Mechanistic Hypotheses on Colorectal Cancer and Red Meat Intake: A Review

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Abstract. Red meat is classified as probably carcinogenic to humans by International Agency for Research on Cancer (IARC) based on evidence on how it may affect the development of colorectal cancer, the third most common cancer worldwide. A plethora of scientific experiments prevailing to establish a positive association between red meat and colorectal cancer suggested different mechanistic hypotheses in order to explain such a phenomenon. This paper aims to discuss major hypotheses related to how red meat consumption may lead to colorectal cancer. Such hypotheses involve the role of natural compounds present in red meat (such as lipid, protein, N-glycolylneuraminic acid and heme iron) and neoformed substances during meat processing (such as heterocyclic amines, polyaromatic hydrocarbons and N-nitroso compounds).

Keywords: colorectal cancer, red meat, hemoglobin

1. Introduction
Colorectal cancer (CRC) is ranked third among the most frequent cancers worldwide, making up approximately 10% of all cancer cases and 9% of global mortality by cancer across the globe. It tends to develop more commonly in men than in women. Its incidence rate is higher in affluent and developed countries, where 60% of cases were reported [1-2]. The survival rate is relatively low, with about 50% of CRC patients survived in 10 years following first diagnostics. Several factors determining the survival rate of CRC patients comprise how advanced the cancer stage is, the possibility of cancer removal, and general health conditions of the patients [3].

World Cancer Research Fund (WCRF) in its latest Continuous Update Project (CUP) in 2018 identified and established risk factors regarding CRC, among which physical activity appears to be the only convincing factor decreasing CRC risk whereas processed meat, alcoholic drinks, body fatness and adult attained height are considered as convincing factors increasing CRC risk. Red meat consumption is categorized a factor that probably increases the risk of CRC [1]. World Health Organization (WHO) defines red meat as all mammalian muscle, including beef, pork, veal, lamb, mutton, goat and horse. In 2015, The International Agency for Research on Cancer (IARC), the cancer agency of WHO, classified red meat as probably carcinogenic to humans (Group 2A) based on strong mechanistic evidence supporting carcinogenic effects of red meat and limited evidence of red meat causing cancer in humans [4]. The latest meta-analysis study regrouping cohort and case control studies was conducted by WCRF and American Institute for Cancer Research (AICR) in order to...
establish a dose-response relationship between CRC and red meat intake. The results concluded an increased CRC risk of 17% (95% CI 1.05-1.31) related to daily red meat intake of 100 g [5].

This paper aims to decipher different major hypotheses on how red meat intake can cause CRC based on existing studies on humans and experiment animals. These hypotheses consist of: (1) diets high in fat correlate positively with insulin resistance or fecal bile acids that promote carcinogenesis, (2) carcinogenic heterocyclic amines and polyaromatic hydrocarbons are formed during meat processing at high temperature, (3) carcinogenic N-nitroso compounds are formed during meat processing and in human body through fermentation by colic bacteria, (4) N-glycolyneuraminic acid naturally present in red meat incites inflammation in the colon, and (5) heme iron naturally present in red meat promotes carcinogenesis directly through its oxidative potential and indirectly through lipoperoxidation that may influence fecal water toxicity [6-7]. All the hypotheses evoked in this paper are summarized in Figure 1.

![Figure 1](image_url)

**Figure 1.** Summary model for mechanistic hypotheses regarding colorectal cancer and red meat intake

### 2. Lipid

The implication of lipid as an etiologic factor for CRC is related to the concept of diet rich in fat increasing the secretion of abrasive bile acid in intestinal lumen [8]. Besides, certain bacteria present in the colon are able to degrade bile acids into carcinogenic N-nitroso compounds (NOC) [9]. High-fat diet is closely related to obesity and insulin resistance, convincing risk factors of CRC [1]. Insulin resistance is associated with the increase of tumor supporting factors in the blood such as free fatty acids, glucose, insulin and IGF-1 (insulin-like growth factor 1) that may promote carcinogenesis by augmenting the proliferation and reducing the apoptosis of cancer cells [10-11].

To demonstrate the link between high-fat diet and colon tumorigenesis, several *in vivo* experiments using rats have been conducted. Some of them prevailed to show such a link [12-15] while some of them failed [16-21], resulting in puzzling discrepancy. Concerning epidemiological studies on high-fat diet and CRC in humans, the results are quite controversial. The latest meta-analysis study summarizing 18 studies reported that dietary fats and fatty acids had no effects on the risk of CRC in humans [22].
3. Heterocyclic amines and polycyclic aromatic hydrocarbons
Heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) are carcinogenic compounds formed during meat processing at high temperature. HCAs are generated through pyrolysis of create(ni)ne with certain amino acids at high temperature, for instance during cooking. Fried, broiled and barbecued meat has been shown to contain high amounts of HCAs. The most abundant HCAs in meat appear to be2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) and 2-amino-3,4,9-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx) [23-25]. HCAs have been reported in vivo to induce colon cancer in rodents and monkeys [26]. PAHs are generated from incomplete combustion of organic compounds. Benzo[a]pyrene (BaP), the most well-studied PAH, is mutagenic and carcinogenic to animals. In humans, BaP is able to form DNA adducts in colon cells, thus disrupting their genetic processes [27]. Following Phase I detoxification system involving cytochromes p450 (CYP1A1 and CYP1A2), transformed BaP turns out to be able to cause mutations on p53, a tumor suppressor gene [28]. In most cases, PAHs enter the human body through consuming smoked meat (notably barbecued meat) and inhaling tobacco smoke [29]. BaP has also been shown to induce colon tumorigenesis in mice [30-31].

Some epidemiological studies on correlation between HCAs, PAHs and CRC in humans showed positive correlation [32-34] while some did not [35-36]. However, the latest meta-analysis concluded a convincing association of HCAs and BaP with CRC risk as follows: PhIP relative risk of 1.20 (95% CI 1.12-1.29), MeIQx relative risk of 1.20 (95% CI 1.08-1.34) and BaP relative risk of 1.15 (95% CI 1.04-1.27) [37]. In addition, polymorphisms on gene CYP1 A2 (cytochrome p450 1A2, a phase I enzyme) and NTA1 (N-acetyl transferase, a phase II enzyme) were shown to result in individuals that were more prone to colorectal carcinogenesis related to cooked meat compared to those not exerting such phenomena [38-39].

4. N-nitroso compounds
Processed meat products include bacon, ham, sausages, jerky, salami, corned beef and meat-based sauces. WHO has classified processed meat as carcinogenic to humans (Group 1 carcinogen) [4]. Nitrite (NO₂⁻) in the form of its salt is often added in the production of processed meat as a curing agent; to enhance color and flavor, prevent spoilage and inhibit microbial growth. Despite its advantageous properties, nitrite can generate carcinogenic N-nitroso compounds (NOCs) through a reaction with secondary amines and N-alkylamides. Some well-studied NOCs are nitrosamides, nitrosamines, nitrosyl iron (FeNO) and S-nitrosothiols. NOCs are able to alkylate DNA bases, thus disrupting normal DNA functions and promoting tumorigenesis [40]. Humans can be exposed to NOCs either exogenously or endogenously. The exogenous route consists mainly in consuming processed meats, smoked fish, cheese or beers in which NOCs are already present [41]. Endogenously, intestinal flora are able to derive NOCs from the ingested nitrates via amino acid decarboxylation [40]. Heme present in red meat can also facilitate the formation of NOCs in human gastrointestinal tract [42]. Since the formation of NOCs in the processed meat involves oxidation, ascorbic acid, due to its antioxidant properties, is often added to prevent the formation of NOCs [43].

Studies in laboratory animals reported that processed meat intake resulted in high concentration of NOCs excreted in the feces, but without any evidence of colon tumorigenesis [44-47]. In humans, the increase of fecal NOCs following the consumption of red meat and processed meat was associated with the risk of rectal cancer [40, 48-50]. However, the latest meta-analysis study reported no significant association between dietary nitrite with CRC [51]. IARC categorized ingested nitrite under conditions that may result in endogenous nitrosation in as probably carcinogenic to humans (Group 2A)[4, 52].

5. N-glycolylneuraminic acid
Sialic acids are monosaccharides that are abundantly present on vertebrate cell surfaces that are involved in cell-cell and cell-extracellular matrix interactions. Two derivatives of sialic acids include...
N-acetylneuraminic acid (NANA) and N-glycolyneuraminic acid (NGNA). NANA can be converted to NGNA by enzyme CMP-N-acetylneuraminic acid hydroxylase (CMAH) [53-54].

The gene expressing CMAH has been irreversibly mutated in humans throughout the evolution and, thus, human cell surface contains only NANA but not NGNA [55]. Nevertheless, NGNA is present on the cell surface of other mammals, including those providing red meat. Despite the human genetical inability to synthesize NGNA, this molecule is somehow detected in the surface of human cells, especially in malignant tissues on which NGNA can be found in extremely higher amount. The intake of mammalian muscle (including red meat) is suspected to be the source of NGNA incorporation in human tissues. Since NGNA is not recognized by human immune system, incorporated NGNA triggers the production of anti-NGNA auto-antibodies that persistently provokes inflammatory reactions in the colon known as xenosialitis [53]. Studies using CMAH-KO mice have demonstrated that xenosialitis due to NGNA ingestion was positively linked to colon tumorigenesis [56-57].

6. Heme iron
The majority of iron in human body exists in the form of heme iron constituting hemoglobin, the red pigment responsible for meat color [58-59]. Heme iron has been shown to possess cytotoxic and hyperproliferative properties towards colonic cells in rats [60]. Luminal iron is able to govern intestinal tumorigenesis following the loss of Adenomatous polyposis coli (APC) gene that marks the transformation of normal cells into preneoplastic ones [61]. The latest meta-analysis study revealed a positive association between heme iron and CRC with a relative risk of 1.15 (95% CI 1.04-1.26) [62]. Interestingly, an in vivo study attempted to weigh the relative contribution of three different hypotheses on CRC and red meat intake (heme iron, NOCs and HCAs) and its results affirmed that only heme iron was associated with the tumor promotion in the colon of rats without any additive or synergistic effects with HCAs or NOCs [47].

In general, heme iron can mediate CRC through three different mechanisms: (1) heme itself is able to generate oxidative stress, (2) heme induces lipid peroxidation in red meat and/or in the gut, thus leading to the formation of CRC-promoting compounds, and 3) heme catalyzes the formation of NOCs in human gut [7, 62].

6.1. Direct effects of heme on tumorigenesis
Hemoglobin has been shown to generate free radicals and exert genotoxic properties when cultured with human colorectal carcinoma cells (HT29 and SW480) and primoculture of colonocytes [63-64]. Generally, such a stress is compensated by cellular hyperproliferation, a risk factor of cancer [65].

Heme iron is a potent oxidant that generates oxidative stress through the formation of extra- and intracellular reactive oxygen species (ROS). When uptaken into cells, heme is degraded by enzyme heme oxygenase-1 (HO-1), releasing biliverdin, carbon monoxide (CO) and ferrous ion(Fe²⁺). Biliverdin is then rapidly converted to bilirubin by biliverdin reductase. The neofomed bilirubin can counteract ROS owing to its powerful antioxidant activity. Fe²⁺, in the presence of ferrooxidase, reduces ROS while being oxidized to less reactive ferric ions (Fe³⁺). However, in case of insufficient bilirubin, Fe²⁺ can react with endogenous hydrogen peroxide (H₂O₂), thus generating ROS that can provoke DNA damage and mutation [66-68]. This mechanism could explain how heme may induce CRC in a direct manner [69].

6.2. Indirect effects of heme on tumorigenesis
Indirectly, heme can promote colorectal carcinogenesis by catalyzing endogenous reactions such as lipid peroxidation and N-nitrosation, thus resulting in the formation of neoformed cyto- and genotoxic compounds that could be responsible for colorectal carcinogenesis. In general, the deleterious effects of such compounds can be inhibited by calcium or chlorophyll by heme-trapping mechanism [70-74].

As previously mentioned, following the consumption of processed meat, heme can catalyze the reaction between nitrites and amines or amides to form endogenous NOCs. Vitamin C and vitamin E
are able to inhibit the reaction [75-78]. NOCs exert their genotoxic properties by inducing DNA damage and mutation. For instance, in rat colon carcinoma, N-methyl-N-nitrosurea can trigger G→A transitions in the oncogenic gene K-RAS [79]. Moreover, nitrosated glycine induced mutation in tumor suppressor gene p53 in yeast[80]. Mutations on both K-RAS and p53 genes are involved in the development of colon cell malignancy [81].

As a potent oxidant, heme is able to catalyze the oxidation of polyunsaturated fatty acids (PUFAs) known as lipid peroxidation. Such a reaction leads to the formation of a myriad of reactive compounds, including but not limited to aldehydes. Some of the major aldehyde products derived from lipid peroxidation found in the fecal extract of rats fed with PUFA and heme iron are malon dialdehyde (MDA), 4-hydroxyhexenal (HHE) and 4-hydroxynonenal (HNE) [82-84]. While MDA can form DNA adducts [85-87], HNE appears to be the most cytotoxic towards preneoplastic colon cells compared to MDA and HHE[88]. HNE has been demonstrated to be more cytotoxic towards normal colon cells compared to preneoplastic ones harboring mutation on APC gene, thus favoring CRC promotion via a Darwinian natural selection-like mechanism [47]. This process has been suggested to involve gut microbiota and Nrf2 (nuclear factor erythroid 2-related factor 2), a transcription factor regulating the expression of antioxidant proteins that protect against oxidative damage[88-90]. Interestingly, consuming food rich in antioxidants such as α-tocopherol and polyphenols has been scientifically proven to limit lipid peroxidation in human gut [91-93].

7. Conclusions
The decision taken by IARC to classify red meat as probably carcinogenic to humans has been a milestone in public health. Based on the existing meta-analysis studies, the carcinogenicity of red meat is mainly due to its heme iron, meaning that red meat possesses carcinogenic properties by its nature, independently on the cooking method. Processing red meat at high temperature can also produce newly formed carcinogenic molecules such as heterocyclic amines and polyaromatic hydrocarbons that have been proven positively associated with colorectal cancer. Despite being probably carcinogenic, it should be realized that red meat also possesses interesting nutritional values beneficial for human health. Removing red meat totally from diet would not be the solution to reduce the incidence of colorectal cancer in a population since it might lead to the increase of undernourished individuals in the population. Public health recommendations and their socialization should be undertaken. WCRF has set a dietary goal recommendation on limiting individual weekly red meat intake to no more than 500 g.

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