Review

Red Meat Carcinogens and Their Role in Colorectal Cancer Development

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Abstract:

Colorectal cancer (CRC) is one of the leading causes of cancer-related morbidity and mortality worldwide. Epidemiological studies have consistently inferred a correlation between high red meat consumption and an increased risk of CRC. This review examines the association between red meat intake and CRC development, emphasizing the role of dietary patterns, cooking methods, and processing techniques. Moreover, carcinogenic compounds such as heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs), and N-nitroso compounds (NOCs) are formed during high-temperature cooking and processing of red meat, potentially contributing to colorectal carcinogenesis. Furthermore, genetic susceptibility and metabolic variations influence individual risk factors. Based on recent findings, dietary recommendations suggest limiting red and processed meat consumption while increasing fiber-rich foods to mitigate CRC risk. This article provides an overview of current evidence, underlying biochemical mechanisms that may impact CRC incidence through dietary modifications.

Keywords: colorectal cancer; red meat; heterocyclic amines; polycyclic aromatic hydrocarbons; N-nitroso compounds; carcinogenesis; nutrition.

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1. Introduction

Colorectal cancer (CRC) represents a major public health concern, with an estimate of 152,810 new cases in the United States for 2024 [1]. As the second leading cause of cancer-related deaths, it is expected to claim approximately 53,010 lives in the same year [1]. Notably, CRC incidence among individuals under 55 has been rising by 1-2% annually since the mid-1990s [2]. Younger adults often face advanced-stage diagnosis due to delayed

detection, making early awareness and prevention crucial [3]. The lifetime risk of developing CRC is approximately 1 in 23 for men and 1 in 25 for women [4]. While genetic predisposition, family history, and lifestyle choices contribute to this risk. Specifically, dietary habits – particularly red and processed meat consumption – have been strongly linked to CRC [4]. Although aging remains a primary risk factor, understanding the role of diet in cancer risk mitigation and prevention is essential [5].

Multiple studies highlight that higher red and processed meat consumption elevates CRC risk, with both total intake and frequency playing a role [6, 7]. A study by Sivasubramanian and colleagues found that processed meat consumption was associated with a higher risk of distal colon cancer, while unprocessed red meat appeared to have an inverse relationship with this cancer subtype [8]. Additional research suggests that consuming grilled or barbecued red and processed meats may further increase CRC risk, particularly among women [9, 10]. While the exact biological mechanisms are still under investigation, strong epidemiological evidence supports reducing red and processed meat intake as a preventive measure against CRC [11, 12].

Red meat, including beef, pork, and lamb, is categorized based on processing methods: (1) processed meats (e.g. sausages, bacon, and deli meats) contain preservatives, high levels of salt, and chemical additives; (2) unprocessed meats are consumed without such additives [13]. Scientific research consistently links high consumption of red and processed meats with an increased CRC risk [14-16]. Leading health organizations, such as the World Cancer Research Fund and the International Agency for Research on Cancer (IARC), to classify processed meats as carcinogenic and suggest that red meat may also contribute to cancer risk [17].

Carcinogens formed during the cooking and processing of red meat are believed to contribute to CRC risk [18]. Key compounds include:

- Heterocyclic amines (HCAs): formed at high cooking temperatures or with prolonged cooking [19]. Studies suggest a link between high dietary HCA intake from well-done red meat and CRC [20].
- Polycyclic aromatic hydrocarbons (PAHs): generated when meats are charbroiled, grilled, or smoked [21].
- N-nitroso compounds (NOCs): found in processed meats containing nitrites or formed endogenously in the colon when nitrosating agents react with amines from red meat [22].

Once absorbed, HCAs [23] and PAHs undergo metabolism in the liver before being excreted into the intestines via bile acids, where they may become locally activated [24]. Meanwhile, NOCs can be directly activated in the colon [25]. These carcinogens require metabolic activation before causing DNA damage, though detoxification and excretion processes can mitigate their harmful effects [26].

2. Observational studies linking red meat consumption to colorectal cancer development

Metabolism is regulated by phase I and phase II enzymes [27], which vary among individuals due to genetic polymorphisms. Some studies suggest that specific genetic variants may influence the effects of high red meat consumption, cooking methods, and doneness level on CRC risk (Table 1). However, overall findings remain inconclusive, and

further research is needed to understand the interaction between genetic factors, metabolism, and dietary carcinogens.

Table 1. Studies upon the effect of red meat consumption and colorectal cancer development published between the years 2020-2025.

Key Findings	Type of evidence	Year	References
High red meat intake increases CRC risk by 18%.	meta-analysis synthesized data	2021	[28]
Increased consumption of red meat is associated with an increased risk of CRC in women	systematic review and meta-analysis of prospective cohort studies	2023	[29]
100 g/d increment of red meat could increase by 11–51% risk of multiple cancer. 50 grams per day increment of processed meat consumption was associated with an 8% to 72% increased risk of various cancers	72 meta-analyses encompassing 20 unique cancer outcomes related to red meat and 19 related to processed meat	2021	[30]
Red meat intake linked to colorectal adenoma formation.	epidemiological study	2022	[31]
Heme iron accumulation associated with DNA oxidative damage.	cohort studies	2021	[32]
Higher red meat consumption is associated with higher cancer incidence.	ecological study	2023	[33]
The death risk attributable to consumption of red meat linearly increased during the past decade ($r = 0.99$; $p < 0.001$)	ecological study	2021	[34]
The temperature cooking of meat such as grilling and smoking contribute to the formation of mutagenic compound	narrative review	2022	[35]
Heme, hydrogen sulfide, lipid peroxidation, nitroso compounds also partake in the process of colorectal carcinogenesis	narrative review	2021	[36]
Each 100 grams per day increase was associated with a 12% increase in CRC risk (RR: 1.12, 95% CI: 1.06–1.19; based on 21 studies). Each 50 grams per day increase was linked to a 17% increase in CRC risk (RR: 1.17, 95% CI: 1.10–1.23; based on 16 studies	systematic review and meta-analysis	2024	[37]

2.1. Biochemical mechanisms linking red meat consumption to colorectal cancer development

Several hypotheses explain the association between CRC and red meat consumption, with the gut microbiome potentially playing a role in modulating cancer progression [38]. One prominent theory suggests that cooking red meat at high temperatures (Figure 1) produces heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs), both of which may contribute to DNA damage and cancer development [39].

$$\text{Creatine} + \text{Amino Acid} + \text{Reducing Sugar} \xrightarrow{\text{Heat}} \text{Intermediate Pyrazines} \xrightarrow{\text{Cyclization}} \text{HCA (MeIQx)}$$

Figure 1. Proposed reaction scheme of high temperatures production of heterocyclic amines during red meat cooking [38]. Abbreviations: HCA = heterocyclic amine; MeIQx = 2-amino-3,8-dimethylimidazo[4,5-f] quinoxaline.

This reaction occurs in grilled, fried, or barbecued meats, leading to the formation of heterocyclic amines, which are known to be potentially carcinogenic [40]. Once formed, HCAs such as MeIQx [40] can undergo further metabolic activation in the body via the cytochrome P450 (CYP1A2), leading to DNA damage and potential carcinogenic effects (Figure 2).

$$\text{HCA} + \text{CYP1A2} \xrightarrow{\text{Bioactivation}} \text{Electrophilic Metabolites} \xrightarrow{\text{DNA Binding}} \text{DNA Mutations}$$

$$\text{Hydrocarbon Radicals} \xrightarrow[\text{Heat } (>150^\circ\text{C})]{\text{Incomplete Combustion}} C_2H_2 \rightarrow C_6H_6 \rightarrow C_{10}H_8 \rightarrow C_{14}H_{10} \rightarrow C_{16}H_{10} \rightarrow C_{20}H_{12}$$

Figure 2. Potential mechanism of carcinogenesis induced by heterocyclic amines [40]. Abbreviations: HCA = heterocyclic amine; CYP1A2 = cytochrome P450.

PAH-DNA adducts [41] are key markers of carcinogenesis, particularly in smoking and high-temperature cooked meats (Figure 3). The formation of $C_{20}H_{14}O_3$ (BPDE) is the critical step in converting PAHs into carcinogenic DNA-damaging agents [42].

$$C_{20}H_{12} + O_2 + NADPH \xrightarrow{\text{CYP1A1}} C_{20}H_{12}O \xrightarrow{\text{Hydrolase}} C_{20}H_{14}O_2$$

$$\xrightarrow{\text{CYP1A1}} C_{20}H_{14}O_3 + \text{DNA} \rightarrow \text{BPDE-DNA Adduct} \rightarrow \text{Mutations} \rightarrow \text{Cancer}$$

Figure 3. Potential mechanism of converting polycyclic aromatic hydrocarbons into carcinogenic DNA-damaging agents [42]. Abbreviations: BPDE = $C_{20}H_{14}O_3$ - a polycyclic aromatic hydrocarbon; CYP1A1 = cytochrome P450.

BPDE is highly reactive and covalently binds to DNA, particularly at the N^2 position of guanine (Figure 4). This results in DNA adducts, which: (1) interfere with DNA replication; (2) cause mutations (especially in tumor suppressor genes like *P53*), and ultimately (3) lead to genomic instability and cancer development [43].

$$\text{BPDE} + \text{DNA (Guanine Base)} \rightarrow \text{BPDE-DNA Adduct} \rightarrow \text{Mutations} \rightarrow \text{Cancer}$$

Figure 4. Potential mechanism of DNA adduct formation and carcinogenesis [43]. Abbreviations: BPDE = $C_{20}H_{14}O_3$ - a polycyclic aromatic hydrocarbon.

The enzyme N-acetyltransferase 2 (NAT2) [44] is involved in metabolizing HCAs, forming DNA adducts that can also induce DNA mutations. Individuals with a rapid NAT2

acetylation phenotype tend to have higher DNA adduct levels than those with slower acetylation. However, a retrospective study indicated that while increased red meat consumption correlates with CRC, NAT2 enzyme activity does not significantly modify the risk [45]. NAT2 plays a dual role (Figure 5) in the metabolism of heterocyclic amines (HCAs) from cooked meat [46], determining their fate through two distinct pathways:

1. Detoxification pathway (N-acetylation):
    - NAT2 transfers an acetyl group from Acetyl-CoA to N-hydroxy-HCAs, forming non-toxic, water-soluble metabolites that are excreted from the body [47].
    - This pathway reduces carcinogenic potential and protects against DNA damage.
2. Bioactivation pathway (O-acetylation):
    - NAT2 facilitates the conversion of N-hydroxy-HCAs into electrophilic intermediates, which can bind to DNA, forming DNA adducts.
    - These adducts may cause mutations, increasing the risk of colorectal cancer (CRC).

The balance between these pathways is influenced by NAT2 genetic polymorphisms [48]. Rapid acetylators exhibit both increased detoxification and bioactivation, potentially raising cancer risk under high HCA exposure. Slow acetylators have reduced bioactivation but may experience longer toxin accumulation, affecting overall susceptibility to CRC.

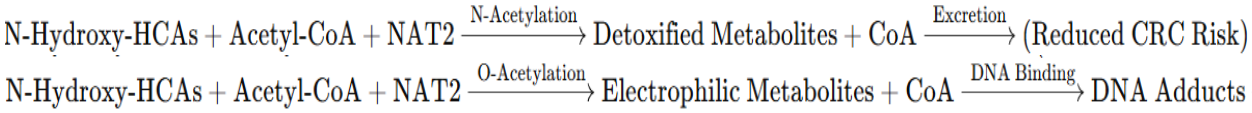

Figure 5. Schematic representation of the biochemical duality of N-acetyltransferase 2 metabolism and its role in colorectal cancer susceptibility [48]. Abbreviations: HCA = heterocyclic amines; NAT2 = N-acetyltransferase 2 ; CoA = coenzyme A.

Another potential mechanism involves nucleotide excision repair (NER) pathways, which are associated with CRC risk and may influence the effects of well-done red meat on cancer development [49]. However, research has yet to confirm a significant impact. NER pathway is a multi-step process that removes bulky DNA lesions (Figure 6), such as BPDE-DNA adducts and UV-induced damage, to maintain genomic integrity [50]. The process begins with damage recognition, where XPC-RAD23B (Global NER) or RNA polymerase II (transcription-coupled NER) detects DNA distortions caused by lesions [51]. Once recognized, TFIIH, a helicase complex containing XPB and XPD, binds to the damaged site and unwinds the DNA, allowing access to repair proteins [52]. Following unwinding, endonucleases XPF-ERCC1 and XPG make precise incisions on the 5' and 3' sides of the lesion, excising a ~24-32 nucleotide fragment containing the damaged sequence [53]. After the lesion is removed, DNA polymerase δ/ε synthesizes a new DNA strand using the undamaged complementary strand as a template. Finally, DNA ligase I or XRCC1-DNA ligase III seals the newly synthesized strand, restoring the DNA to its original structure and completing the repair process [54]. This pathway is critical in preventing mutations, and defects in NER proteins (XPC, XPD, XPG, ERCC1) have been associated with an increased risk of CRC due to the accumulation of DNA damage.

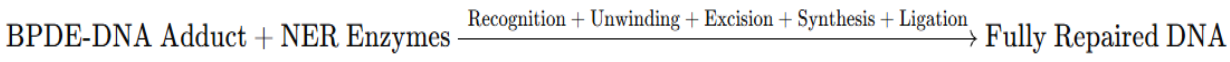

Figure 6. Summary of NER pathway integrating the recognition, excision, and repair of bulky DNA lesions [54].

Last but not least, the class of N-nitroso compounds (NOCs) are commonly found in processed meats that contain sodium nitrite ($NaNO_2$) as a preservative [55]. During processing and cooking, nitrites react with amines, leading to the formation of NOCs such as: nitrosamines, nitrosamides and nitrosoguanidines [57]. These compounds are known for their mutagenic and carcinogenic properties, as they can form DNA adducts, leading to genetic mutations (Figure 7) [57].

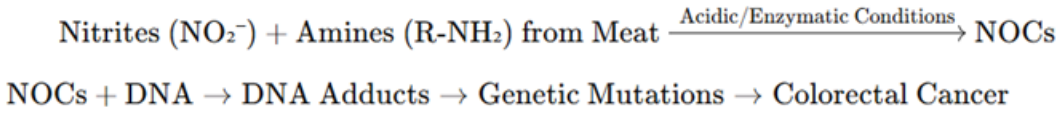

Figure 7. Schematic representation of the biochemical pathway leading from N-nitroso compounds (NOCs) to potential colorectal cancer risk [55].

2.2. Implications for public health, colorectal cancer and dietary recommendations

Given the evidence linking red meat consumption to CRC development [58], public health initiatives should emphasize dietary guidelines that promote reduced red and processed meat intake [59]. Encouraging alternative protein sources such as fish, poultry, and plant-based proteins may mitigate CRC risk [60]. Furthermore, increasing awareness of cooking methods that minimize the formation of mutagenic compounds can serve as an additional preventive measure [61].

Genetic predisposition to CRC is influenced by hereditary syndromes (e.g., Lynch syndrome, FAP, MAP), high-penetrance gene mutations (APC, TP53, KRAS), and polygenic risk factors (SNPs) [62]. The MSI and CIN pathways represent major genetic mechanisms underlying CRC progression. Understanding these genetic predispositions is crucial for early detection, targeted therapies (e.g., immunotherapy for MSI-H tumors), and preventive strategies in at-risk individuals [63]. While genetic predisposition and other lifestyle factors contribute to CRC risk, dietary habits remain a crucial modifiable factor. The collective findings from these studies highlight the importance of adopting a balanced diet with limited red meat consumption to reduce the global burden of colorectal cancer [64].

3. Discussion

The evidence linking red and processed meat consumption to CRC employs multiple epidemiological and clinical studies reinforcing the association [65]. The presence of carcinogenic compounds such as heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs), and N-nitroso compounds (NOCs) in cooked and processed meats provides a plausible biological mechanism for the increased CRC risk observed in high meat consumers [66]. Furthermore, genetic factors and metabolic variations may further

modulate individual susceptibility to CRC, although findings in this area remain to date inconclusive.

The role of cooking methods and processing techniques in influencing the carcinogenic potential is proven to be particularly significant [67]. High-temperature cooking methods such as grilling, smoking, and barbecuing lead to the formation of HCAs and PAHs, while processed meats often contain added nitrites, which can form NOCs. These compounds are known to cause DNA damage and promote colorectal carcinogenesis. As a result, dietary guidelines emphasize both the reduction of red and processed meat consumption and the adoption of safer cooking practices to mitigate CRC risk [68, 69].

In addition to meat consumption, other dietary and lifestyle factors play a crucial role in CRC risk modulation. A high-fiber diet, rich in fruits, vegetables, and whole grains, has been shown to offer protective benefits, possibly by enhancing gut microbiota composition, reducing inflammation, and improving bowel transit time [70]. Given the rising incidence of CRC, particularly among younger adults, public health efforts should focus on comprehensive dietary education, promoting healthier protein alternatives, and advocating for regular screenings to facilitate early detection [71].

4. Conclusion

The association between red and processed meat consumption and colorectal cancer is well-supported by scientific evidence. Carcinogenic compounds formed during meat processing and high-temperature cooking contribute to CRC risk, while genetic factors may influence individual susceptibility. Given the public health implications, reducing red and processed meat intake, opting for healthier cooking methods, and increasing fiber-rich foods in the diet are essential strategies for CRC prevention.

While dietary modifications alone may not entirely eliminate CRC risk, they represent a significant and modifiable factor that can substantially reduce disease incidence. Future research should continue to explore the genetic and metabolic factors that mediate this risk, as well as identify effective public health strategies for reducing CRC through dietary interventions. Encouraging a balanced diet with alternative protein sources and promoting awareness of cooking methods that limit carcinogen formation can collectively contribute to lowering the global burden of colorectal cancer.

Author Contributions:

Conceptualization, S.A., C.N.; Methodology, A.-M.C., M.B.; Formal Analysis, A.-M.C., M.B., A.D., A.C., M.R.; Investigation, A.-M.C., M.B., A.D., A.C., M.R.; Resources, S.A., C.N.; Data Curation, A.D., A.C.; Writing—Original Draft Preparation, A.-M.C., M.B., A.D.; Writing—Review & Editing, A.C., M.R., C.N., S.A.; Visualization, A.-M.C., M.B.; Supervision, S.A., C.N.

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References

1. Siegel, R.L.; Giaquinto, A.N.; Jemal, A. Cancer statistics, 2024. *CA Cancer J Clin* 2024, 74, 12–49. doi:10.3322/caac.21820
2. Bray, F.; Laversanne, M.; Sung, H.; Ferlay, J.; Siegel, R.L.; Soerjomataram, I.; Jemal, A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024, 74, 229–263. doi: 10.3322/caac.21834
3. Busico, A.; Gasparini, P.; Rausa, E.; Cattaneo, L.; Bozzi, F.; Silvestri, M.; Capone, I.; Conca, E.; Tamborini, E.; Perrone, F.; Vitellaro, M.; Ricci, M.T.; Casanova, M.; Chiaravalli, S.; Bergamaschi, L.; Massimino, M.; Milione, M.; Sozzi, G.; Pruneri, G.; Ferrari, A.; Signoroni, S. Molecular profiling of pediatric and young adult colorectal cancer reveals distinct genomic landscapes and potential therapeutic avenues. *Sci Rep* 2024, 14, 13138. doi: 10.1038/s41598-024-64149-7
4. Kim, K.; Hyeon, J.; Lee, S.A.; Kwon, S.O.; Lee, H.; Keum, N.; Lee, J.K.; Park, S.M. Role of Total, Red, Processed, and White Meat Consumption in Stroke Incidence and Mortality: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. *J Am Heart Assoc* 2017, 6, e005983. doi: 10.1161/JAHA.117.005983.
5. Farah, E.; Hutchinson, J.M.; Ruan, Y.; O'Sullivan, D.E.; Hilsden, R.J.; Brenner, D.R. The Association between Red Meat Consumption and Advanced Colorectal Adenomas in a Population Undergoing a Screening-Related Colonoscopy in Alberta, Canada. *Cancers (Basel)* 2024, 16, 495. doi: 10.3390/cancers16030495.
6. Aykan, N.F. Red Meat and Colorectal Cancer. *Oncol Rev* 2015, 9, 288. doi: 10.4081/oncol.2015.288. doi: 10.4081/oncol.2015.288.
7. Mehta, S.S.; Arroyave, W.D.; Lunn, R.M.; Park, Y.-M.; Boyd, W.A.; Sandler, D.P. A Prospective Analysis of Red and Processed Meat Consumption and Risk of Colorectal Cancer in Women. *Cancer Epidemiol Biomarkers Prev* 2020, 29, 141–150. doi: 10.1158/1055-9965.EPI-19-0459
8. Boyle, P.; Boffetta, P.; Autier, P. Diet, nutrition and cancer: public, media and scientific confusion. *Ann Oncol* 2008, 19, 1665–1667. doi: 10.1093/annonc/mdn561.
9. Omaye, A.T.; Omaye, S.T. Caveats for the Good and Bad of Dietary Red Meat. *Antioxidants (Basel)* 2019, 8, 544. doi: 10.3390/antiox8110544
10. Darooghegi Mofrad, M.; Mozaffari, H.; Sheikhi, A.; Zamani, B.; Azadbakht, L. The association of red meat consumption and mental health in women: A cross-sectional study. *Complement Ther Med* 2021, 56, 102588. doi: 10.1016/j.ctim.2020.102588.
11. Carr, P.R.; Walter, V.; Brenner, H.; Hoffmeister, M. Meat subtypes and their association with colorectal cancer: Systematic review and meta-analysis. *Int J Cancer* 2016, 138, 293–302. doi: 10.1002/ijc.29423
12. Zhao, Z.; Yin, Z.; Zhao, Q. Red and processed meat consumption and gastric cancer risk: A systematic review and meta-analysis. *Oncotarget* 2017, 8, 30563–30575. doi: 10.18632/oncotarget.15699.
13. Meinilä, J.; Virtanen, J.K. Meat and meat products - a scoping review for Nordic Nutrition Recommendations 2023. *Food Nutr Res* 2024, 68. doi: 10.29219/fnr.v68.10538.
14. Vieira, A.R.; Abar, L.; Chan, D.S.M.; Vingeliene, S.; Polemiti, E.; Stevens, C.; Greenwood, D.; Norat, T. Foods and beverages and colorectal cancer risk: A systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. *Ann Oncol* 2017, 28, 1788–1802. doi: 10.1093/annonc/mdx171
15. Kim, S.Y.; Wie, G.A.; Cho, Y.A.; Kang, H.H.; Ryu, K.A.; Yoo, M.K.; Jun, S.; Kim, S.A.; Ha, K.; Kim, J.; Cho, Y.H.; Shin, S.; Joung, H. The Role of Red Meat and Flavonoid Consumption on Cancer Prevention: The Korean Cancer Screening Examination Cohort. *Nutrients* 2017, 9, 938. doi: 10.3390/nu9090938.

16. Kim, S.R.; Kim, K.; Lee, S.A.; Kwon, S.O.; Lee, J.K.; Keum, N.; Park, S.M. Effect of Red, Processed, and White Meat Consumption on the Risk of Gastric Cancer: An Overall and Dose-Response Meta-Analysis. *Nutrients* 2019, 11, 826. doi: 10.3390/nu11040826.
17. Wang F, Chandler PD, Zeleznik OA, Wu K, Wu Y, Yin K, Song R, Avila-Pacheco J, Clish CB, Meyerhardt JA, Zhang X, Song M, Ogino S, Lee IM, Eliassen AH, Liang L, Smith-Warner SA, Willett WC, Giovannucci EL. Plasma Metabolite Profiles of Red Meat, Poultry, and Fish Consumption, and Their Associations with Colorectal Cancer Risk. Nutrients. 2022 Feb 25;14(5):978. doi: 10.3390/nu14050978
18. Pogorzelska-Nowicka, E.; Kurek, M.; Hanula, M.; Wierzbicka, A.; Półtorak, A. Formation of Carcinogens in Processed Meat and Its Measurement with the Usage of Artificial Digestion - A Review. *Molecules* 2022, 27, 4665. doi: 10.3390/molecules27144665.
19. Dolan, L.; Smith, K.S.; Marlin, M.B.; Bell, L.N.; Blythe, E.; Greene, M.W.; Frugé, A.D. Food Security, Obesity, and Meat-Derived Carcinogen Exposure in US Adults. *Food Chem Toxicol* 2021, 155, 112412. doi: 10.1016/j.fct.2021.112412.
20. Ruiz-Saavedra, S.; García-González, H.; Arboleya, S.; Salazar, N.; Labra-Gayo, E.; Díaz, I.; Gueimonde, M.; González, S.; Reyes-Gavilán, C.G. Intestinal Microbiota Alterations by Dietary Exposure to Chemicals from Food Cooking and Processing. Application of Data Science for Risk Prediction. *Comput Struct Biotechnol J* 2021, 19, 1081–1091. doi: 10.1016/j.csbj.2021.01.037.
21. Dubrow, R.; Darefsky, A.S.; Park, Y.; Mayne, S.T.; Moore, S.C.; Kilfoy, B.; Cross, A.J.; Sinha, R.; Hollenbeck, A.R.; Schatzkin, A.; Ward, M.H. Dietary components related to N-nitroso compound formation: A prospective study of adult glioma. *Cancer Epidemiol Biomarkers Prev* 2010, 19, 1709–1722. doi: 10.1158/1055-9965.EPI-10-0225.
22. Hughes, R.; Cross, A.J.; Pollock, J.R.A.; Bingham, S. Dose-dependent effect of dietary meat on endogenous colonic N-nitrosation. *Carcinogenesis* 2001, 22, 199–202. doi: 10.1093/oxfordjournals.carcin.a000409.
23. Hasnol, N.D.S.; Jinap, S.; Sanny, M. Effect of different types of sugars in a marinating formulation on the formation of heterocyclic amines in grilled chicken. *Food Chem* 2014, 145, 514–521. doi: 10.1016/j.foodchem.2013.08.086
24. Chiang, J.Y.L.; Ferrell, J.M. Bile Acid Metabolism in Liver Pathobiology. *Gene Expr* 2018, 18, 71–87. doi: 10.3727/105221618X15156018385515.
25. Joosen, A.; Kuhnle, G.; Aspinall, S.; Barrow, T.; Lecommandeur, E.; Azqueta, A.; Collins, A.; Bingham, S. Effect of processed and red meat on endogenous nitrosation and DNA damage. *Carcinogenesis* 2009, 30, 1402–1407. doi: 10.1093/carcin/bgp130
26. Basu, A.K. DNA Damage, Mutagenesis and Cancer. *Int. J. Mol. Sci.* 2018, 19, 970. Doi: 10.3390/ijms19040970
27. Chan, D.S.; Lau, R.; Aune, D.; Vieira, R.; Greenwood, D.C.; Kampman, E.; Norat, T. Red and processed meat and colorectal cancer incidence: Meta-analysis of prospective studies. *PLoS One* 2011, 6, e20456. doi: 10.1371/journal.pone.0020456.
28. Farvid, M.S.; Sidahmed, E.; Spence, N.D.; Mante Angua, K.; Rosner, B.A.; Barnett, J.B. Consumption of red meat and processed meat and cancer incidence: A systematic review and meta-analysis of prospective studies. *Eur J Epidemiol* 2021, 36, 937–951. doi: 10.1007/s10654-021-00741-9.
29. Sivasubramanian, B.P.; Dave, M.; Panchal, V.; Saifa-Bonsu, J.; Konka, S.; Noei, F.; Nagaraj, S.; Terpari, U.; Savani, P.; Vekaria, P.H.; Samala Venkata, V.; Manjani, L. Comprehensive Review of Red Meat Consumption and the Risk of Cancer. *Cureus* 2023, 15, e45324. doi: 10.7759/cureus.45324.

30. Huang, Y.; Cao, D.; Chen, Z.; Chen, B.; Li, J.; Guo, J.; Dong, Q.; Liu, L.; Wei, Q. Red and processed meat consumption and cancer outcomes: Umbrella review. *Food Chem* 2021, 356, 129697. doi: 10.1016/j.foodchem.2021.129697.
31. Grosso, G.; La Vignera, S.; Condorelli, R.A.; Godos, J.; Marventano, S.; Tieri, M.; Ghelfi, F.; Titta, L.; Lafranconi, A.; Gambera, A.; Alonzo, E.; Sciacca, S.; Buscemi, S.; Ray, S.; Del Rio, D.; Galvano, F. Total, Red and Processed Meat Consumption and Human Health: An Umbrella Review of Observational Studies. *Int. J. Food Sci. Nutr.* 2022, 73, 726–737. doi: 10.1080/09637486.2022.2050996.
32. Abu-Ghazaleh, N.; Chue, W.J.; Gopalan, V. Intestinal Microbiota and Its Association with Colon Cancer and Red/Processed Meat Consumption. *J Gastroenterol Hepatol* 2021, 36, 75–88. doi: 10.1111/jgh.15042
33. Ma, H.; Qi, X. Red Meat Consumption and Cancer Risk: A Systematic Analysis of Global Data. *Foods* 2023, 12, 4164. doi: 10.3390/foods12224164.
34. Mattiuzzi, C.; Lippi, G. Epidemiologic Burden of Red and Processed Meat Intake on olorectal Cancer Mortality. *Nutr. Cancer* 2021, 73, 562–567. doi: 10.1080/01635581.2020.1765259.
35. Diakité, M.T.; Diakité, B.; Koné, A.; Balam, S.; Fofana, D.; Diallo, D.; Kassogué, Y.; Traoré, C.B.; Kamaté, B.; Ba, D.; Ly, M.; Ba, M.; Koné, B.; Maiga, A.I.; Achenbach, C.; Holl, J.; Murphy, R.; Hou, L.; Maiga, M. Relationships Between Gut Microbiota, Red Meat Consumption and Colorectal Cancer. *J. Carcinog. Mutagen.* 2022, 13, 1000385.
36. Kossenas, K.; Constantinou, C. Epidemiology, Molecular Mechanisms, and Clinical Trials: An Update on Research on the Association Between Red Meat Consumption and Colorectal Cancer. *Curr. Nutr. Rep.* 2021, 10, 435–467. doi: 10.1007/s13668-021-00377-x.
37. Pouzou, J.G.; Zagmutt, F.J. Observational Dose-Response Meta-Analysis Methods May Bias Risk Estimates at Low Consumption Levels: The Case of Meat and Colorectal Cancer. *Adv. Nutr.* 2024, 15, 100214. doi: 10.1016/j.advnut.2024.100214.
38. Loke, Y.L.; Chew, M.T.; Ngeow, Y.F.; Lim, W.W.D.; Peh, S.C. Colon Carcinogenesis: The Interplay Between Diet and Gut Microbiota. *Front. Cell. Infect. Microbiol.* 2020, 10, 603086. doi: 10.3389/fcimb.2020.603086
39. Lee, C.; Lee, S.; Yoo, W. Metabolic Interaction Between Host and the Gut Microbiota During High-Fat Diet-Induced Colorectal Cancer. *J. Microbiol.* 2024, 62, 153–165. doi: 10.1007/s12275-024-00123-2.
40. Bendaly, J.; Zhao, S.; Neale, J.R.; Metry, K.J.; Doll, M.A.; States, J.C.; Pierce, W.M. Jr.; Hein, D.W. 2-Amino-3,8-dimethylimidazo-[4,5-f] quinoxaline-induced DNA Adduct Formation and Mutagenesis in DNA Repair-Deficient Chinese Hamster Ovary Cells Expressing Human Cytochrome P4501A1 and Rapid or Slow Acetylator N-acetyltransferase 2. *Cancer Epidemiol. Biomarkers Prev.* 2007, 16, 1503–1509. doi: 10.1158/1055-9965.EPI-07-0305
41. Balam, M.; Albores, A. DNA Damage Caused by Polycyclic Aromatic Hydrocarbons: Mechanisms and Markers. In *Selected Topics in DNA Repair*, Chen, C., Ed.; InTech: 2011; ISBN 978-953-307-606-5.
42. Ewa, B.; Danuta, M.Š. Polycyclic Aromatic Hydrocarbons and PAH-Related DNA Adducts. *J. Appl. Genet.* 2017, 58, 321–330. doi: 10.1007/s13353-016-0380-3
43. Fang, A.; Smith, W.; Vouros, P.; Gupta, R. Identification and Characterization of a Novel Benzo[a]pyrene-Derived DNA Adduct. *Biochem. Biophys. Res. Commun.* 2001, 281, 383–389. doi: 10.1006/bbrc.2000.4161.
44. Baxter, N.T.; Ruffin, M.T.; Rogers, M.A.; Schloss, P.D. Microbiota-Based Model Improves the Sensitivity of Fecal Immunochemical Test for Detecting Colonic Lesions. *Genome Med.* 2016, 8, 37. doi: 10.1186/s13073-016-0290-3
45. Burkitt, D.P. Epidemiology of Cancer of the Colon and Rectum. *Cancer* 1971, 28, 3–13.

46. Rabstein, S.; Brüning, T.; Harth, V.; Fischer, H.P.; Haas, S.; Weiss, T.; Spickenheuer, A.; Pierl, C.; Justenhoven, C.; Illig, T.; Vollmert, C.; Baisch, C.; Ko, Y.D.; Hamann, U.; Brauch, H.; Pesch, B.; GENICA Network. N-acetyltransferase 2, Exposure to Aromatic and Heterocyclic Amines, and Receptor-Defined Breast Cancer. *Eur. J. Cancer Prev.* 2010, 19(2), 100–109. doi: 10.1097/CEJ.0b013e328333fbb7
47. Quan, L.; Chattopadhyay, K.; Nelson, H.H.; Chan, K.K.; Xiang, Y.B.; Zhang, W.; Wang, R.; Gao, Y.T.; Yuan, J.M. Differential association for N-acetyltransferase 2 genotype and phenotype with bladder cancer risk in Chinese population. *Oncotarget.* 2016, 7(26), 40012-40024. doi: 10.18632/oncotarget.9475.
48. Delfino, R.; Sinha, R.; Smith, C.; West, J.; White, E.; Lin, H.; Liao, S.Y.; Gim, J.; Ma, H.; Butler, J.; Anton-Culver, H. Breast Cancer, Heterocyclic Aromatic Amines from Meat and N-acetyltransferase 2 Genotype. *Carcinogenesis* 2000, 21, 607–615. doi: 10.1093/carcin/21.4.607.
49. Steck, S.E.; Butler, L.M.; Keku, T.; Antwi, S.; Galanko, J.; Sandler, R.S.; Hu, J.J. Nucleotide Excision Repair Gene Polymorphisms, Meat Intake and Colon Cancer Risk. *Mutat. Res.* 2014, 762, 24–31. doi: 10.1016/j.mrfmmm.2014.02.004.
50. Liu, L.; Lee, J.; Zhou, P. Navigating the Nucleotide Excision Repair Threshold. *J. Cell Physiol.* 2010, 224(3), 585–589. doi: 10.1002/jcp.22205
51. Schärer, O.D. Nucleotide Excision Repair in Eukaryotes. *Cold Spring Harb. Perspect. Biol.* 2013, 5(10), a012609. doi: 10.1101/cshperspect.a012609.
52. Tsutakawa, S.E.; Tsai, C.L.; Yan, C.; Bralić, A.; Chazin, W.J.; Hamdan, S.M.; Schärer, O.D.; Ivanov, I.; Tainer, J.A. Envisioning How the Prototypic Molecular Machine TFIIH Functions in Transcription Initiation and DNA Repair. *DNA Repair (Amst.)* 2020, 96, 102972. doi: 10.1016/j.dnarep.2020.102972.
53. Yu, J.; Yan, C.; Dodd, T.; Tsai, C.L.; Tainer, J.A.; Tsutakawa, S.E.; Ivanov, I. Dynamic Conformational Switching Underlies TFIIH Function in Transcription and DNA Repair and Impacts Genetic Diseases. *Nat. Commun.* 2023, 14(1), 2758. doi: 10.1038/s41467-023-38416-6.
54. Kienzler, A.; Bony, S.; Devaux, A. DNA Repair Activity in Fish and Interest in Ecotoxicology: A Review. *Aquat. Toxicol.* 2013, 134-135, 47–56. doi: 10.1016/j.aquatox.2013.03.005
55. Cheng, T.; Chaousis, S.; Kodagoda Gamage, S.M.; Lam, A.K.; Gopalan, V. Polycyclic Aromatic Hydrocarbons Detected in Processed Meats Cause Genetic Changes in Colorectal Cancers. *Int. J. Mol. Sci.* 2021, 22(20), 10959. doi: 10.3390/ijms222010959.
56. Duedahl-Olesen, L.; Ionas, A.C. Formation and Mitigation of PAHs in Barbecued Meat—A Review. *Crit. Rev. Food Sci. Nutr.* 2021, 1–16. doi: 10.1080/10408398.2020.1867056
57. Parnaud, G.; Pignatelli, B.; Peiffer, G.; Taché, S.; Corpet, D.E. Endogenous N-Nitroso Compounds, and Their Precursors, Present in Bacon, Do Not Initiate or Promote Aberrant Crypt Foci in the Colon of Rats. *Nutr. Cancer* 2000, 38(1), 74–80. doi: 10.1207/S15327914NC381_11.
58. Kenfield, S.A.; Philip, E.J.; Phillips, S.M.; Meyerhardt, J.A.; Chan, J.M.; Atreya, C.E.; Kim, M.O.; Harris, Q.; Steiding, P.; Macaire, G.; McCullough, M.L.; Piawah, S.; Johnson, W.Y.; Kurttila, F.A.; Lewis, W.L.; Pesmen, C.; Watson, Y.; Van Blarigan, E.L. Optimizing Intervention Tools to Improve Nutrition and Physical Activity for Colorectal Cancer Survivors (Tools To Be Fit): Study Protocol of a Randomized Factorial Experiment. *Contemp. Clin. Trials* 2022, 123, 107009. doi: 10.1016/j.cct.2022.107009.
59. Zheng, Y.; Meng, L.; Liu, H.; Sun, L.; Nie, Y.; Wu, Q.; Fan, D.; Li, M. Let Food Be Thy Medicine: The Role of Diet in Colorectal Cancer: A Narrative Review. *J. Gastrointest. Oncol.* 2022, 13(4), 2020–2032. doi: 10.21037/jgo-22-32.

60. Fryer, E.; Martin, R.M.; Haycock, P.; Yarmolinsky, J. Investigating the Causal Effect of Previously Reported Therapeutic Agents for Colorectal Cancer Prevention: Protocol for a Mendelian Randomization Analysis. *Wellcome Open Res.* 2024, 9, 30. doi: 10.12688/wellcomeopenres.20861.2.
61. Rezende, L.F.M.; Malhão, T.A.; da Silva Barbosa, R.; Schilithz, A.O.C.; da Silva, R.C.F.; Moreira, L.G.M.; Ferrari, G.; Machado, P.A.N.; Diogenes, M.E.L. The Current and Future Costs of Colorectal Cancer Attributable to Red and Processed Meat Consumption in Brazil. *BMC Health Serv. Res.* 2023, 23(1), 1182. doi: 10.1186/s12913-023-10169-4.
62. Rebuzzi, F.; Ulivi, P.; Tedaldi, G. Genetic Predisposition to Colorectal Cancer: How Many and Which Genes to Test? *Int. J. Mol. Sci.* 2023, 24, 2137. doi: 10.3390/ijms24032137
63. Valle, L.; Vilar, E.; Tavtigian, S.V.; Stoffel, E.M. Genetic Predisposition to Colorectal Cancer: Syndromes, Genes, Classification of Genetic Variants and Implications for Precision Medicine. *J. Pathol.* 2019, 247(5), 574–588. doi: 10.1002/path.5229.
64. Boushey, C.; Ard, J.; Bazzano, L.; Heymsfield, S.; Mayer-Davis, E.; Sabaté, J.; Snetselaar, L.; Van Horn, L.; Schneeman, B.; English, L.K.; Bates, M.; Callahan, E.; Venkatramanan, S.; Butera, G.; Terry, N.; Obbagy, J. Dietary Patterns and All-Cause Mortality: A Systematic Review [Internet]. Alexandria (VA): USDA Nutrition Evidence Systematic Review; 2020 Jul. doi: 10.52570/NESR.DGAC2020.SR0108
65. Mann, N. Dietary Lean Red Meat and Human Evolution. *Eur. J. Nutr.* 2000, 39, 71–79. doi: 10.1007/s003940050005
66. Sinha, R.; Peters, U.; Cross, A.J.; Kulldorff, M.; Weissfeld, J.L.; Pinsky, P.F.; Rothman, N.; Hayes, R.B. Meat, Meat Cooking Methods and Preservation, and Risk for Colorectal Adenoma. *Cancer Res.* 2005, 65(17), 8034–8041. doi: 10.1158/0008-5472.CAN-04-3429.
67. Bulanda, S.; Janoszka, B. Consumption of Thermally Processed Meat Containing Carcinogenic Compounds (Polycyclic Aromatic Hydrocarbons and Heterocyclic Aromatic Amines) versus a Risk of Some Cancers in Humans and the Possibility of Reducing Their Formation by Natural Food Additives—A Literature Review. *Int. J. Environ. Res. Public Health* 2022, 19(8), 4781. doi: 10.3390/ijerph19084781.
68. Zheng, W.; Lee, S.A. Well-Done Meat Intake, Heterocyclic Amine Exposure, and Cancer Risk. *Nutr. Cancer* 2009, 61, 437–446. doi: 10.1080/01635580802710741.
69. Ali, A.; Waly, M.; Devarajan, S. Chapter 11. Impact of Processing Meat on the Formation of Heterocyclic Amines and Risk of Cancer. In *Food and Health*; 2019; pp. 187–200. doi: 10.1039/9781788015813-00187.
70. Zhou, Z.; Kleis, L.; Depetris-Chauvin, A.; Jaskulski, S.; Damerell, V.; Michels, K.B.; Gigic, B.; Nöthlings, U.; Panagiotou, G. Beneficial Microbiome and Diet Interplay in Early-Onset Colorectal Cancer. *EMBO Mol. Med.* 2025, 17(1), 9–30. doi: 10.1038/s44321-024-00177-0
71. Kim, J.; Lee, H.K. Potential Role of the Gut Microbiome in Colorectal Cancer Progression. *Front. Immunol.* 2022, 12, 807648. doi: 10.3389/fimmu.2021.807648.