Consumption of Red and Processed Meat and Elevated Risk of Cancer to Humans

Formation of carcinogenic substances, mechanisms of carcinogenesis and risk assessment for colorectal and other types of cancer

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Abstract

Epidemiological studies established that diet and obesity are responsible for a considerable proportion of human cancers. Studies in the last decade provided an overwhelming support that high consumption of fresh red meat and processed meat are associated with an elevated risk of developing bowel cancer, especially colorectal carcinoma, as well as stomach, pancreas and prostate cancers. Red meat is very important for human diet, because of high biological value proteins, animal fat and important micronutrients such as B vitamins, iron (both free iron and haem iron), selenium and zinc. In October, 2015, a Working Group at the International Agency for Research on Cancer (IARC) in Lyon (France) evaluated the carcinogenicity of the consumption of red and processed meat. Red meat includes all fresh, minced and frozen beef, veal, pork and lamb. Processed red meat is any type that is preserved by smoking, curing, salting, air-drying, heating, etc, and includes ham, bacon, sausages, tinned meat, etc.

The Working Group assessed more than 800 epidemiological (mostly prospective cohort studies) and other studies that investigated the association of cancer with consumption of red or processed meat in many countries, from several continents, with diverse ethnicities and diets. Epidemiological data from 14 cohort studies found positive associations for colorectal cancer. Findings were seen with high versus low consumption of red meat in half of those studies, including a cohort from ten European countries spanning a wide range of meat consumption, Sweden and Australia. Also, positive associations of colorectal cancer with consumption of processed meat were reported in 12 of the 18 cohort studies, including studies in Europe, Japan, and the USA. The working group used also other studies. A meta-analysis of colorectal cancer in 10 cohort studies reported a statistically significant dose–response relationship, with a 17% increased risk per 100 g per day (consumption) of red meat and an 18% increase per 50 g per day of processed meat. Also, there were positive associations between consumption of red meat and cancers of the pancreas and the prostate (mainly advanced prostate cancer), and between consumption of processed meat and cancer of the stomach. The mechanistic evidence for carcinogenicity of red and processed meat was assessed. Formation of carcinogenic substances (including cooking at high temperature), genotoxicity, oxidative stress, lipid peroxidation products and increases the bacterial mutagenicity of human urine after consumption of red meat was established. Overall, the working group classified (according to standards of IARC Monographs) the consumption of processed meat as “carcinogenic to humans” (Group 1) on the basis of sufficient evidence for colorectal cancer. Additionally, a positive association with the consumption of processed meat was found for stomach cancer. The Working Group classified consumption of red meat as “probably carcinogenic to humans” (Group 2A). These results were widely published all over the world, appeared in the international news, newspapers, television and radio. This review examines the most important findings of epidemiological studies, and explains why carcinogenic substances are formed in red meet during the phase of processing, cooking and preservation. Finally, this review presents the recommendations of scientists for the prevention of colorectal cancer by decreasing the amounts of weekly consumption of red and processed meat.

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Introduction: Diet , Nutrition, Obesity and Cancer

The relationship between diet, nutrition, obesity and cancer has advanced in the last decades. Diet and dietary components play an important role on the development of cancer, especially the cancers of the digestive tract, breast, prostate etc. Evidence from clinical trial outcomes, epidemiological observations, preclinical models and cell culture systems have all provided positive results for a positive association of diet and cancer.[1-3]

Cancer is the second most important factor of morbidity and mortality in developing countries. Cancer varies worldwide and tends to change with migration and changes in dietary and lifestyle factors. From 1980s, the Committee on Diet, Nutrition, and Cancer of the National Research Council (USA) conducted a comprehensive evaluation for high fat diet associated with increased susceptibility to cancer of different sites (particularly, breast, colon and prostate). Epidemiological observations have led to the concept that environmental or extrinsic factors (diet, smoking, sunlight, occupational exposure, alcohol, lifestyle factors, etc) are the most important in carcinogenesis compared to genetic factors. Diet, nutrition and obesity were found to play a major role in carcinogenesis. Diet and nutrition are viewed more appropriately as modifiers, rather than initiators, of tumourigenesis. Caloric intake, type and amount of fat (animal or vegetable), protein, red or processed meat, vitamins, minerals, fiber, and other dietary constituents have been studied in regard to their influence on the development of neoplasms. Epidemiological studies found that frequent consumption of certain fruits and vegetables, especially citrus fruits and carotene-rich and cruciferous vegetables, was associated with a lower incidence of cancers at various sites.[4] Reports from the IARC and the World Cancer Research Fund (WCRF) have shown an association of obesity with many types of cancer (endometrial, esophageal adenocarcinoma, colorectal, breast, prostate and renal).[5,6] Updated studies of meta-analyses confirm a prominent and consistent inverse association provided by adherence to an Mediterranean Diet in relation to cancer mortality and risk of several cancer types.[7]

Figure 1. The Mediterranean diet is considered appropriate for disease prevention and healthy life until old age. Fruits and vegetables, olive oil, whole grains, beans, and low consumption of red meat are considered very beneficial to human health.

Increased Red Meat Consumption in Human Diet and Health

From the 1990s researchers investigating the association of high intake of red and processed meat and risk of gastrointestinal system, especially colorectal cancer, by prospective epidemiological studies.[8-10] Although red and processed meat intake in relation to cancer risk has received considerable attention in recent years, intake of "white meat" (poultry and fish) has not been as extensively investigated in epidemiologic studies. The 2007 report from the World Cancer Research Fund and the American Institute for Cancer Research concluded that the evidence for poultry intake and cancer risk was "too limited in amount, consistency, and quality to draw any conclusions," whereas the evidence for fish intake was "limited to suggestive" of lower cancer risk and based primarily on studies of colorectal cancer. More studies in recent years considered that poultry can be generally considered a nutritious lean meat alternative to red meat. Also, the consumption of fish has potential benefits to human health and is linked with anti-inflammatory and anticarcinogenic effects of its long-chain *n-3* fatty acids content.[11-14] But in the last decade many more prospective studies have reported an inverse association (decrease risk) between colon cancer risk and prolonged consumption of poultry and fish. [15-17]

Increased fresh red meat and processed meat consumption in developed and developing countries has become an environmental and health issue in recent years. The Food and Agricultural Organization (FAO) published a report ("*Livestock's Long Shadow* ") on the environmental impact of livestock as a major stressor on many ecosystems and on the planet as a whole. Globally livestock production is one of the largest sources of environmental pollution, soil desertification, emissions of greenhouse gases and one of the leading causal factors in the loss of biodiversity and leading source of water pollution because of animal waste.[18]

The scientific literature contains scientific evidence that links excess meat consumption, particularly of red and processed meat, with heart disease, stroke, type 2 diabetes, obesity and certain cancers.[19-22] The opposite is true for diets high in vegetables, fruits, whole grains and beans that help prevent these diseases *and* promote health in a variety of ways.[23]

Global Consumption of Fresh Red and Processed Meat

Meat production and consumption on a global scale have increased rapidly in recent decades in developed and developing countries. Worldwide meat production has tripled over the last four decades and increased 20% percent in just the last 10 years. Global annual meat production is predicted to rise from a level of 218 million tones (1999) to 376 million tones by 2030. Worldwide, per capita/year meat consumption increased to 42 kg in 2010. People in the advanced industrial countries consume on average 80 kg/year/person, more than double compared to people in developing countries (32 Kg/year/person). Consumption is also different in various countries (in 2002): USA (125 kg/person/year), Denmark 145 (the highest in the world), France 100, Spain 120, Brazil 82, China 50, Germany 82, Greece 79 (Kg/person/year).[24] The consumption of meat in Greece according to international food statistics (ICAP Group) in 2010 was 905 million tones. The Greek production was 503 million tones and imports 432 million tones. In Greece (from international statistics, 2002-2005) the mean daily intake/person for total meat was 79 (men), 47(women), of which 55 g (m) and 31 g (w) of red and processed meat. For comparison, Spain : total meat 170 g (m) and 99 g (w) of which 126g (m) and 67g(w) red and processed, United Kingdom: total 108 g(m), 72 g(w) of which 78 g(m), 46 g(w) red and processed meat.[25]

The USA is a typical developing country where meat consumption is very high. More than half of the meat products Americans consume are red meat, and nearly 1/4 are processed meats. In 2007 US people consumed daily ~240 g/capita/day total meat, of which 125 was red and processed meat, 85 poultry and 30 fish.[26]

Figure 2. Fresh read meat is considered a very important for human diet because it contains high biological value proteins, micronutrients such as B vitamins, iron (both free iron and haem iron) selenium and zinc. Processed meat is a broad category of meat products after processing (sausages, salami, bacon, ham, hot dogs, corned beef, etc).

Fresh red meat, such as beef, veal, pork, lamb, mutton, horse, or goat meat—including minced or frozen meat; it is usually consumed cooked. Processed meat refers to meat that has been transformed through salting, curing, fermentation, smoking, or other processes to enhance flavour or improve preservation. Most processed meats contain pork or beef, but might also contain other red meats, poultry, or meat byproducts such as blood. Processed meat and poultry products are a very broad category of many different types of products all defined by having undergone at least one further processing or preparation step such as grinding, adding an ingredient or cooking, which changes the appearance, texture or taste. The ready-to-cook category also includes uncooked smoked sausages that are mildly cured through the addition of sodium nitrite, an ingredient that imparts a characteristic pink colour and distinct taste. Processed meat like fresh is rich in protein and absorbable essential vitamins and minerals including iron, zinc, and vitamin B_6, B_{12}, selenium, choline, thiamine, niacin, and riboflavin.[27]

Epidemiological studies and meta-analysis of results showed that daily consumption of high quantities of red and processed meat is associated with increasing risk of obesity. Obesity has been established many years ago as a contributing factor for various cancers. A systematic recent review (2014) and a meta-analysis were conducted with 21 and 18 studies, respectively. Meta-analysis showed that consumption of higher quantities of red and processed meats was a risk factor for obesity (Odds ratios, OR: 1.37, 95% CI, Confidence limits: 1.14-1.64). The analysis of the data revealed that red and processed meat intake is directly associated with risk of obesity.[28]

The Report of IARC: Evaluation of Carcinogenicity of Red and Processed Meat

The International Agency for Research on Cancer (IARC, Lyon, France, established in 1965) is the specialized cancer agency of the World Health Organization (WHO). The objective of IARC is to promote international collaboration in cancer research and to bring together skills in epidemiology, laboratory sciences and biostatistics to identify the causes of cancer. IARC has the expertise in coordinating research on cancer across countries and organizations on a global scale and has published more than 110 Monographs on the Evaluation of Carcinogenic Risks to Humans. These monographs identify environmental factors that can increase the risk of human cancer. Interdisciplinary working groups of expert scientists review the published studies and evaluate the weight of the evidence. Since 1971, more than 900 agents have been evaluated. The Monographs of Working Groups include epidemiological evidence, animal bioassays, and mechanistic and other relevant data to reach conclusions as to the carcinogenic hazard to humans from exposure to chemical substances, physical and biological agents, environmental factors and occupations.

International Agency for Research on Cance

World Health Organization

Evaluation of carcinogenic factors leads to Classification in four groups (1, 2A, and 2B, 3, 4)

Group 1 Sufficient evidence in humans or sufficient evidence in animals and strong mechanistic data in humans

Group 2A Limited evidence in humans and sufficient evidence in animals

Group 2B Limited evidence in humans and less than sufficient evidence in animals

Group 3 Inadequate in humans and inadequate or limited in animals

Group 4 Lack of carcinogenicity in humans and in animals (*in vivo*)

Figure 3. International Agency for Research on Cancer (Lyon, France), operates under the auspices of the WHO. IARC convenes groups of expert scientists from around the globe to evaluate the weight of the evidence that an agent, chemical compound, complex mixtures (including individual foods), occupational exposures, physical and biological agents and lifestyle factors, can influence the risk of cancer in humans.

In October 2015, 22 scientists from ten countries met at IARC (Lyon, France) to evaluate the carcinogenicity of the consumption of red meat and processed meat. These assessments in extensive details will be published in volume 114 of the IARC Monographs (2015). Scientists from the experts group Véronique Bouvard, Dana Loomis, Kathryn Z Guyton, Yann Grosse, Fatiha El Ghissassi, Lamia Benbrahim-Tallaa, Neela Guha, Heidi Mattock, and Kurt Straif published a short paper-review: "*Carcinogenicity of consumption of red and processed meat*" in the journal *Lancet Oncol*ogy (October 2015). The highlights of the report are presented below and included references to scientific studies.

"......Red meat refers to unprocessed mammalian muscle meat—for example, beef, veal, pork, lamb—including minced or frozen meat; it is usually consumed cooked. Processed meat refers to meat (beef, pork, poultry, etc) that has been transformed through salting, curing, fermentation, smoking, or other processes to enhance flavour or improve preservation. Processing of meat, such as curing and smoking, can result in formation of carcinogenic chemicals, including N-nitroso-compounds (NOC) and polycyclic aromatic hydrocarbons (PAHs. Cooking can also produce known or suspected carcinogens, including heterocyclic aromatic amines (HAA) and PAHs High-temperature cooking by panfrying, grilling, or barbecuing generally produces the highest amounts of these chemicals.[29,30]

The report included some statistics on the consumption of red and processed meat. "...Depending on the country (high income developed mostly) red meat consumption varies worldwide. A high proportion of people consumes meat every day. The mean intake of red meat by those who consume it is about 50–100 g per person per day, with high consumption equalling more than 200 g per person per day".[31]

".....The Working Group assessed more than 800 epidemiological studies that investigated the association of cancer with consumption of red meat or processed meat in many countries, from several continents, with diverse ethnicities and diets. For the evaluation, the greatest weight was given to prospective cohort studies done in the general population. High quality population-based case-control studies provided additional evidence. The largest body of epidemiological data concerned colorectal cancer. Data on the association of red meat consumption with colorectal cancer were available from 14 cohort studies. Positive associations were seen with high versus low consumption of red meat in half of those studies, including a cohort from ten European countries spanning a wide range of meat consumption and other large cohorts in Sweden and Australia.[32–34] Of the 15 informative case-control studies considered, 7 reported positive associations of colorectal cancer with high versus low consumption of red meat. Positive associations of colorectal cancer with consumption of processed meat were reported in 12 of the 18 cohort studies that provided relevant data, including studies in Europe, Japan, and the USA".[33, 35, 36,37,38]

"....Supporting evidence came from 6 of 9 informative case-control studies. A meta-analysis of colorectal cancer in 10 cohort studies reported a statistically significant dose–response relationship, with a 17% increased risk (95% CI 1·05–1·31) per 100 g per day of red meat and an 18% increase (95% CI 1·10–1·28) per 50 g per day of processed meat".[39]

".....Data were also available for more than 15 other types of cancer. Positive associations were seen in cohort studies and population-based case control studies between consumption of red meat and cancers of the pancreas and the prostate (mainly advanced prostate cancer), and between consumption of processed meat and cancer of the stomach.
On the basis of the large amount of data and the consistent associations of colorectal cancer with consumption of processed meat across studies in different populations, which make chance, bias, and confounding unlikely as explanations, a majority of the Working Group concluded that there is sufficient evidence in human beings for the carcinogenicity of the consumption of processed meat. The Working Group concluded that there is limited evidence in human beings for the carcinogenicity of the consumption of red meat..."

"......There is inadequate evidence in experimental animals for the carcinogenicity of consumption of red meat and of processed meat. In rats treated with colon cancer initiators and promoted with low calcium diets containing either red meat or processed meat, an increase in the occurrence of colonic preneoplastic lesions was reported in three and four studies, respectively".[40,41,42]

"....The mechanistic evidence for carcinogenicity was assessed as strong for red meat and moderate for processed meat. Mechanistic evidence is mainly available for the digestive tract. A meta-analysis (2013) reported a modest but statistically significant association between consumption of red or processed meat and adenomas (preneoplastic lesions) of the colorectum that was consistent across studies".[43] "....For genotoxicity and oxidative stress, evidence was moderate for the consumption of red or processed meat".[44] Consuming well done cooked red meat increases the bacterial mutagenicity of human urine. In three intervention studies in human beings, changes in oxidative stress markers (either in urine, faeces, or blood) were associated with consumption of red meat or processed meat.[45] Red and processed meat intake increased lipid oxidation products in rodent faeces.[40] Substantial supporting mechanistic evidence was available for multiple meat components [N-nitroso compounds (NOC), haem iron, and Heterocyclic Aromatic Amines (HAA)]. Consumption of red meat and processed meat by man induces NOC formation in the colon. High red meat consumption (300 or 420 g/day) increased levels of DNA adducts putatively derived from NOC in exfoliated colonocytes or rectal biopsies in two intervention studies.[46,47]

".....Meat heated at a high temperature contains HAA (highly genotoxic), and the extent of conversion of HAA to genotoxic metabolites is greater in man than in rodents. Meat smoked or cooked over a heated surface or open flame contains PAHs. These chemicals cause DNA damage, but little direct evidence exists that this occurs following meat consumption".

"....Overall, the Working Group classified consumption of processed meat as "carcinogenic to humans" (Group 1) on the basis of sufficient evidence for colorectal cancer. Additionally, a positive association with the consumption of processed meat was found for stomach cancer. The Working Group classified consumption of red meat as "probably carcinogenic to humans" (Group 2A). In making this evaluation, the Working Group took into consideration all the relevant data, including the substantial epidemiological data showing a positive association between consumption of red meat and colorectal cancer and the strong mechanistic evidence. Consumption of red meat was also positively associated with pancreatic and with prostate cancer".

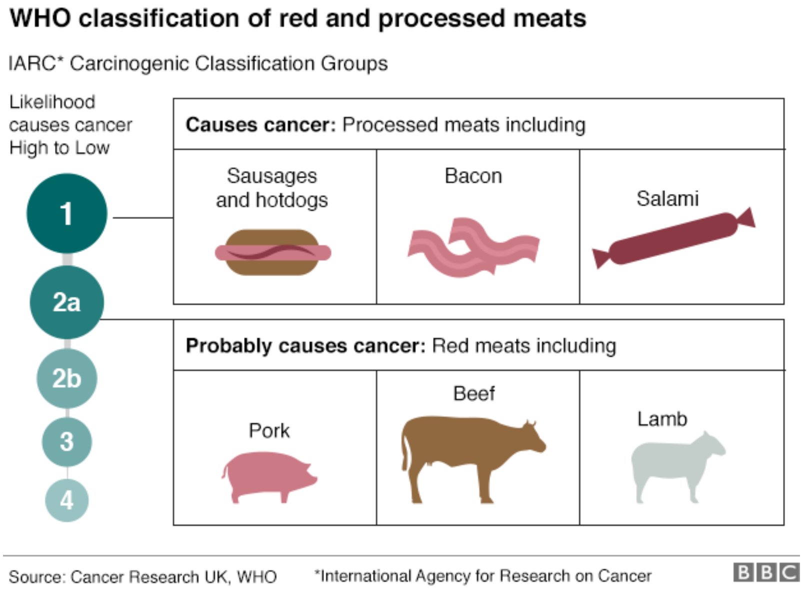


Figure 4. The IARC carcinogenic classification into groups 1, 2A, 2B, 3 and 4 is a standard procedure depending on the evidence of scientific studies. Working groups of IARC include cancer and toxicology experts decide on the associations of scientific data with cancer risk.

Why Does Meat Consumption Increases the Risk for Cancer of Digestive Tract?

After the IARC announcement, it was obvious that people will be questioning the carcinogenic potential of fresh red meat as a natural product. Studies give several reasons: Red and processed meat are high in saturated fat and cholesterol content (which increase risk for cardiovascular diseases but also promote lipid peroxidation and inflammation, both promoters of genotoxicity mechanisms), red meat has high energy density, and contains high amounts of iron and haem-iron that can act in initiation reactions of carcinogenesis. Also, high-temperature cooking (panfrying, barbequed, etc) can form carcinogenic compounds, such as heterocyclic aromatic amines (HAA) and polycyclic aromatic hydrocarbons (PAHs). Curing substances in processed meat, such as sodium nitrite, potentially can form N-nitroso compounds which under certain digestive conditions can be carcinogenic.

Heterocyclic Aromatic Amines and Polycyclic Aromatic Hydrocarbons

Heterocyclic Aromatic Amines (HAAs or HCAs) and Polycyclic Aromatic Hydrocarbons (PAHs), N-nitroso compounds (NOC) are chemicals formed when muscle meat, including beef, pork, fish, or poultry, is cooked using high-temperature methods. Curing and smoking meat for processed meat products increases the concentration of PAHs.

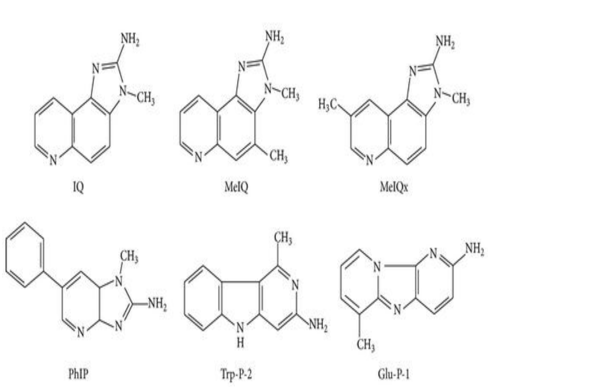
 

Figure 5. The National Cancer Institute (USA) advise people to be aware of red meat and cooking at high temperatures. Some carcinogens and mutagen are formed during cooking [http://www.cancer.gov/about-cancer/causes-prevention/risk/diet/cooked-meats-fact-sheet].

Studies showed that panfrying at high temperatures, deep-frying, charcoal grilling, and roasting, produces conformational changes in protein structure and HAAs, which are potent mutagens and carcinogens. Metabolic behaviour of HAAs is very unique, they interfere in the activity of many enzymes, modify the metabolic pathways, and lead to the mutagenic adduct formation of DNA.[48]

These chemicals (HAAs, PAHs, N-nitroso compounds, NOC) contribute to carcinogenic effects because they are involved in mechanisms of inflammation and oxidative stress.[49] In laboratory experiments HAAs are formed when amino acids (the building blocks of proteins), sugars, and creatine (a substance found in muscle) react at high temperatures. The organic chemical constituents of meat burn or their chemical molecules breaks down at high temperatures. Under high temperatures complex series of chemical reactions called Maillard reactions take place in meat. The Maillard reactions take place between amino acids and reducing sugars that gives browned food its desirable flavor. Meat steaks, pan-fried dumplings, cookies, breads, and many other foods undergo this reaction. Amino acids of meat react with reducing sugars (glucose, fructose, and lactose) in the presence of heat in excess of 155 °C (310 °F) to produce a range of poorly characterized molecules responsible for those flavours we love to chase. Prolonged heat or temperatures too high will quite suddenly change those precious golden browns to tarry black, burnt food (acrid smelling smoke). Tar is well known that contains a high amount of carcinogens and stable free radicals embedded in the porous carbonaceous material (very similar to the tar of cigarette smoke). The browning reactions that occur when meat is roasted or seared are complicated and are followed by a variety of other chemical reactions, including the breakdown of the tetrapyrrole rings of the muscle protein myoglobin.[50,51]

PAHs are formed when fat and juices from meat grilled directly over an open fire drip onto the fire, causing flames. These flames contain PAHs that then adhere to the surface of the meat. PAHs can also be formed during other food preparation processes, such as smoking of meats.[52,53] PAHs and HAA become capable of damaging DNA only after they are metabolized by specific enzymes in the body, a process called “bioactivation.” Studies have found that the activity of these enzymes, which can differ among people, may be relevant to cancer risks associated with exposure to these compounds.[54,55]



Examples of HAAs. IQ: 2-amino-3-methylimidazo[4,5-f]quinoline; MeIQ: 2-amino-3,4-dimethylomidazo[4,5-f]quinoline; etc.

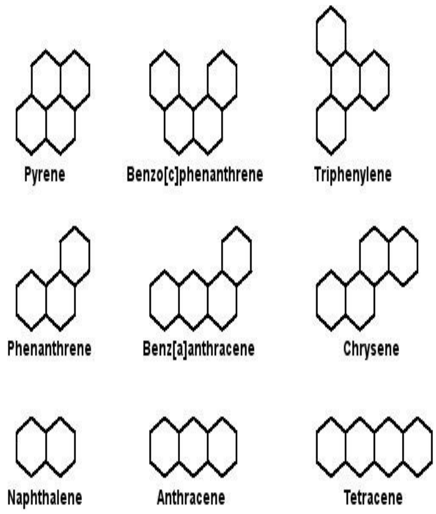


Figure 6. Examples of chemical structures of heterocyclic aromatic amines (HAAs or HCAs) and polycyclic aromatic hydrocarbons (PAHs) that are formed during cooking. These compounds have the potential for mutagenic/carcinogenic activity.

Sodium nitrite ($NaNO_2$) is a compound that is used to "cure" meats. Cured meats have a characteristic colour, unique taste and a longer shelf life. Centuries ago, nitrate was used to cure meats (before refrigeration) for preventing the growth of the bacteria *Clostridium botulinum*, which causes the very deadly disease botulism. In the 20th century, meat processors used sodium nitrite because it was more reliable in its effects. No cases of botulism have been linked to these products in the U.S. Cured meats contribute very little nitrite to the total diet – less than 5%. The major source of human nitrite exposure is vegetables, especially root vegetables like beets and leafy greens. These foods contain nitrate and when nitrate reacts with your saliva in the mouth, it becomes nitrite. In the 1970s, a single study that was later discounted cast a dark cloud over nitrite, alleging that its use in cured meats could cause cancer. In response, the U.S. National Toxicology Program (NTP) began a multi-year rat and mouse feeding study to determine if nitrite posed a health risk. In May 2000, a panel of experts reviewed NTP's findings and concluded that nitrite was safe at the levels used and did not belong on the national list of carcinogens.[56]

The Underlying Mechanisms for Red Meat Carcinogenesis

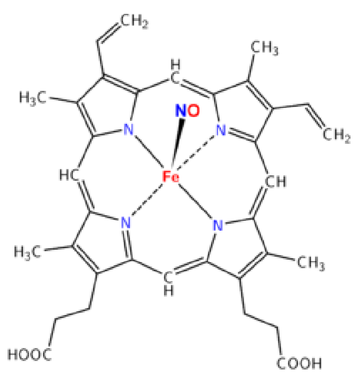
Scientists studying mechanisms of carcinogenesis have investigated several hypotheses that have been proposed for the association of red and processed meat consumption with cancers of the digestive tract, especially colorectal cancer. Tests have observed that there is higher intestinal mutagenic load among people who consume high amounts of red and processed meat The suggested candidate mechanisms of induced colorectal carcinogenesis are mainly three: i) increased N-nitrosation and oxidative load leading to DNA adducts and lipid peroxidation in the intestinal epithelium, ii) proliferative stimulation of the epithelium through haem (or heme) or food-derived metabolites that either act directly or subsequent to conversion and iii) higher inflammatory response, which may trigger a wide cascade of pro-malignant processes.[57]

Formation of Nitrosyl haem in the Digestive Tract

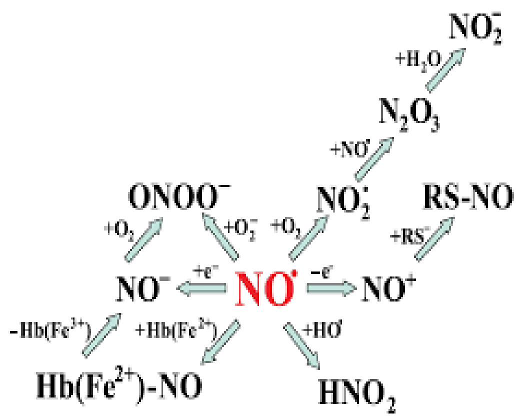
In foodstuffs and in the gastro-intestinal tract, nitrosation and nitrosylation do not have the same consequences on consumer health. Nitrosylation is adding a nitrosyl ion NO^- to a metal or a thiol. For example with iron (Fe) leads to nitrosyl iron Fe-NO (e.g., in nitrosylated haem). Nitroso- compounds (NOC) where a N=O group is attached to an organic moiety. Such as nitrosoalkanes (R-N=O), nitrosamines [$R^1N(-R^2)$-N=O], and alkyl nitrites (RO-N=O). Nitrosation is adding a nitrosonium ion NO^+ to an amine ($R\text{-}NH_2$) leading to a nitrosamine. These reactions occur at acidic pH, particularly in the stomach.

$$NO_2^- + H^+ \rightleftarrows \text{HO-N=O (nitrous acid)}$$
$$\text{HONO} + H^+ \rightleftarrows H_2O + NO^+ \text{ (nitrosonium ion)}$$
$$C_6H_5NH_2 + NO^+ \rightarrow C_6H_5N(H)N{=}O + H^+ \text{ (N-phenylnitrosamine)}$$

Meat processed by curing contains nitrite and has a pH of around 5, where almost all nitrite is present as NO_2^-. Sodium ascorbate is also added to cured meat (Vitamin C) which inhibits nitrosation of amines to nitrosamine, because ascorbate reacts with NO_2^- to form NO. Ascorbate and pH 5 thus favour nitrosylation of haem iron, forming nitrosyl-haeme, a red pigment when included inside myoglobin, and a pink pigment when it has been released by cooking. It participates to the "bacon flavour" of cured meat: nitrosyl-haem.[58-60]



Nitrosylated-haem (or heme)

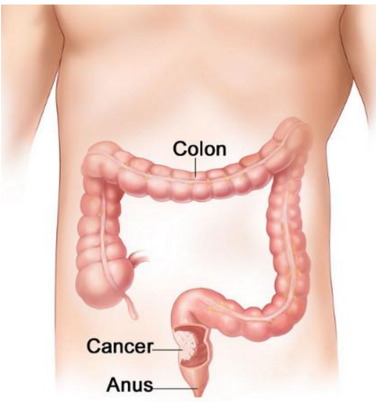


Reactions of NO, Hb =haemoglobin

Figure 7. Nitrosylation. Haem-iron reactions in the haemoglobin are considered to initiate carcinogenesis through lipid peroxidation, which is a typical process of inflammation and initiation of DNA damages.

Haem iron, heterocyclic amines, and endogenous N-nitroso compounds are proposed to explain the carcinogenic potential of red and processed meat, but their relative contribution is unknown. A study with rats and mice aimed at determining (at nutritional doses) which is the main factor involved in the mechanism of cancer promotion by red meat. The molecular mechanisms (genotoxicity, cytotoxicity) were analyzed *in vitro* in normal and Apc-deficient cell lines and confirmed on colon mucosa. Haem-iron increased the number of preneoplastic lesions, but dietary HAAs and NOC had no effect on carcinogenesis in rats. Dietary haemoglobin increased tumour load in Min mice. Genotoxicity was also observed in colon mucosa of mice given haemoglobin. These results highlighted the role of heme-iron in the promotion of colon cancer by red meat. The initiation of carcinogenesis from haem-iron could is suggested to occur through lipid peroxidation.[61] Another study with 21 healthy male volunteers investigated levels of NOC with high red meat diet, vegetable protein, ferrous iron and haem iron. The results showed that endogenous N-nitrosation occurred from digestion of haem and red meat but not inorganic iron or protein.[62]

Meta-analysis of prospective cohort studies (566,607 individuals, 4,734 cases of colon cancer) explored the role of haeme iron of red meat in the promotion of colon cancer. The relative risk was 18% for subjects in the highest category of haem iron (from fresh and processed meat) intake compared with those in the lowest category. Analysis of experimental studies in rats with chemically-induced colon cancer showed that dietary haemoglobin and red meat consistently promote aberrant crypt foci, a putative pre-cancer lesion. Although the mechanisms are not known, scientists propose a catalytic effect on the formation of N-nitroso compounds and cytotoxic/genotoxic aldehydes through lipoperoxidation.[63]



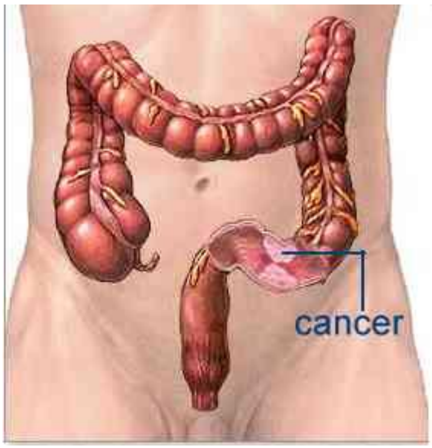


Figure 8. Red and processed meat is considered as one of the dietary factors for increasing risk of colorectal cancer of the digestive tract. The compounds formed during cooking and curing are able to be metabolised into cancer causing substances in the colon and rectum.

Epidemiological Evidence of Red and Processed Meat Consumption and Cancer Risk

A large epidemiological study (it was included in the IARC report, reference No. 20) evaluated the role of diet, but especially red meat consumption, for the most important causes of mortality, namely cardiovascular diseases and cancer. Scientists observed prospectively and for 23 years, 37,698 men (from the Health Professionals Follow-up Study, USA, 1986-2008) and for 28 years 83,644 women (Nurses' Health Study, USA, 1980-2008).The number of people was 2.96 million person-years of follow-up. Researchers validated food frequency questionnaires (every 4 years) about fresh red and processed meat consumption. The study documented 23,926 deaths (including 5,910 CVD and 9,464 cancer deaths) during 2.96

million person-years of follow-up. The pooled hazard ratio (HR) of total mortality for a 1-serving-per-day increase was 13% for fresh red meat and 20% for processed red meat. The corresponding HRs were 18% and 21% for CVD mortality and 10% and 16% for cancer mortality. Scientists estimated that substitutions of red meat with fish, poultry, nuts, legumes, low-fat dairy, and whole grains were associated with a 7% to 19% lower mortality risk. In conclusion, the researchers found that greater consumption of unprocessed (fresh) and processed red meats is associated with higher mortality risk. Compared with red meat, other dietary components, such as fish, poultry, nuts, legumes, low-fat dairy products, and whole grains, were associated with lower risk. These results indicate that replacement of red meat with alternative healthy dietary components may lower the mortality risk.[21]

The number of studies on red and processed meat and risk of cancer increased substantially in the last years and some aspects of pathogenesis has been explored. A recent study used data from two large cohorts in the USA (Nurses' Health Study with number of women participating 87,108, 1980-2010, and Health Professionals follow-up Study, 47,389 men, 1986-2010) to establish subtypes of colon and rectum cancers (CRC). The results showed that processed meat intake was positively associated with risk of CRC, particularly distal cancer.[64]

A recent study investigated the association of red and processed meat, seafood and poultry and risk to prostate cancer. Associations were examined in a consortium of 15 cohort studies (follow-up, 52,683 incident prostate cancer cases, including 4,924 advanced cases, were identified among 842,149 men). Results do not support a substantial effect of total red, unprocessed red and processed meat for all prostate cancer outcomes. For seafood, no substantial effect was observed for prostate cancer regardless of stage or grade. Poultry intake was inversely associated with risk of advanced and fatal cancers.[65]

Prostate cancer risk and red meat was investigated in another recent study. A comprehensive literature search was performed and 26 publications from 19 different cohort studies were included. Random effects models were used to calculate summary relative risk estimates (SRREs) and additionally, meta-regression analyses and stratified intake analyses were conducted to evaluate dose-response relationships. No significant relative risks were observed for any of the meat cooking methods, HAA, or heme iron analyses. Dose-response analyses did not reveal significant patterns of associations between red or processed meat and prostate cancer. In conclusion, the results do not support an association between red meat or processed consumption and prostate cancer.[66]

Other epidemiological studies for the association between red and processed meat intake and the risk of breast cancer have yielded inconsistent results. A recent review was conducted for a comprehensive meta-analysis (14 prospective studies) to evaluate the association of red and processed meat intake with breast cancer risk. The results indicated that increased intake of red and processed meat is associated with an increased risk of breast cancer.[67]

Can we Reduce Risk of Cancer with Changes in Our Diet?

From epidemiological and other studies has been found that diet and nutrition can explain as much as 30%–50% of the worldwide incidence of colorectal cancer. Research evidence focus on dietary animal fat, fresh red and processed meat, dairy, as well effects of nutrients such as calcium, folate, and vitamin D. The most important factors in reducing risk for cancer is to change dietary habits and especially reducing down daily consumption of red and processed meat, reduce daily consumption of animal fat, increase fruit, vegetables and fiber intake, reduce obesity.[68,69]

The EPIC (European Prospective Investigation into Cancer and Nutrition) study (an ongoing multicentre prospective cohort study designed to investigate the associations between diet, lifestyle, genetic and environmental factors and various types of cancer) showed that dietary fibre intake was inversely associated with colorectal cancer risk, but results from some large cohort studies do not support this finding. Scientists in a recent study explored whether the association remained after longer follow-up with a near threefold increase in colorectal cancer cases, and if the association varied by gender and tumour location**.** Their results showed that the association between total dietary fibre and risk of colorectal cancer risk did not differ by age, sex, or anthropometric, lifestyle, and dietary variables. Fibre from cereals and from fruit and vegetables were similarly associated with colon cancer; but for rectal cancer, the inverse association was only evident for fibre from cereals.[70,71,72,73] A number of epidemiological studies in the last decade have reported inconsistent associations between cruciferous vegetable (cauliflower, cabbage, garden cress, broccoli, brussels sprouts) intake and colorectal cancer. A meta-analysis in 2013 provided evidence that high intake of CV was inversely associated with the risk of CRC and colon cancer in humans.[74] Greek scientists investigated the association of adherence to Mediterranean diet with colorectal cancer risk in the European Prospective Investigation into Cancer and nutrition study. The results of the study showed that reduced risk and Mediterranean diet are more evident among women, mainly for colon cancer risk. These findings suggested that following a Mediterranean diet may have a modest beneficial effect on colon cancer risk.[75]

Most health authorities in developed countries advise people who eat more than 90 g (cooked weight) of red and processed meat a day to cut down to 70 g or lower and to replace red meat with white meat (poultry and fish). Some studies showed that increased daily white meat (poultry, fish) intake and an equal decrease in red meat was associated with a statistically significant reduced (3%-20%) risk of cancers of the esophagus, liver, colon, rectum, anus, lung, and pleura. As the dietary recommendations intend, the inverse association observed between white meat intake and cancer risk may be largely due to the substitution of red meat. Scientists suggested that simply increasing fish or poultry intake, without reducing red meat intake, may be less beneficial for cancer prevention.[17, 76,77,78]

Conclusions

High daily intake of fresh red meat (beef, lamb and pork) and processed meat (sausages, ham, bacon, etc) has been increased globally in the last decades. In the same period scientists were alarmed to discover an increase of gastrointestinal cancers, especially colorectal cancer. Large prospective epidemiological studies in the last decade investigated in a systematic way the association of high daily red meat consumption and colorectal cancer. The majority of scientific results were positive and can be explained by a number of factors, such as carcinogenic substances, mechanisms of inflammation in the colon, oxidative stress and lipid peroxidation. A higher risk has been recorded by epidemiological studies for eating a lot of red processed meat that increased risk of bowel (colorectal) cancer.

Most health authorities in developed countries advise people who eat more than 90 g (cooked weight) of red and processed meat a day to cut down to 70 g or lower. Although red meat is a good source of protein, fat and provides vitamins and minerals, higher consumption on a daily basis increase the risk for gastrointestinal cancer at old age in humans. The IARC monograph (25.10. 2015) highlighted the risk of colorectal cancer and the scientific epidemiological and other studies behind these findings.

In the last decade a variety of studies showed that diets rich in high-fiber plant foods such as whole grains, legumes, vegetables, and fruits offer a measure of protection. Fiber greatly speeds the passage of food through the colon, effectively removing carcinogens, and fiber actually changes the type of bacteria that is present in the intestine, so there is reduced production of carcinogenic secondary bile acids. Plant foods are also naturally low in fat and rich in antioxidants and other anti-cancer compounds. Also, poultry and fish (white meat) consumption has been proved to reduce risk for bowel cancer in the long term. People who ate an 80g portion of fish a day reduced their bowel cancer risk by a third compared to people who ate less than that in a week. Fish oils are especially rich in polyunsaturated omega-3 fatty acids, but there is no strong evidence that these can reduce the risk of cancer. Poultry consumption has been steadily increasing in developed countries and the replacement of red meat has been proved beneficial in reducing risk to gastrointestinal cancers.

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