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Effect of Dietary Red Meat on Colorectal Cancer Risk—A Review

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Abstract: Heme iron overload has been implicated as the main cause of the increased risk of cancer due to the consumption of red meat. However, fish and shellfish, teas, and spices contain up to five times more iron than red meat. There is insufficient evidence that iron intake in dietary red meat is the primary causal factor for colorectal cancer. In addition, harmful substances produced during the preparation of red meat, including heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs), N-nitroso compounds, and acrylamide, are extrinsic factors that increase carcinogenicity. HCAs are produced during the cooking of red meat, poultry meat, and fish. PAHs may also be produced during the cooking of diverse food groups, such as dairy products, fruits, vegetables, and cereals. The average daily intake of red meat among Korean individuals is 62 g; the amount of PAHs entering the body via red meat is less than the average amount of PAHs the body is exposed to in the air. Therefore, it is difficult to conclude that dietary red meat is the main cause of colorectal cancer. Rather, there may be an intricate influence of multiple factors, including fruit and vegetable intake, alcohol consumption, smoking, overweight, obesity, and stress.

Keywords: colorectal cancer, heterocyclic amines, N-nitroso compounds, polycyclic aromatic hydrocarbons, red meat

Introduction

On October 26, 2015, the Intl. Agency for Research on Cancer (IARC), an affiliated organization of the World Health Organization, evaluated the carcinogenicity associated with the consumption of red and processed meats. Red meat was classified as probably carcinogenic to humans (Group 2A), based on limited causal evidence in human cancers and strong mechanistic evidence supporting a carcinogenic effect. Processed meat was classified as carcinogenic to humans (Group 1), based on sufficient evidence that its consumption causes colorectal cancer in humans. This has raised strong dissenting views from governments and organizations in different countries. For example, the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) opined that since cancer is a complex disease, the risk due to the intake of a particular type of food should be evaluated by a balanced consideration of the nutritional benefits of the food. ANSES recommended a balanced diet with a moderate intake of various types of meat (500 g/week) (ANSES, 2015). The Food Safety Authority of Ireland (FSAI) announced that dietary red meat does not have to be avoided entirely because a moderate intake of red meat (approximately 100 g/day) is crucial for a healthy diet (FSAI, 2015). The Food Safety Commission of Japan stated that the IARC report assessed whether there was a risk of cancer associated with consumption of red meat and processed meat without determining the level of risk due to intake or predicting the magnitude of the influence of red meat on human health (Food Safety Commission of Japan, 2015).

The 2015 World Health Organization/IARC report delineated the correlation of red meat and processed meat consumption with cancer incidence using a meta-analysis. Chan et al. (2011) examined 28 cohort studies concerning red meat and processed meat products in a meta-analysis. The results indicated that the daily intake of 100 g of red meat increased the risk of colorectal cancer by 17% and with an additional intake of 50 g of processed meat the risk was increased by 18%. The 28 articles included three cohort studies on individuals from the Asia-Pacific region. These three studies were separately analyzed, and the relative risk of red meat intake was 1.01 (95% confidence interval 0.69 to 1.48), which could be interpreted as indicating only a 1% increase in the risk of colorectal cancer with a daily consumption of 100 g of red meat; furthermore, the finding was not statistically significant.

The collective results highlight the limitations of applying the IARC report findings to the Korean population (Hur, Jo, Yoon, Jeong, & Lee, 2019). Most of the included studies were cohort studies involving individuals from Western countries. Data on individuals from the Asia-Pacific region are less robust and a correlation between dietary red/processed meat and colorectal cancer risk in this population has not yet been verified.

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A single specific factor, such as red meat consumption, should not be regarded as the main cause of the increase in colorectal cancer risk. Instead, the induction of colorectal cancer is more correlated with a myriad of complex factors that include age, genetic factors, dietary habits, environment, and lifestyle. The relative lack of cohort studies on individuals from Korea and Asia implies the implausibility of applying findings from Westerners to Asians.

A relatively higher incidence of colorectal cancer has been reported among Koreans than among people from Western countries, although the intake of red meat or processed meat products is less in Korea (Lee et al., 2017). The finding may have been influenced by other factors, such as high volume of alcohol consumption, rate of smoking, stress level, and salt consumption (Boada, Hernandez, & Luzardo, 2016; Hur et al., 2019). Therefore, an epidemiological study is needed to identify the correlation between such factors and the incidence of colorectal cancer, as are more objective and accurate data on the safety of red meat.

The present study was undertaken to identify the main cause of colorectal cancer and provide fundamental data for its prevention, by analyzing diverse factors influencing the pathogenesis of colorectal cancer with respect to the intake of red meat specifically and of food in general.

Dietary Red Meat and Colorectal Cancer Incidence

This study examined the correlation between dietary red meat and the pathogenesis of colorectal cancer by collecting and analyzing the latest academic data and systematic statistical data related to the safety of red meat consumption published since March 2016. As an intrinsic factor of carcinogenicity exhibited by dietary red meat, the excessive intake of heme iron should be considered. The mechanism for an increased risk of colorectal cancer due to the intake of heme iron in red meat remains unclear. However, two main causes have been suggested. One is the increased production of carcinogenic N-nitroso compounds (NOCs) due to heme iron overload. The second is DNA damage caused by the products of lipid peroxidation (Robbiano, Mereto, Corbu, & Brambilla, 1996). The iron content in red meat varies according to animal species. On a per gram basis, pork contains 1.2 mg iron (0.0012%), beef contains 3.2 mg (0.0032%), and lamb contains 2.0 mg (0.002%). Pork is the main raw material in the production of processed meat (Rural Development Administration – National Institute of Agricultural Sciences [RDA-NIAS], 2011). However, the iron content is markedly lower in pork than other red meat types. In addition, fish and shellfish, teas, and spices contain up to three to five times more iron than red meat (RDA-NIAS, 2011). Thus, the available evidence seems insufficient to claim that red meat, such as pork, is the main cause of colorectal cancer due to its iron content because food products other than red meat also contain considerable amounts of iron.

An extrinsic factor of the carcinogenic risk posed by dietary meat is the harmful substances that may be produced during cooking. These include heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs), NOCs, and acrylamide (AA) (Figure 1). HCAs have carcinogenic potential even at milligram levels. However, the amount of HCAs produced during meat cooking is in the order of nanograms (Bogen, 1994). Thus, we assume that the carcinogenic potential of HCAs produced while cooking red meat is relatively low. HCAs are also produced during the cooking of poultry meat and fish. PAHs may also be produced during the cooking of diverse food groups that include dairy products, fruits, vegetables, and cereals. The average daily intake of red meat by Korean individuals is 62 g (Korea Centers for Disease Control & Prevention, 2016). Hence, for Koreans, the amount of PAHs entering the body through red meat (4.52 μg/kg) is less than the average amount of PAHs the body is exposed by inhalation of air (2.7 μg/kg) (Menzie, Potocki, & Santodonato, 1992). Several studies (Chiavarini, Bertarelli, Minelli, & Fabiani, 2017; Cross & Sinha, 2004 ; Zheng & Lee, 2009) have reported that the intake of HCAs or PAHs is related to colorectal cancer. In contrast, Le et al. (2016) concluded that the intake of meat mutagens (HCAs) was not significantly associated with colorectal cancer risk over 14 years of follow-up in the Nurses' Health Study and the Health Professional follow-up study cohorts. As mentioned in this paper, we concur that due to the varied routes of HCA and PAH intake, further investigation of complex factors will be required instead of simply concluding that the intake of substances such as HCAs and PAHs is the only cause of colorectal cancer.

The analysis of academic papers and research data related to the harmful substances produced during the cooking of dietary meat has indicated that several cooking conditions and methods could reduce the production of harmful substances (Meurillon & Engel, 2016; Singh, Varshney, & Agarwal, 2016). These include:

1) Lowing the cooking temperature and minimizing the cooking time;
2) Microwave pretreatment to prevent prolonged cooking of meat;
3) Avoiding direct contact of meat with the heat source as well as avoiding smoking of meat during grilling;
4) Avoiding eating the gravy and residues on the pan produced during cooking;
5) Adding vinegar or natural seasoning-based marinades, spices, and antioxidants during cooking, and;
6) Removing the casing of smoked sausages prior to consumption.

The incidence of colorectal cancer in the Korean population was 45 per 100,000 individuals in 2012, which was the highest (Ferlay et al., 2013). However, Shin, Jung, Woo, and Jeong (2016) pointed out that the result was based on the data until 2009 that was estimated in 2012; when data from 2008 to 2012 were collected and reestimated, the colorectal cancer incidence in 2012 (per 100,000 individuals, age-standard incidence rates) was 37.3 in Korea, which was below that of Japan (38.4), the Netherlands (38.5), Australia (43.2), and New Zealand (43.5). The annual meat consumption in Korea in 2013 was 63.61 kg, which was one-half to two-thirds of the levels of most Western countries (Food and Agriculture Organization [FAO], 2016). Thus, it is difficult to claim a correlation between the incidence of colorectal cancer in Korea and the total intake of meat or red meat. Analyzing the statistical data regarding the intake of fruits and vegetables, alcohol consumption, smoking, the ratio of overweight and obese individuals, and life expectancy in addition to the red meat intake highlighted the difficulty in assigning a single specific factor as the cause of colorectal cancer. Surya et al. (2016) argued that the evidence supporting the intake of red meat and a diet rich in heme iron as increasing the incidence of colorectal cancer was based on the roles of red meat and dietary heme in positively selecting preneoplastic cells. Da Silva, Wernhoff, Dominguez-Barrera, and Dominguez-Valentin (2016) explained that a potential mechanism for the increase in carcinogenicity related to red meat intake may be the lectin-like activity of human anti-Neu5Gc antibody. However, Alisson-Silva, Kawanishi, and Varki (2016) reported that red meat intake cannot

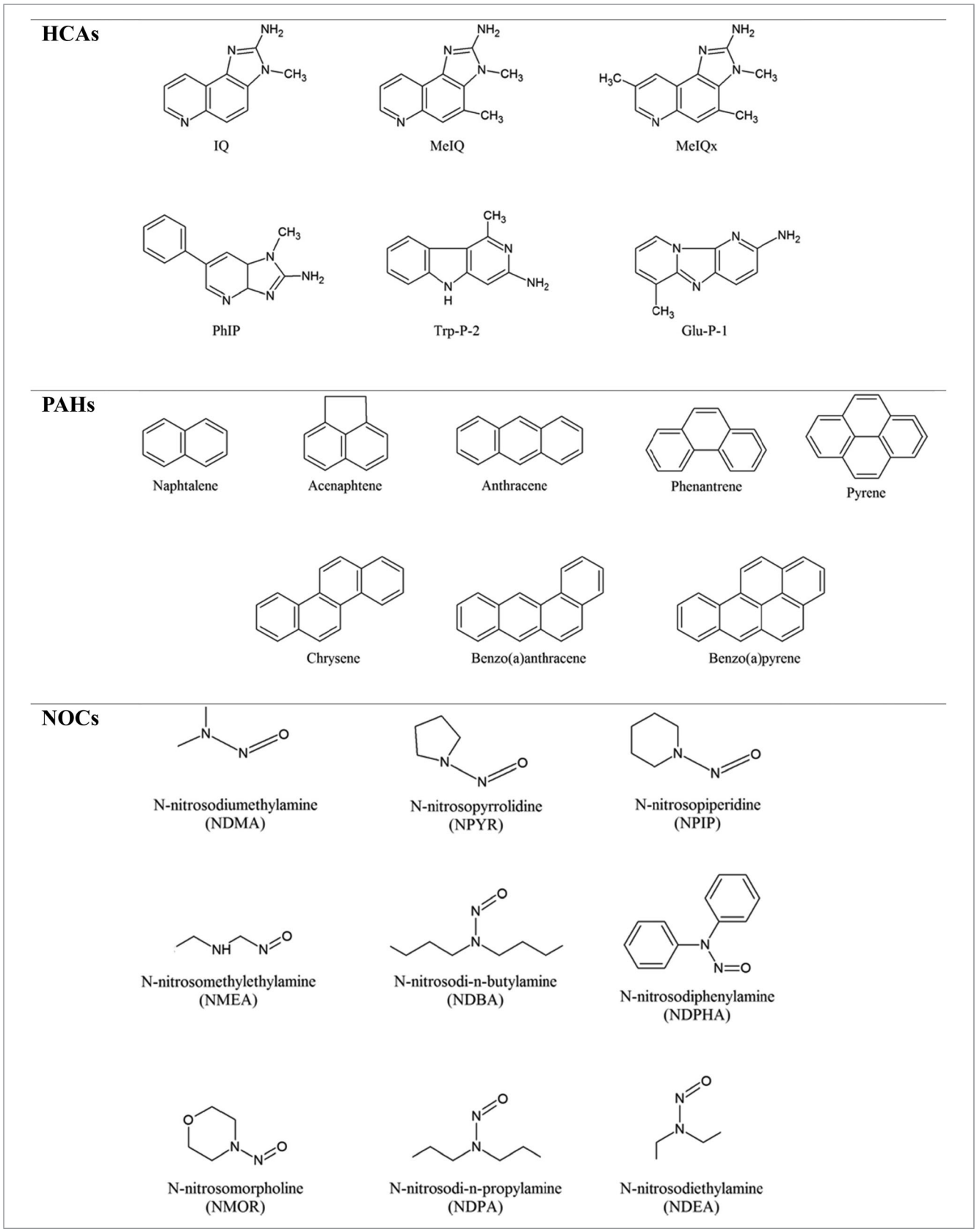

Figure 1–Chemical structures of some harmful substances produced during the preparation of red meat.

be singled out as the cause of any disease despite the various proposed mechanisms of the effects of red meat on diseases, which include saturated fats, high salt intake, microbial production of trimethylamine-N-oxide, and environmental contaminants of red meat. Demeyer, Mertens, De Smet, and Ulens (2016) reported that although carcinogenic PAHs and HCAs strongly influence colorectal cancer, the high intake of red meat in an unbalanced diet may promote several stages of colorectal cancer development. No mechanism has yet been identified that can perfectly explain the hypotheses relating colorectal cancer incidence to the intake of red meat and processed meat. Turney and Lloyd (2017) reported that, despite the central role of heme iron or HCAs in relating red meat intake to carcinogenicity, the amount of harmful substances considered in most studies substantially exceeded the amount found in human diet. The authors stated that there is insufficient evidence to prove the correlation between the risk of colorectal cancer and the intake of red meat, which is currently a part of a healthy diet pattern. The authors also pointed out that the experiments to date used overly excessive amounts of harmful substances compared to actual human intake and then correlated it to the incidence of cancer, and that the experimental designs of those previous studies were not suitable to investigate the carcinogenic potency in human red meat intake. Thus, experiments that are designed to consider the actual intake are needed.

Jun, Ha, Chung, and Joung (2016) analyzed the effects of the intake of meat and milk in Korea, where the diet is based mainly on rice. The authors reported that the correlation between cancer and the intake of meat and milk varied according to the cancer type and it was not a robust correlation in Korea and other Asian countries. Yang et al. (2016) carried out a prospective study on individuals who received a health checkup involving the colon at Seoul Natl. Univ. Hospital. The findings indicated a lack of a significant correlation between the intake of dietary fat and colorectal adenoma. The authors also reported the absence of a significant correlation between the prevalence of colorectal adenoma (benign tumor) and the total energy intake, intake of animal and vegetable fats, and total intake of animal and vegetable proteins. Bellavia, Stilling, and Wolk (2016) reported that the risk of cancer mortality was not correlated with red meat consumption between the low and high consumption groups. Ekmekcioglu et al. (2018) suggested that it would be advisable to reduce the intake of dietary meat because the current level of intake is too high, even though dietary meat has many nutritional benefits. Sobiecki, Appleby, Bradbury, and Key (2016) emphasized the need for the intake of foods with high nutritional values; while the high content of dietary fibers and beneficial fatty acids in a vegetarian diet may provide protection against cardiac disorders, it may bring about nutritional imbalance, especially in regard to vitamin B_{12}, zinc, selenium, and iodine.

Regarding the IARC report that stated, "The intake of processed meat and red meat increases the risk of colorectal cancer," Klurfeld (2016) argued that the data used by the IARC in deriving this conclusion were limited by the lack of evidence for a cause-effect relationship, and that the animal experiment did not provide supporting evidence for the epidemiological data. The authors further argued that the questionnaire on food intake frequency that was used to estimate the meat intake in the IARC study could not accurately measure the amount of protein consumed, and that the valid data were insufficient to categorize red meat or processed meat as carcinogenic. Demeyer et al. (2016) mentioned the uncertainty regarding the factors involved in the incidence of colorectal cancer and suggested the need to identify a new mechanism or revise the conventional theory that does not clearly explain the relationship between the intake of processed meat and red meat and the risk of colorectal cancer. Vineis and Stewart (2016) pointed out that the report on obesity and the intake of processed meat being a cause of cancer in humans has created unease, and that cancer is influenced by various causes and just being obese or eating red meat does not indicate a high risk of cancer. The authors also reported that the incidence of colorectal cancer for individuals who frequently ate red meat was 5%, whereas the rate for individuals with an average intake was 6%. Furthermore, they explained that although an additional daily intake of 50 g of processed meat increases the incidence of colorectal cancer by approximately 18%, the absolute increase they observed was low.

The general public and media should also accurately recognize the difference between "degree of evidence" and "strength of the risk increase." The IARC report could better have distinguished between the terms "carcinogen" and "cause of cancer." The findings from the many studies conducted so far have not clearly elucidated the correlation between red meat and colorectal cancer, and have generated considerable controversy. The global prevalence of aged people is increasing, reflecting advancements in medical and pharmacological therapies, as well as the enhanced quality of life. Among all lifestyle factors, good nutritional status is a crucial element in maintaining good health. While dietary red meat and its processed products are indispensable for nutrient intake, the scientific evidence for their health value remains debatable. Ultimately, it is advisable to view this as a problem related to the amount and mode of intake.

Despite lower meat consumption (63.61 kg per capita in 2013), Korea has an incidence of colorectal cancer comparable to that in Denmark and the Netherlands. In addition, when compared to Australia and New Zealand, the meat consumption ratio of Korea was 54.7% and 62.7%, respectively (FAO, 2016). Thus, total and red meat (beef and pork) consumption in Korea and the incidence of colorectal cancer are thought to be unrelated. Moreover, recent data showed that the Korean annual vegetable consumption of 172.38 kg per capita was notably higher than that of the other countries studied (FAO, 2016). In 2014, the average alcohol consumption among Koreans over the age of 15 years was 9.0 L, similar to that in Denmark and the Netherlands and the average number of cigarettes smoked was 14.7 per day, similar to the trends in most other countries included in the investigation (OECD, 2015). Furthermore, the ratio of overweight and obese to normal BMI individuals was lower in Korea than in Western countries (OECD Health Statistics, 2016).

Altogether, compared to other countries with a high incidence of colorectal cancer, meat consumption in Korea is relatively low, fish and vegetable consumption is higher, and the ratio of overweight and obese to normal BMI individuals is low. Thus, the claim that red meat consumption triggers physiological, and carcinogenic changes driving the pathogenesis of colorectal cancer is questionable. Although iron overload may induce oxidative stress, the iron content of pork is as low as that of poultry meat and fish. Moreover, the diverse bioactive substances in vegetables, which are highly consumed in Korea, may suppress the lipid peroxidation mediated by iron. Hence, a diet rich in vegetables would likely contribute to the prevention of cancer. In addition, although cooking meat produces various harmful substances, making consumers uneasy, the levels of these substances are in the order of nanograms, which is extremely low. Moreover, they can be reduced further using several methods. It is noteworthy that cooking foods other than meat also produces harmful substances. Since

cancer development is influenced by multiple factors, red meat consumption alone should not be directly correlated with cancer (Vineis & Stewart, 2016).

Meat mutagens, including HCAs, PAHs, and NOCs, may be involved in colorectal carcinogenesis, depending on their activation or detoxification by phase I and II xenobiotic metabolizing enzymes (XME) in the liver and the colon (Gilsing et al., 2012; Wang et al., 2012). Single nucleotide polymorphisms (SNPs) in the genes encoding these XMEs may modify the ability to activate or detoxify carcinogens (Gilsing et al., 2012). These enzymes vary in their metabolic activity across the human population; hence, it is biologically plausible that the inheritance of specific allelic variants of metabolizing genes may influence colorectal cancer risk (Wang et al., 2012).

Iron Intake and Incidence of Colorectal Cancer

A trace amount of iron is found in the human body; nevertheless, it is a mineral that is absolutely essential for metabolic activities in humans and a component of hemoglobin that supplies oxygen throughout the body. Iron also enables cellular proliferation and growth, while it participates directly in the redox cycle. Thus, it can be regarded as an essential mineral for cell survival (Torti & Torti, 2013). On the other hand, a state of iron overload may cause dysfunction in iron metabolism, where Fe^{2+} ions in the cytoplasm facilitate the production of reactive oxygen species that induce oxidative stress and cytotoxicity that may lead to increased risk of cancer. The highly reactive bivalent free iron would undergo the Fenton reaction with hydrogen peroxide to produce hydroxyl radicals that have markedly more acute toxicity. This inflicts DNA damage and lipid peroxidation (Huang, 2003). Thus, it is important to understand the iron content in food as the main source of iron and the physiological activities of iron. Heme produces the apparent total NOCs endogenously in the gastrointestinal tract and facilitates lipid peroxidation. Consequently, heme has been predicted to be a factor that may increase the risk of colorectal cancer (Bastide, Pierre, & Corpet, 2011; Czerwonka & Tokarz, 2017). Meanwhile, calcium salts and chlorophyll, vitamin C, and various polyphenols (Mirvish, 1986; Ross & Kasum, 2002), as well as appropriate packaging and storage of food products, have been reported as factors that suppress the harmful effects of heme (Santarelli, Pierre, & Corpet, 2008). Oxidative stress has a potential influence on the correlation between the incidence of colorectal cancer and the intake of red meat and processed meat, and the iron found in dietary meat is considered the main cause of oxidative stress (Toyokuni, 1996).

Iron is found in various foods where it exists as either heme or nonheme iron. Heme iron is the form where the iron atom is bound to the heme. It is abundant in animal food products. Since heme iron has higher bioavailability than nonheme iron, animal food products are regarded as an essential iron source. Vegetable food products that mainly contain nonheme iron are another important iron source (HealthLinkBC, 2017).

In advanced countries, red meat is the most abundant source of dietary iron, and the iron content varies according to meat type and portion. Pork contains approximately 0.5 to 1.2 mg/100 g of iron, and beef contains approximately 1.4 to 2.9 mg/100 g of iron (U.S. Dept. of Agriculture [USDA], 2015). The largest proportion of total iron content (40% to 90%) in red meat comprises heme iron (Czerwonka & Tokarz, 2017). In dietary meat, heme iron comprises 70% of the total iron content, and beef has higher iron content than pork (USDA, 2015). The iron content in dietary meat may be altered based on the cooking method. Since the iron in dietary meat is enclosed by a protein structure upon heating, the iron content in heated foods is enhanced and increases by approximately 10% to 40% (Czerwonka & Tokarz, 2017; USDA, 2015). While red meat is an excellent source of dietary iron, other foods like fish, cereals, beans, eggs, and dark green vegetables also supply ample amounts of iron (European Food Safety Authority, 2015; Tapiero, Gaté, & Tew, 2001). The ratio of heme iron to total iron intake is 10% to 15% in advanced countries, which is a far lower level compared to that of nonheme iron. The iron intake through food products other than dietary meat is also quite high because approximately 50% of the absorbed iron originates from porphyrin (Hunt, 2003; Jiang et al., 2004).

Potential Harmful Substances Produced During Cooking and Processing

The harmful substances that may be produced during the cooking of dietary meat widely include HCAs, PAHs, NOCs, and AA.

HCAs

HCAs are potential mutagenic compounds produced during the cooking of foods. They are largely produced from proteinaceous foods, such as meat and fish, cooked at temperatures of 150 to 300 °C. HCAs are mainly classified into 2-amino-3-methylimidazo[4,5-f]quinoline (IQ)-type HCAs or aminoimidazoazaarenes and non-IQ-type HCAs or aminocarbolines. IQ-type HCAs are formed by the heat generated by the Maillard reaction involving creatine (or creatinine), amino acids, and sugars (Gibis, 2016). The reaction proceeds when foods are cooked at temperatures of 150 to 300 °C. Non-IQ-type HCAs are usually formed by the pyrolysis of amino acids and proteins at high temperatures above 300 °C (Gibis, 2016).

PAHs

PAHs include more than 250 known species. Among them, 15 exhibit mutagenic and carcinogenic potency. The EU Scientific Committee on Food has defined 15 species of PAHs, with benzo[α]pyrene (BaP) being the best known. Since 2002, BaP has been used as an indicator of carcinogenic PAHs found in foods (European Commission Scientific Committee on Foods, 2002). PAHs generated during cooking tend to be distributed on the food surface. They may occur naturally on fruits and vegetables as airborne particles can fall onto their surfaces. Compared to fresh vegetables, grilled vegetables contain a higher level of carcinogenic PAHs. PAHs are also detected in fish, meat, dairy products, and vegetable fats and oils. The use of cooking methods, such as grilling, roasting, and frying, as well as processing methods like smoking and drying is the major contributor to PAHs produced from foods, which are affected by the fat content in meat and cooking conditions, such as cooking time and heating temperature.

NOCs

NOCs consist of nitrosamine [$R_1N(NO)R_2$] and nitrosamide [$R_1N(NO)COR_2$]. Nitrosamines include dialkylnitrosamines like N-nitrosodimethylamine (NDMA), and cyclic nitrosamines like N-nitrosopyrrolidine. Nitrosamine is carcinogenic when activated by a cytochrome P450 isozyme that catalyzes the insertion of a hydroxyl group to the carbon atom closest to the N-nitroso (NNO) group. The hydroxyl alkyl group in this product splits by hydrolysis, and the resulting alkyldiazonium cation mediates the alkylation of DNA bases to cause mutagenesis and ultimately cancer. Such

substances are formed when reactions occur among the factors that cause nitrification (nitrate, nitrite, and nitrogen compounds) that are added to foods in the form of preservatives; primary, secondary, and tertiary amines; amides; proteins; peptides; and amino acids during the processing and preservation processes. NOCs generally accumulate in foods that have been stored long term at ambient temperature or in fermented foods (Mirvish, 1986). Since heme produces the total NOCs in the gastrointestinal tract, it could contribute to increased risk of colorectal cancer. As shown in Table 11, the concentration of NOCs in cooked beef, pork, and fish ranged between 1.8 and 5.0 μg/g, and comparisons between cooking methods showed the highest concentration with the firewood-grill method. Park, Seo, Lee, and Kwon (2015) reported that NDMA concentrations in processed meats, such as sausages, hams, and bacons, ranged from 0.31 to 1.54 μg/kg, lower than the concentration found in vegetables and fruits.

Production of Harmful Substances Based on Cooking Conditions

The amount of harmful substances produced during meat cooking can vary according to cooking conditions such as cooking temperature, cooking time, and cooking methods.

Cooking temperature and time

With increasing temperature and time of cooking, the quantity of harmful substances produced from meat increases. Liao, Xu, and Zhou (2009) described that HCAs were not detected in uncooked pork, but were formed when pork was stir-fried using strong heat and a small amount of oil, with the formation of HCAs increasing as the cooking temperature increased. Others reported that although HCAs were not detected or detected in only a very small quantity in meat grilled at 150 °C, the formation of HCAs increased as the cooking temperature was raised to 175, 200, and 225 °C (Skog, Steineck, Augustsson, & Jägerstad, 1995). When pork chop, pork belly, bacon, minute steak, and ground beef were cooked at 150, 175, 200, and 225 °C, respectively, the amount of HCAs produced from each meat sample increased with increasing temperature (Table 1). A particularly steep increase in HCAs occurred upon grilling the meat at a high temperature of 225 °C. Although no HCAs (MeIOx, DiMeIOx, and PhIP) were detected when the pork chop and pork belly were heated to 150 °C, PhIP levels of the pork chop and pork belly increased to 4.8 and 12.4 ng/g, respectively, when heated to 225 °C. Similarly, when bacon was heated to 225 °C, MeIQx levels increased from 0 to 23.7 ng/g (Skog et al., 1995).

Gibis (2016) analyzed the amount of HCAs produced from bacon slices that were pan-fried for 3, 4, 5, and 6 min at 150 to 170 °C, and for 2 and 3 min at 200 to 220 °C. The higher the temperature and longer the cooking time, the higher was the production of HCAs. Aygun and Kabadayi (2005) investigated the production of BaP from red meat by cooking beef and lamb using direct heat at high temperature for 6 min (grilled) and 8 to 9 min (overgrilled). Compared to the 6-min grilled meat, the 8 to 9-min overgrilled beef and lamb displayed higher production of BaP (Table 2).

Cooking method

The use of different cooking methods can also change the amount of harmful substances produced from meat. In one study, when beef was cooked using three different methods (sous-vide, boiling, and pan-frying) to compare the total production of HCAs, the respective production of total HCAs was 0.036 to 0.123, 0.032, and 0.252 to 0.940 ng/g, respectively. There was a significant increase with pan-frying (Oz & Zikirow, 2015). The results of measurements of HCAs when pork patties were cooked at different temperatures and methods (Table 3) revealed that boiling produced the lowest total HCAs (Puangsombat, Gadgil, Houser, Hunt, & Smith, 2012; Shin, 2005).

Most mutagenic substances were produced upon the cooking of red meat using heat at temperatures ranging from 120 to 230 °C. High-temperature cooking methods include grilling, roasting, and frying. On the contrary, the methods for cooking stew or soup, where the meat is immersed in water, involve heating temperatures between 98 and 120 °C; dietary carcinogens are rarely formed using these methods (Tareke, Rydberg, Karlsson, Eriksson, & Tornqvist, 2002). The amount of harmful substances produced during cooking can also differ according to the cooking utensil, the "doneness" of the meat (that is, raw, medium raw, medium, and well-done), direct or indirect contact with the heat source, and the type of heat source. Oz and Yuzer (2016) compared the production of HCAs and PAHs from beef steaks grilled on iron or stone plates. They reported that the beef grilled on an iron plate produced more HCAs and less PAHs and that the HCAs generated also depended on the thickness of meat and its distance from the fire. The authors also made comparisons based on the type of heat source and reported that when charcoal and wood chips were used together for meat barbecue, the production of HCAs tended to be higher. Grilling pork and beef at high temperatures and in direct contact with the heat source led to the formation of four types of PAHs—benzo[a]anthracene (B[a]A), chrysene (Chr), benzop[b]fluoranthene (B[b]F), and BaP—which could be reduced by removing the gravy that fell from the pan and the smoke produced during cooking. By removing the fat from pork and beef produced during cooking, the four types of PAHs were reduced by 48% to 49%. By removing the smoke produced during cooking, they were reduced by 41% to 74%. These findings indicated that the smoke arising from the incomplete combustion upon the meat fat falling onto the heat source during cooking might be a very influential factor in the production of PAHs (Lee et al., 2016).

For the grilling of pork belly using charcoal, refined charcoal, ultraviolet, electric grill, and grill pan for direct heating, BaP formation was the greatest using charcoal (Table 4). BaP was formed when the cooking involved the use of a direct heat source. Use of indirect heat source did not lead to detectable formation of BaP, irrespective of the cooking time or the addition of other substances (Park, Pyo, Kim, & Yoon, 2017). Thus, the greatest hazards of BaP production are likely direct contact between the meat and the heat source, and meat fat falling onto the heat source (Park et al., 2017).

Addition of other substances

The amount of harmful substances produced during cooking could be influenced by the addition of various other substances.

Addition of vitamins. When the content of HCAs was measured after the cooking of beef meat patties at 200 °C for 3 min, preceded by the addition of water-soluble vitamins, the total production of HCAs decreased. Among the 12 types of water-soluble vitamins, the addition of pyridoxamine, pyridoxine, nicotinic acid, biotin, thiamine, and L-ascorbic acid reduced the formation of HCAs, and the addition of pyridoxamine resulted in the most effective reduction (Table 5) (Wong, Cheng, & Wang, 2012).

Similarly, an inhibitory effect on mutagenesis was observed in a study that measured the rate of inhibition on mutagenesis in the manufacture of pork sausages, following the addition of L-ascorbic

Table 1–Production of heterocyclic amines according to meat type and cooking temperature and time.

Samples	Cooking temperature (°C)	Cooking time (min)	MeIQx (ng/g)	DiMeIQx (ng/g)	PhIP (ng/g)
Pork chop	150	6 + 3.5	ND*	ND	ND
	175	6 + 5	0.2	0.04	0.02
	200	6 + 3	0.2	0.05	0.02
	225	6 + 2	2.6	1.1	4.8
Pork belly	150	2 + 2	ND	ND	0.0
	175	2 + 2	ND	ND	0.7
	200	2 + 2	0.4	ND	0.3
	225	4 + 4	2.9	0.7	12.4
Bacon	150	2 + 2	ND	0.2	0.3
	175	2 + 2	0.1	0.2	0.2
	200	2 + 2	0.7	0.3	0.6
	225	4 + 4	23.7	1.4	4.5
Minute steak	150	1.5 + 1	ND	ND	0.02
	175	1.5 + 1	0.2	0.06	0.03
	200	1.5 + 1	0.6	0.1	0.3
	225	2 + 2	6.2	2.7	12.7

Notes: Modified from the original study (Skog et al., 1995). MeIQx: 2-amino-3,8-dimethylimidazo [4,5-*f*]quinoxaline; DiMeIQx: 2-amino-3,4,8-trimethyl-imidazo [4,5-*f*]quinoxaline; PhIP: 2-amino-1-methyl-6-phenylimidazo [4,5-*b*]pyridine.

Table 2–Production of benzopyrene from grilled meat according to cooking time.

Beef		Lamb	
Grilled (6 min)	Overgrilled (8 to 9 min)	Grilled (6 min)	Overgrilled (8 to 9 min)
31.33 ± 0.94	37.60 ± 3.84	43.80 ± 1.80	62.60 ± 3.72

Notes: Modified from the original study (Aygun & Kabadayi, 2005). Results are presented as μg/kg ± relative standard deviation.

Table 3–Production of HCAs from pork patty according to the cooking method, temperature, time, and core temperature.

Cooking method	Cooking temperature (°C)	Cooking time (min)	Core temperature (°C)	MeIQx (ng/g)	DiMeIQx (ng/g)	PhIP (ng/g)	Total HCAs (ng/g)
Boiling	100	8	71	0.4 ± 0.1	ND	ND	0.4
	100	10	77	0.8 ± 0.2	ND	ND	0.8
	100	16	88	1.0 ± 0.2	ND	ND	1.0
Broiling	177	12	71	1.2 ± 0.3	0.3 ± 0.2	ND	1.5
	177	12	77	1.4 ± 0.6	0.5 ± 0.3	ND	1.9
	225	19	88	1.6 ± 0.5	0.7 ± 0.4	2.7 ± 0.4	5.0
Pan-frying	177	9	71	0.6 ± 0.2	0.3 ± 0.1	0.3 ± 0.1	1.2
	177	11	77	0.9 ± 0.3	0.4 ± 0.1	0.5 ± 2.0	1.8
	225	21	88	5.0 ± 0.8	1.7 ± 0.7	10.5 ± 0.8	17.2

Notes: Modified from the original study (Shin, 2005).
ND, not detected.

Table 4–Production of benzopyrene from grilled pork bellies according to the cooking method and utensil.

Cooking method	Cooking utensil	Production of benzopyrene (μg/kg)
Direct heat source	Charcoal	8.04 ± 0.03
	Refined charcoal	1.28 ± 0.03
	Ultraviolet	ND
Indirect heat source	Electric grill	ND
	Grill pan	ND

Notes: Modified from the original study (Park et al., 2017).
ND, not detected.

Table 5–Production of HCAs from grilled beef patty according to the addition of vitamins (0.2 mmol).

	HCAs (ng/g beef meat patty; mean ± standard deviation) and level of reduction (%)			
Treatment	PhIP	4,8-diMeIQx	MeIQx	Total HCAs
Control	7.44 ± 1.12	2.46 ± 0.32	7.39 ± 0.84	17.3
Ascorbic acid	6.02 ± 0.13 (19)	2.12 ± 0.04 (14)	6.13 ± 0.25 (17)	14.3 (17)
Niacin	6.03 ± 0.27 (19)	2.09 ± 0.09 (15)	5.99 ± 0.20 (19)	14.1 (18)
Pyridoxamine	4.24 ± 0.45 (43)	1.53 ± 0.16 (38)	4.29 ± 0.49 (42)	10.0 (42)

Notes: Modified from the original study (Wong et al., 2012).

acid and α-tocopherol (Pourazrang, Moazzami, & Fazly Bazzaz, 2002).

Addition of spices. The amount of harmful substances produced during cooking can be changed according to the spices that are added. The addition of pepper corn powder during the frying of high-fat meat balls reduced the total HCAs (Table 6). Meat balls cooked without the addition of pepper corn powder produced 1.40 ng/g HCAs at the cooking temperature of 175 °C, which was reduced to 0.93 ng/g when cooking involved pepper corn powder. When the cooking temperature was 200 °C, the total HCAs decreased from 5.70 to 5.03 ng/g, and at 225 °C, the total HCAs were reduced from 37.81 ng/g to an undetectable level, indicating that the addition of pepper corn powder reduced the total production of HCAs (Oz & Kaya, 2011). Oz and Kaya

Table 6–Production of HCAs from meat, pan residue, and gravy according to cooking method and meat type.

Food product	8-MeIQx (ng/g)	4,8-DiMeIQx (ng/g)	PhIP (ng/g)	Reference
Beef burger meat	0.03 to 2.8	ND to 0.7	ND to 1.5	Johansson, Fredholm, Bjerne, and Jagerstad (1995)
Pan residue	0.6 to 5.3	ND to 1.8	ND to 13.3	Johansson et al. (1995)
Roasted beef	ND	ND	ND	Sinha et al. (1998)
Gravy	7.1	1.1	4.1	
Pork fillet meat	ND to 4.6	ND to 3.3	ND to 13.4	Skog et al. (1995)
Pan residue	0.6 to 5.6	0.08 to 4.2	0.3 to 32.0	
Pork meat	ND to 2.9	ND to 1.1	ND to 12.4	Skog, Augustsson, Steineck, Stenberg, and Jägerstad (1997)
Pan residue	ND to 1.9	ND to 0.5	0.02 to 4.0	

Notes: Modified from the original study (Janoszka et al., 2009).
ND, not detected.

(2011) described the reduced formation of HCAs by the addition of chili as well as pepper corn powder when beef was pan-fried at 175, 200, and 225 °C. Pan-frying the beef at 225 °C resulted in the detection of 2.63 ng/g HCAs, which decreased to 0.64 ng/g when the meat was pan-fried with added chili. Total HCAs were reduced by 75% to 100% based on the addition of chili during cooking (Oz & Kaya, 2011). Studies have reported that the use of spices, including turmeric, lemongrass, torch ginger, and curry leaves, in the roasting of beef meat was associated with a reduced content of harmful HCAs. For medium roasted beef (70 °C), seasoning the meat with 4 g/100 g turmeric could reduce the produced IQ by as much as 82 ng/100 g. In addition, seasoning the meat with 10 g/100 g lemongrass reduced the IQ by 44.4 ng/100 g, seasoning with 10 g/100 g torch ginger reduced the MeIQX by 83 ng/100 g, and seasoning with 10 g/100 g of curry leaves reduced the IQ by 78.50 ng/100 g (Jinap, Iqbal, & Selvam, 2015).

Addition of other foods. Janoszka (2010) reported that when pan roasting pork neck, pork chop, and ground pork, the addition of onion and garlic led to the reduced production of aminoazaarenes (HCAs) and azaarenes (aza-PAHs). Adding 30 g onion to 100 g pork meat reduced the production of HCAs by 31% to 49%, while the production of aza-PAHs was reduced by 21% to 48%. Similarly, adding 15 g garlic to 100 g pork meat reduced the production of HCAs by 26% to 36% and aza-PAHs by 33% to 40%. For roasting pork belly, the use of tea marinades enhanced the antioxidant activity and prevented lipid oxidation, depending on the concentration of tea and the time of marination (Park et al., 2017). Among the tea marinades, yerba mate tea was more effective than green tea in preventing the formation of BaP during cooking. The optimal concentration of tea marinade for preventing the formation of BaP was 0.5%, and 8-hr marination had the strongest effect (Park et al., 2017). Consistent with this, green tea marinade significantly reduced the HCA compounds PhIP and 2-amino-9H-pyrido[2,3-b]indole (AαC) upon the pan roasting of beef at 180 to 200 °C for 4 min. The longer the marination time, the more significant reduction was shown in the concentration of HCAs when marinated meat was roasted (Quelhas et al., 2010). The production of PAHs was reduced when beef meat was roasted after marination compared to that without marination. Among the various marinades, use of an acidic marinade containing 1.2% lemon juice significantly reduced the production of PAHs by approximately 70% (Farhadian, Jinap, Hanifah, & Zaidul, 2011).

Addition of other substances. When low-molecular-weight chitosan and medium-molecular-weight chitosan were spread on the cut surface of beef chop before cooking at 150, 200, and 250 °C, total HCAs were reduced by 14.3% to 100%, which reflected the increased moisture content in meat mediated by chitosan (Oz & Cakmak, 2016). When conjugated linoleic acid (CLA) was added to beef meat balls before grilling at 150, 200, or 250 °C, the total HCAs varied. Addition of 0.25% CLA and grilling at 150 °C led to the detection of the lowest level of total HCAs (Oz & Cakmak, 2016). The addition of an antioxidant, such as the antioxidant of bamboo leaves, liquorice extract, green tea polyphenol, phytic acid, and sodium ascorbate, was effective in suppressing the production of HCAs (Table 6) (Janoszka, Blaszczyk, Damasiewicz-Bodzek, & Sajewicz, 2009; Zhang, Yu, Mei, & Wang, 2013).

Other cooking conditions. Heating marinated ground pork meat in a covered pan to 98 °C led to the detection of a higher level of HCAs in the gravy remaining on the pan than from the cooked meat itself (Lan, Kao, & Chen, 2004). This agreed with the report by Lan and Chen (2002), in which a higher level of HCAs was detected from the gravy produced from cooking than from the meat itself. In addition, the amount of harmful substances produced from meat differed according to reheating of the cooked meat, storage method, and various processing conditions upon the manufacture of processed meat products. Reheating of cooked meat or storage at a warm temperature did not affect the formation of mutagenic sources (Choe et al., 2018). Roasting the meat at 200 °C was associated with the greatest formation of mutagenic compounds during the first 6 min of cooking, and cooking for an additional 25 min did not lead to the formation of a new mutagenic source. Reheating the roasted pork patty to a core temperature of 70 °C or storing the meat at 60 °C for up to 9 hr did not significantly influence mutagenic activity (Berg, Overvik, & Gustafsson, 1990). Upon the processing of dry-fermented sausages, collagen casing reduced the production of total PAHs by approximately three times more than did hog casing, regardless of the fat content or the method of smoking. Although the casing accounts for only 1% to 2% of the total mass of a sausage, it accounts for 5% to 21% of the total PAHs, suggesting that a relatively high level of PAHs is formed on the casing. Thus, the casing of sausages should be removed before eating (Gomes, Santos, Almeida, Elias, & Roseiro, 2013). The amount of HCAs formed during the grilling of mature beef sirloin can increase with increasing maturation time (Polak, Dosler, Zlender, & Gasperlin, 2009).

Formation of Harmful Substances in Food Products, Except Red Meat

Heterocyclic HCAs

Iwasaki et al. (2010) described the rapid increase in the levels of HCAs, including PhIP, MeIQx, and 4,8-DiMeIQx, upon cooking red meat and fish until they were fully cooked. Pan-fried chicken meat, beef, pork, sardine, and salmon all produced PhIP, with production being higher in chicken meat, a type of white meat, than in red meat, such as beef meat and pork meat (Table 7). Pan- and grill-roasted chicken showed 34.6 and 27.4 ng/g HCAs (PhIP), while pan- and grill-roasted beef showed 0.58 and 16.3 ng/g PhIP, respectively. In comparison, pan-roasted pork, sardine, and salmon showed PhIP concentrations of 7.25, 2.28, and

Table 7–Production of PhIP (ng/g) according to food type and cooking method.

Cooking method	Food type				
	Chicken meat (including the skin)	Beef meat	Pork meat	Sardine	Salmon (including the skin)
Pan-roasted	34.6	0.58	7.25	2.28	7.37
Grill-roasted	27.4	16.3	ND	–	–

Notes: Modified from its original study (Iwasaki et al., 2010).
ND, not detected

Table 8–Production of PAHs from various food groups.

Food group	Representative food	Detection range of total PAHs (μg/kg)
Dairy products	Milk	5.4 to 147.2
	Cheese	0.2 to 1,643.18
	Powdered milk	11.8 to 78.4
	Yogurt	7.12 to 12.8
	Others (butter, vegetable cream, margarine, mayonnaise, and so on)	1.7 to 21.7
Fruits and vegetables	Cooked	1.097 to 335.7
Cereal grains	Cooked	0.57 to 880
Egg or meat-based food products	Egg	49.6 to 496.26
	Chicken meat	1.1 to 31.74
	Pork meat	0.15 to 34.65
	Fish	1.59 to 1,068.8
	Others (crab meat, sea food, beef sausage, and so on)	0.22 to 2,618.4
Sugar products	Sugar	0.07 to 4.03
	Salt	0.33 to 7.02
	Others (honey, chocolate, cocoa butter, and so on)	0.17 to 235.91
Beverages	Tea and coffee	3.8 to 3,091.1
	Alcoholic beverage	0.2 to 172.3
	Sugarcane-based beverage	0.013 to 51.57
Oils	Vegetable oil	0.548 to 234.30
	Fish oil	9.5 to 35
Nuts	Dried and processed	0.94 to 4.57

Notes: Modified from the original study (Singh et al., 2016).

Table 9–Production of PAHs during the cooking of vegetables and fish.

PAHs	Vegetables (mean) (μg/kg)	Grilled vegetables (mean) (μg/kg)	Fish (nonsmoked) (μg/kg)	Fish (smoked) (μg/kg)
Acenaphthene	0.10	1.4	–	–
Anthracene	0.11	0.1	–	–
Benz[a]anthracene	0.05	0.2	TR to 0.09	ND to 86
Benzo[k]fluoranthene	0.02	0.1	–	–
Benzo[ghi]perylene	–	–	TR to 0.39	ND to 25
Benzo[a]pyrene	0.09	0.3	TR to 0.35	ND to 18
Dibenz[a,h]anthracene	ND	ND	–	–
Fluoranthene	1.26	1.1	–	–
Fluorene	ND	ND	–	–
Indeno[1,2,3-cd]pyrene	–	–	ND to 0.33	ND to 37
Phenanthrene	2.22	4.5	–	–
Pyrene	0.28	1.0	–	–

Modified from the original study (Tamakawa, 2008).
TR, trace; ND, not detected.

7.37 ng/g, respectively, whereas PhIP was undetected in grill-roasted pork, sardine, and salmon (Table 7).

Puangsombat et al. (2012) analyzed the content of HCAs produced from fish upon frying or grilling. Formation of larger amounts of HCAs was observed upon frying. Similar results were obtained for pork and fish. When the intake of harmful substances produced from barbecued meat product was calculated based on 100 g consumption of grilled meat, beef, and salmon contained similar amounts of non-IQ-type HCAs, while chicken meat contained twice the amount (Viegas, Novo, Pinto, Pinho, & Ferreira, 2012). Markedly higher levels of IQ-type HCAs were observed in salmon and chicken meat, but beef contained low levels. Salmon displayed the highest amount of PAHs, with markedly lower levels of PAHs formed from beef (Viegas et al., 2012).

PAHs

Singh et al. (2016) described that PAHs are present in most food groups, including dairy products, fruits and vegetables, cereal grains, fish, sea food, sugar products, beverages, fats and oils, and nuts (Table 8). Among them, comparatively higher amounts of PAHs were detected from a type of coffee called Dark Sumatra (3091.1 μg/kg) and, among sea foods, crab meat (2618.4 μg/kg) (Table 8).

As the formation of PAHs in red meat is influenced by cooking time, temperature, and method, the amount of PAHs produced during coffee roasting can also vary according to the roasting conditions that include time, roasted state, and the tools used in roasting (Jimenez, Adisa, Woodham, & Saleh, 2014; Mostafa, 2002; Vieira et al., 2010). In a study conducted in the United Kingdom, the food products exhibiting the strongest influence on the content of dietary PAHs were cereal grains, fats, and oils, rather than meats, with each accounting for approximately one-third of the total level of exposure to PAHs per individual (Phillips, 1999). Fruits, vegetables, and sugars also occupied a large proportion, whereas meat, fish, milk, and beverages had only a marginal influence on the PAHs. In a study conducted in Germany,

Table 10–Production of PAHs from various food products according to cooking method.

Food product	Cooking method	Benzopyrene (μg/kg)	Carcinogenic PAH (μg/kg)	Total PAHs (μg/kg)
Calf meat	Unprocessed	0.04	0.11	8.34
	Fried	0.04	0.17	24.83
	Grilled	0.04	0.13	12.07
Pork loin	Unprocessed	0.04	0.12	4.47
	Fried	0.04	0.15	21.45
	Grilled	0.04	0.18	7.87
Lamb meat	Unprocessed	0.04	0.12	5.47
	Fried	0.04	0.17	16.91
	Grilled	0.04	0.12	8.03
Chicken meat	Unprocessed	0.04	0.19	4.51
	Fried	0.04	0.18	14.96
	Grilled	0.04	0.16	6.25
	Roasted	0.04	0.20	27.93
Tuna fish	Unprocessed	0.04	0.13	15.56
	Fried	0.04	0.14	29.51
	Grilled	0.04	0.13	16.41
Olive oil	Unprocessed	0.15	1.25	100.74
	Heated 1	0.15	0.93	90.25
	Heated 2	0.14	0.81	48.56
Rice	Unprocessed	0.04	0.12	2.19
	Boiled	0.04	0.13	5.22

Notes: Modified from the original study (Perello et al., 2009).

Table 11–Production of N-nitroso compounds from various cooked and uncooked food products, and according to the cooking method.

	N-nitroso content (μg/g) × 10^{-3}			
Sample	Raw meat	Oven-grilled	Firewood-grilled	Charcoal-grilled
Beef	2.0 ± 0.01	3.0 ± 0.01	3.9 ± 0.02	3.7 ± 0.02
Pork	3.1 ± 0.02	3.4 ± 0.02	5.0 ± 0.01	4.3 ± 0.01
Wild animal meat	1.8 ± 0.03	2.3 ± 0.01	2.0 ± 0.01	2.9 ± 0.01
Fish	2.8 ± 0.01	3.7 ± 0.03	4.7 ± 0.03	4.1 ± 0.01
White yam	2.8 ± 0.03	2.8 ± 0.01	3.5 ± 0.02	3.3 ± 0.01
Peanut	1.1 ± 0.01	1.2 ± 0.01	2.0 ± 0.01	1.9 ± 0.03
Cocoyam	1.2 ± 0.03	1.4 ± 0.01	2.9 ± 0.01	2.4 ± 0.01
Corn (yellow)	1.3 ± 0.01	1.7 ± 0.02	2.8 ± 0.02	2.7 ± 0.01
Corn (white)	0.2 ± 0.02	1.1 ± 0.01	1.9 ± 0.01	1.6 ± 0.02
Cashew nut	1.8 ± 0.01	3.7 ± 0.03	4.0 ± 0.02	3.4 ± 0.01
Coconut	0.7 ± 0.03	1.2 ± 0.01	2.3 ± 0.02	2.0 ± 0.01
Plantain	1.3 ± 0.01	1.7 ± 0.01	2.7 ± 0.01	2.2 ± 0.02

Notes: Modified from the original study (Ogunmodede et al., 2016).

Table 12–Production of N-nitrosamine from various food products.

Product	Sample count	NDMA (μg/kg, μg/L)	NDEA (μg/kg, μg/L)
Dietary meat and byproduct	57	ND to 2.26	ND to 9.5
Processed meat product	129	0.04 to 9.3	ND to 12
Agricultural product	252	ND to 6.9	ND to 3.9
Seafood product	163	ND to 322.92	ND to 50.27
Dairy product	74	ND to 5.8	ND to 4
Vegetable oil	133	ND to 11	ND to 0.16
Soybean paste, soy sauce, seasoning, sauce	40	ND to 13.48	ND to 1.49
Alcoholic beverage	55	ND to 2.5	ND to 1.14

Notes: Modified from its original study (Park et al., 2015).
ND, not detected.

likewise, cereal grains and fats and oils were the food products mainly contributing to PAHs (de Vos, van Dokkum, Schouten, & de Jong-Berkhout, 1990; Phillips, 1999). In addition, when a vegetarian diet that promotes a high level of intake of leafy vegetables and unrefined grains was compared with a general diet, the vegetarian diet was shown to increase the intake of PAHs (Menzie et al., 1992). Food products other than meat also produced more PAHs after cooking than they did before cooking. Compared to fresh vegetables, higher production of PAHs was detected in grilled vegetables (Tamakawa, 2008; Tateno, Nagumo, & Suenaga, 1990). Similarly, fish also showed higher production of PAHs after smoking (McGill, Mackie, Parsons, Bruce, & Hardy, 1982; Tamakawa, 2008) (Table 9).

Perello, Marti-Cid, Castell, Llobet, and Domingo (2009) reported that the total PAHs in uncooked pork were less than those in calf meat or lamb, which are also red meats (Table 10). In addition, the total PAHs in pork (red meat) and chicken meat (white meat) were comparable, while being appreciably higher than that in tuna or olive oil. Although the total PAHs increased in cooked pork when compared to raw meat, the level of carcinogenic PAHs did not change significantly after cooking.

NOCs

Ogunmodede, Ojo, and Jegede (2016) compared the content of NOCs in various food products before and after cooking. Pork and all other food products displayed the formation of a larger amount of NOCs in the samples cooked by grilling using an oven, firewood, or charcoal, compared to the period before cooking (Table 11).

Park et al. (2015) measured the content of N-nitrosamine in various food samples, including dietary meat and processed meat products. Among the N-nitrosamines, NDMA and NDEA are categorized by IARC as Group 2A probable carcinogens. Thus, it was determined that their contents would be significant in relation to harmful substances, which became the focus of comparison. NDMA and NDEA contents in dietary meat and processed meat products may at first appear as being higher than other food products; however, the contents were far lower than in sea food. Furthermore, in the case of NDMA, markedly lower amounts were formed in dietary meat than in sauce and vegetable oil products (Table 12). To sum up the findings of the investigation, the correlation between red meat and colorectal cancer may have two scientific explanations. First, iron overload caused by red meat may induce oxidative stress and lead to carcinogenesis. Second, the production of harmful substances including HCAs, PAHs, and NOCs during the cooking and processing of red meat may induce cancer. Apart from extrinsic factors, such as processing and cooking, the only intrinsic factor of red meat that may contribute to carcinogenesis is the iron content. Food products other than red meat (0 to 6.4 mg/100 g), including fruits (0 to 3.7 mg/100 g), vegetables (0.2 to 11 mg/100 g), fish (0.3 to 18.3 mg/100 g), teas (2.4 to 22.6 mg/100 g), and spices (8.2 to 30.7 mg/100 g), also exhibit high iron content (HealthLinkBC, 2017). Hence, to state that red meat is a carcinogen due to its iron content lacks a logical basis. Moreover, the iron content in pork, a representative red meat, has been demonstrated to be lower than that in beef or lamb. While it is true that various harmful substances are produced during the cooking and processing of red meat, their contents are in the order of nanograms, and so are one-in-a-millionth below the amounts thought to be relevant as carcinogens. Furthermore, a similar level of harmful substances was found in food products other than red meat, including agricultural products, marine products, vegetable oil, dairy products, alcoholic beverages, and soy bean paste. Thus, it is implausible to confine the explanation of carcinogenic behavior based on such harmful substances to red meat only. In addition, the fact that the production of harmful substances may vary according to the method of processing and cooking should be taken into account for all food products including red meat. Notably, when the statistical data on the intake of red meat, fish, fruits and vegetables, and the rate of alcoholic drinking, tobacco smoking, overweight, and obesity, as well as life expectancy were analyzed for the Korean population, it was more than challenging to explain the pathogenesis of colorectal cancer based on a single specific factor.

Conclusions

Our review of recent research indicates that red meat cannot be held solely responsible as the main cause of the increased incidence of colorectal cancer. The incidence of cancer, including colorectal cancer, is complex, and induced by various other factors including age, genetic factors, dietary habits, environment, and lifestyle. It suggests the necessity to carry out a cohort study targeting diverse races and regions, which may have different natural environment and food consumption cultures. Furthermore, despite the lower consumption of red meat or processed meat products in Korea, the fact that the incidence of colorectal cancer is higher than that in Western countries seems unmatched. Colorectal cancer is the third most common type of cancer in the world and one of the main causes of death by cancer. This may be due to the influence of other factors, such as excessive consumption of alcohol, rate of smoking, stress level, or salt consumption. Therefore, to state that the intake of red meat by Asians, including Koreans, is the main cause of the pathogenesis of colorectal cancer lacks a logical basis. Epidemiological studies should be carried out to identify the correlation between the various factors and the incidence of colorectal cancer in the specific region or country. Moreover, little is known about the genetic factors that might contribute to increased susceptibility to colorectal cancer in the Korean population that consumes red meat. Thus, future research is needed to determine the relationship between genetic characteristics and colorectal cancer risk. Also, more objective and accurate data on the safety of dietary red meat are essential.

Conflicts of Interest

The authors declare no potential conflict of interest.

Author Contributions

Conceptualization: Lee, Jo, Yoon, Jeong, and Hur; Validation: Lee; Writing: Hur and Yoon; Review & editing: Jo, Jeong, and Lee.

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