).

Table 1. Carcinogenic compounds in red meat: Formation and implications

Carcinogenic Agents in Red Meat	Key Points	Details
PAHs	PAHs are mutagenic agents formed during high-temperature cooking of meat.	Their concentrations depend on meat type, cooking method (e.g., well-seared, grilled, fried meats yield higher amounts), and doneness. Lower temperatures or slower cooking generally result in lower levels (17, 19, 32, 44, 75, 76).
Nitrosamines	Red meat is a dose-dependent inducer of nitrosamines.	After eating red or processed meat, nitrosamines may be produced in the body by reactions between nitrites and amines. These substances can hurt DNA and increase the chances of colorectal and other digestive cancers (5, 20, 23, 59, 63, 77).
HAAs	HAAs are mutagenic agents formed during high-temperature cooking.	Like PAHs, their concentrations are influenced by meat type, cooking method, and doneness. While many studies show symmetrical HAAs are carcinogenic in animals, their typical dietary ingestion levels are very low relative to carcinogenic effects (8, 26, 66, 67, 74, 78).

*List of abbreviations: PAH: Polycyclic Aromatic Hydrocarbons, HCA: Heterocyclic Aromatic Amines

Conclusion

At present, red meats are believed to be a risk factor for many neoplasias, particularly colorectal. There should then be a medical consideration on the relationship between red meat and cancer, and possible pathophysiological mechanisms in this context. Among the most physiologically credible mediators should be some examples of mutagenic agents involving meats, namely, polycyclic aromatic hydrocarbons (PAHs), nitrosamines, and heterocyclic aromatic amines HCAs) (see for other examples figure 4). Studies: Of course, a lot of studies show that red meat is a dose-dependent inducer of nitrosamines, but we still need to understand the carcinogenic transformation of every nitrosamine species. We also require more epidemiological proof to substantiate the relevance of nitrosamines' carcinogenic potential (5, 73).

The concentrations of heterocyclic aromatic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) in meats will depend not only on the type of meat but also on the cooking method and the degree of doneness. Well-seared, grilled, or fried meats may yield sufficient reactions to yield some particular concentration(s). It may be assumed that at lower temperatures or slower cooking, lower levels of HCAs and PAHs may, on average, result. Usually, their concentrations do not lead to straightforward conclusions on account of most studies showing that symmetrical hetero-cyclic aromatic amines are carcinogenic in animals. It must be stressed that the ingestion of these compounds by average diets has very low values concerning carcinogenic effects (5, 74).

Beef replacements with white meat merit further study; possible meta-analyses of studies looking at white meat consumption and cancer should also be undertaken. Future lines of inquiry will further look at the assessment of exposure to carcinogenic compounds mentioned earlier. The time has come for current dietary recommendations on red meat consumption to be reconsidered and possibly revised for those at risk. Future research would consider the influence of cooking red meat on genetic predisposition to oncogene activation, and some methods would be considered. The interaction of different food patterns in the processes that either synergistically or antagonistically influence other food components with oncogene regulation will likewise be scrutinized. That will take the understanding of diet and cancer forward (20). In summary, this research underscores the intricate relationship between red meat consumption and oncogene activation, highlighting the necessity for more nuanced dietary recommendations and further exploration of dietary influences on oncogenic processes. These findings provide a foundation for refining public health strategies and directing future research toward a more thorough understanding of the dietary factors influencing cancer development. Table 1 provides a concise summary of the main findings and mechanistic insights discussed throughout the article.

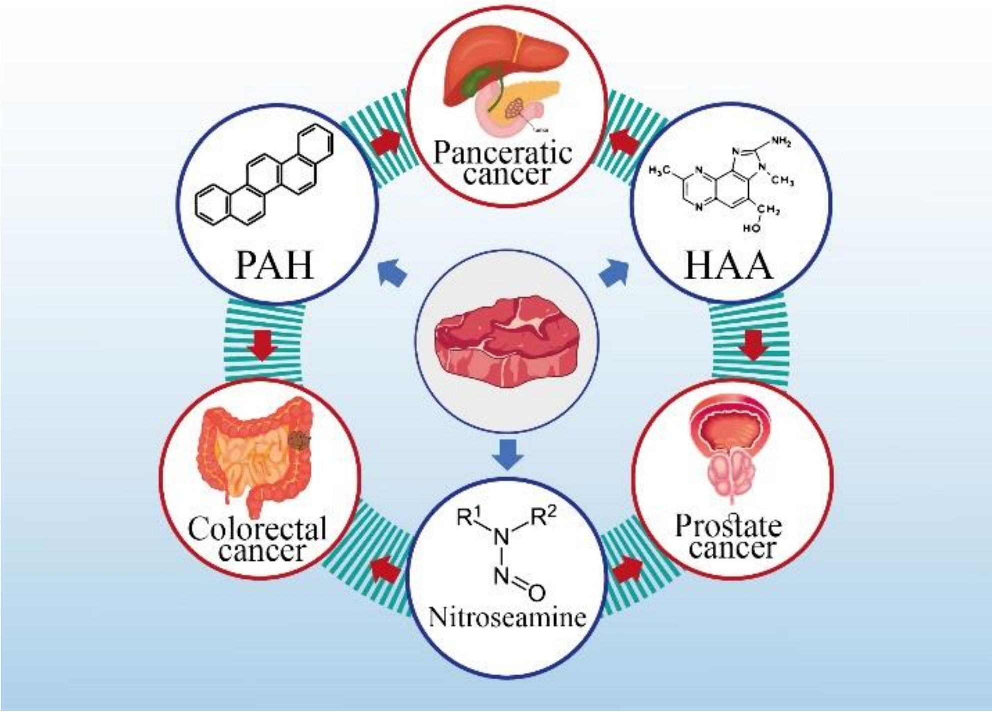

Figure 4. Proposed mechanisms for mutagenic compounds linked to meat, including polycyclic aromatic hydrocarbons, nitrosamines, and heterocyclic aromatic amines

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