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REVIEW ARTICLE

Colon cancer and the consumption of red and processed meat: an association that is medium, rare or well done?

SM Kassier[a]*

[a]*Dietetics and Human Nutrition, University of KwaZulu-Natal, Pietermaritzburg, South Africa*
**Email: kassiers@ukzn.ac.za*

In 2015, the International Agency for Research on Cancer (IARC) indicated that red meat is a probable cause of colon cancer, while processed meat was classified as carcinogenic. The 2010 indicators of lifetime risk for developing colorectal cancer among South African (SA) males and females was 1:114 and 1:182 respectively, while its prevalence as a newly diagnosed cancer was seventh for males and sixth for females. SA consumers have increased their meat expenditure over the past decade as a result of class mobility. This has resulted in an increase in the proportion of middle-class consumers. Although the consumption of red meat has increased, it has been surpassed by chicken. Due to a lack of national food consumption data regarding processed meat, it is not clear what local consumption trends are. The 2015 Consumer Price Index (CPI) documented a significant urban food price increase for chicken, cheaper cuts of beef and polony. However, when comparing urban food prices, a processed meat like polony is 27% cheaper per kilogram than whole chicken. Hence it is possible that the relative affordability of processed meat could contribute to its consumption among many South Africans (SAs) and in so doing, could contribute to colon cancer risk. In relation to the above, it is important for future SA public health recommendations to take cognisance of the World Cancer Research Fund and American Institute for Cancer Research recommendations of limiting red meat consumption to less than 500 g/week and avoiding processed meat.

Keywords: colon cancer, colorectal cancer, haem iron, processed meat, red meat

Introduction

In October 2015, the International Agency for Research on Cancer (IARC), the cancer agency of the World Health Organisation (WHO), issued a press release after the consumption of red and processed meat was evaluated for its carcinogenicity.[1] This was based on a comprehensive review of epidemiological studies[1,2] by the IARC Monographs Programme.[1,2] Reviewed data included 800 studies from numerous countries and several continents with diverse ethnicities and diets, including 14 cohort studies. For the evaluation, prospective cohort studies conducted in the general population were weighted more than other study designs. Additional evidence was provided by high-quality population-based case-control studies.[2] Based on the above evaluation, red meat was classified as probably carcinogenic to humans (Group 2A) as there was limited evidence that consuming red meat was responsible for causing colon cancer in humans, but with strong mechanistic evidence supporting a carcinogenic effect. Although this association was mainly observed for colorectal cancer, associations were also found for pancreatic and prostate cancer. Processed meat was classified as carcinogenic to humans (Group 1), as there was sufficient evidence in humans that consuming processed meat causes colorectal cancer (IARC 2015).[1,2]

Hence, for the purpose of this review, the focus will be on investigating the incidence of colorectal cancer among South Africans (SAs) as well as their red and processed meat consumption patterns. An interpretation of the IARC classification of carcinogens will follow, as well as the definition of red and processed meat. Current recommendations regarding the consumption of red and processed meat and the cooking methods associated with an increased risk of carcinogenicity will be reviewed, followed by a discussion of the compounds and mechanisms proposed to be responsible for carcinogenesis. This will be followed by assessing the feasibility of promoting a vegetarian diet in order to prevent colon cancer.

Incidence of colorectal cancer among South Africans

The 2010 statistics regarding the incidence of colorectal cancer among SAs issued by the National Cancer Registry, documented the lifetime risk for developing colorectal cancer among males and females as 1:114 and 1:182 respectively.[3] The highest race- and gender-specific lifetime risk was documented for coloured females (1:94), followed by white females (1:94), coloured males (1:68) and Asian males (1:58).[3]

Colorectal cancer was the seventh most prevalent newly histologically diagnosed cancer among South African (SA) males, followed by sixth position for females. Among Asian males and females, colorectal cancer was the second most commonly histologically diagnosed cancer, accounting for 13.6% and 7.39% of total cancers respectively. It accounted for only 3.8% and 2.5% of confirmed cancers amongst black males and females. White females had a higher percentage of newly diagnosed colorectal cancers than males at 5.2% versus 4.8%.[3] Stefan[4] explains that the variation in the above race-specific colorectal cancer statistics can be attributed to diversity in terms of genetics, diet, culture, lifestyle and exercise habits. It is therefore not surprising that a comparison of colon cancer risk between healthy middle aged African Americans (65:100 000) and rural SAs (< 5:100 000) found the stronger association in the former to be related to a higher intake of animal protein and fat, as well as a lower fibre consumption.[5] Although the above statistics seem modest, they could be important for future public health messages when reflecting on increasing urbanisation, acculturation and the adoption Westernised eating habits by many SAs.

Table 1: Classification of carcinogenic agents and their description

Agent	Category	Description
Group 1	Carcinogenic to humans	Sufficient evidence of carcinogenicity in humans[13,14,15]
Group 2A	Probably carcinogenic to humans	Limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. In certain cases, there is inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals, as well as strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans[13,14,15]

Table 2: Colon cancer and associated carcinogenic agents

Cancer site	Carcinogenic agents with sufficient evidence in humans (Group 1)[2,14,16]	Agents with limited evidence in humans (Group 2A)[2,14,16]
Colon	Alcoholic beverages Smoking X-radiation, gamma radiation Processed meat consumption	Asbestos *Schistosoma japonicum* Red meat consumption

South African red and processed meat consumption patterns

The Global Agricultural Information Network (GAIN) Report[6] stated that, over the past two decades, steady economic growth and an increase in the average income of SAs has resulted in a rapid increase in meat consumption patterns. Although mention of beef, poultry, pork and lamb consumption is made within this report, processed meat was not referred to. The increase in meat consumption can be accounted for by class mobility, a phenomenon related to an increase in the proportion of SAs being classified as middle-class consumers. However, the increase in red meat consumption can be described as moderate when compared with that of chicken.[6] The latter trend was echoed by a report on SA food consumption studies to determine the mean intake of foods most commonly consumed. Findings were that amongst 1- to 9-year-olds, chicken was the tenth most commonly consumed, whereas among those 10 years of age and older, it was the ninth most commonly consumed.[7]

Processed meat consumption was not referred to in the above report.[7] However, a study that investigated fast food consumption among black 17-year-olds in Soweto, which formed part of the Birth to Twenty cohort,[8] reported that children and adolescents living in urban areas (including townships and settlements) are increasingly exposed to the influences of a Western lifestyle as a result of urbanisation and the resultant nutrition transition.[9,10] Hence, townships have an increasingly large variety of commercial and informal food vendors that sell fast-food items such as a 'quarter, which proved to be most popular amongst the above cohort. The ingredients of a quarter included white bread, fried chips, a slice of cheese and a variety of processed meats such as polony, Russians (a spiced processed meat sausage), sausage, viennas (a processed meat sausage), *mangola*, white liver and special. The latter three are all fatty processed meats. Other processed meats consumed by the cohort included sausage rolls, boerewors (sausage) rolls, hot dogs and hamburgers.[8] These findings are of importance, as Popkin[10] explained how available evidence suggests that developing countries like SA have been undergoing transition at a more rapid rate over the past decade or so compared with high-income developed countries. In addition, in townships like Soweto it is likely that fast food makes a significant contribution to total energy intake.[11] It can therefore be postulated that where fast foods contain processed meats, their use could be related to the fact that the 2015 urban Consumer Price Index (CPI)[12] indicated that processed meats like polony (R36.43/kg), are more affordable per kilogram than whole chicken (R49.85/kg), hence making them a preferred component of fast foods.

Classification and interpretation of carcinogenicity

The classification of carcinogenic agents used by the IARC monographs is depicted in Table 1 and is based on scientific judgement that reflects the strength of evidence derived from studies in humans and experimental animals, as well as mechanistic and other relevant data.[13,14]

The Group 1 classification of processed meat and its carcinogenicity in relation to the development of colon cancer is used when there is sufficient, convincing evidence of carcinogenicity in humans, thus implying that there is convincing evidence based on epidemiologic studies that show the development of cancer in exposed humans.[2,15]

The Group 2A classification of red meat and the use of the term 'limited' relates to limited evidence from epidemiologic studies showing positive associations between red meat consumption and the development of colon cancer. In addition, strong mechanistic evidence for this relationship and the development of colon cancer is present. However, other explanations for the observation including chance, bias or confounding factors cannot be ruled out.[2,15]

When assessing colon cancer risk and the associated carcinogens with sufficient evidence in humans versus those with limited evidence (Table 2), processed meat is strongly associated with colon cancer, while the consumption of red meat is based on limited evidence.[16]

The reason why processed meat was classified along with smoking and the consumption of alcohol does not imply that they are equally carcinogenic. It merely describes the strength of scientific evidence regarding the carcinogen, rather than assessing the level of risk.[15] Burden of disease is a quantitative measure of population health outcome using information on

Table 3: Classification of red meat and processed meat

Red meat	Processed meat including salting, curing and smoking
Beef	Bacon
Goat	Beef patties
Lamb	Biltong
Mutton	Braaivleis (smoking occurs when cooking meat over a charcoal or wood fire when the dripping of fat and meat juices onto the fire causes flames and smoke[22])
Pork	Canned meat
Horse	Corned beef
Veal	Frankfurters
	Ham
	Hot dogs
	Meat-based preparations and sauces made from meat drippings
	Polony
	Russians
	Salami
	Sausages
	Smoked chicken
	White liver

mortality and morbidity as well as recovery in the population.[17] According to the most recent estimates of the Global Burden of Disease Project, globally 34 000 annual cancer deaths can be attributed to diets high in processed meat. Although red meat has not yet been established as a carcinogen, should the reported associations be proven to be causal, it is estimated that diets high in red meat could be responsible for 50 000 global deaths annually. In contrast, about one million annual global deaths are caused by smoking, 600 000 are due to the consumption of alcohol, and more than 200 000 can be attributed to air pollution.[15]

The above association between red and processed meat and the development of colon cancer was reported in a press release issued by the IARC.[1] Subsequently the WHO indicated that due to numerous queries, expressions of concern and requests for clarification resulting from the press release, a question-and-answer document was being released,[15] based on the paper published by the IARC Monograph Working Group in Lancet Oncology.[2] When reviewing the Q&A issued by the WHO,[15] it became evident which aspects of the IARC report generated the most questions and queries. Hence, an in-depth discussion of some of these aspects will follow.

Definition of red and processed meat

When referring to red and processed meat, the meat and meat products listed in Table 3 can be used for clarification purposes.[1,2,15,18]

Processed meats such as polony, Russians and white liver referred to in the Sowetan Birth to Twenty Cohort[8] are presumed to be consumed by many SAs. Although they did not feature in the international classification of processed meat,[1,2,15,19,20] when reviewing the South African National Standards (SANS) on processed meat products[21] it is evident that these products can be included in the classification.

Amount of meat consumed in relation to colorectal cancer risk

An increase in colorectal cancer risk was generally associated with the amount of processed meat consumed. A meta-analysis of data from 10 studies estimated that for every 50 grams of processed meat consumed on a daily basis, the risk of colorectal cancer increased by 18%.[1,15,18,22] It was also found that colon cancer risk increased in a linear fashion with an increase in the consumption of red and processed meat, i.e. total meat intake, up to approximately 140 g/day. Beyond this level, the increase in risk was less prominent. In studies that analysed risk in relation to total meat intake (red and/or processed meat), colorectal cancer risk increased up to 22% with intakes ranging from 20 g/day to 140 g/day, after which the increase became stable.[18] Results generated by the European Prospective Investigation into Cancer and Nutrition (EPIC) study found a 35% increase in colon cancer risk when more than 160 g/day of red and processed meat was consumed, compared with less than 20 g/day.[23]

The cancer risk associated with the consumption of red meat is more difficult to estimate as available evidence linking the consumption of red meat to colon cancer is not as strong. However, should the association between the consumption of red meat and colorectal cancer prove to be causal, it is suggested that the risk of developing colorectal cancer could be increased by 17% for every 100 g portion consumed on a daily basis.[15,18,22] As the increase in cancer risk in the IARC report was related to the amount of meat consumed, available data did not permit a conclusion regarding the existence of a safe level.[15]

Mechanism associated with carcinogenicity

Although there is a lack of clarity regarding the mechanism involved in colon carcinogenesis, evidence points towards certain compounds found in meat itself as well as in processed meat.[2, 15] Red meat consists of compounds such as haem iron (HI) that facilitates the endogenous formation of N-nitroso compounds (NOCs) such as nitrosylated haeme iron,[24,30] catalysing its formation from natural precursors in the gastrointestinal tract (GI),[2,20,25,26] as well as through lipid peroxidation in the GI.[2,18] In addition, HI can induce oxidative stress,[26] colonocyte proliferation through the lipid–peroxidation pathway[17,20,28] and induce the production of genotoxic free radicals in the colonic stream.[26]

The carcinogenic compounds that form during processing and cooking include NOCs and polycyclic aromatic hydrocarbons (PAHs).[2,15,26,29] NOCs are introduced exogenously from nitrates

and nitrites added during the preservation process[20,29] but can also be formed endogenously[20,26,29] as alluded to previously. In processed meat, HI is nitrosylated because curing salt contains nitrate or nitrite. There is evidence that nitrosylated HI promotes carcinogenesis at doses that are five to six times lower than non-nitrosylated HI.[14]

Cooking red or processed meat at high temperatures such as during pan frying or direct grilling over an open flame produces mutagens such as PAHs and heterocyclic aromatic amines (HAAs),[2,15,19,20,38] also found in other foods, cigarette smoke and car exhaust fumes.[2,15] HAAs are genotoxic and the extent to which HAAs' conversion to genotoxic metabolites occurs as a result of amino acids and creatinine reacting at high cooking temperatures is higher in humans than in experimental animals such as rodents.[2] HAAs become DNA alkylating agents, inducing DNA mutations after activation by various metabolising enzymes.[20] The intestinal microbiote adapts to meat intake and HAAs. As a result, HAAs might be more genotoxic in those with a high meat intake. However, the majority of studies investigating meat and phenotype interactions are not convincing. It is probable, though, that heat-induced mutagens found on the surface of well-done red meat can cause colon cancer in those with a genetic predisposition.[26]

NOCs, PAHs and HAAs are considered to be genotoxic by acting directly on DNA, causing point mutations, deletions and insertions.[17] However, there is little direct evidence that this occurs following meat consumption.[2] A high consumption of HI (but not other forms of iron), NOCs, HAAs and PAHs has been associated with an increased risk of colorectal tumours, albeit with a few exceptions.[19,29] Genetic variations in NOCs' and HAAs' metabolism may alter the relationship between the consumption of red meat and the risk of developing colon cancer.[19] However, there is substantial supporting mechanistic evidence regarding HI, NOCs and HAAs being involved in colon carcinogenesis.[19,31,32] A high consumption of red meat (300–420 g/day) increased levels of DNA adducts, presumed to be derived from NOCs, in exfoliated colonocytes or rectal biopsies.[31,32]

Impact of cooking methods on carcinogenicity

Although high-temperature cooking methods generate compounds that may contribute to carcinogenic risk, their role in carcinogenesis is not yet fully understood.[15] What is known is that consuming well done cooked meat increases the bacterial mutagenicity of human urine.[2,33] Despite the fact that cooking improves the digestibility and palatability of meat,[2] carcinogenic compounds are produced when meat is heated beyond 100°C (205°F), when it is cooked directly over an open flame such as barbecuing, grilling or over a hot surface such as pan frying.[2,26,27] These cooking methods are associated with producing the largest amounts of carcinogens that include PAHs and HAAs,[2,15,20,26,29,34,35] with levels varying according to meat type, temperature, cooking time and method.[18,29] As a result, the consumption of well-done grilled meat (heated to 71.1°C/160°F or higher) has been reported to be associated with the highest risk of colorectal cancer.[18] Insufficient data resulted in the IARC Working Group being unable to conclude whether the cooking method of meat affects cancer risk.[15] A possible reason why studies investigating carcinogen formation during the cooking of meat was inconclusive could be related to interactions with genetic polymorphisms such as the acetylator phenotypes, as well as difficulties in assessing dietary carcinogen intake.[24] When comparing the burden of disease estimate attributed to red meat consumption prepared according to different cooking methods, the cooking method that led to the largest health loss due to colorectal cancer was barbecuing/grilling, followed by pan frying.[29]

Current public health recommendations to reduce the risk of colon cancer

The evaluation conducted by the IARC reinforces a previous recommendation by the WHO that those who eat red meat should consume processed meat in moderation to reduce the risk of colorectal cancer. Other dietary guidelines also recommend limiting the consumption of red or processed meat but are predominantly focused on reducing the intake of fat and sodium as risk factors for cardiovascular disease and obesity. Hence, recommendations that address cancer risk could consider the introduction of a guideline that promotes a reduction in the consumption of red or processed meat until updated guidelines specifically related to cancer prevention have been developed.[15]

The World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) recommendations are to limit the consumption of red meat to less than 500 g/week and to avoid processed meat (0 g/week). However, the choice of these limits was not clearly substantiated in the report.[29] The 4th European Code against Cancer Working Group developed recommendations in order to reduce cancer risk. The guideline related to consuming a healthy diet includes a recommendation stating: 'avoid processed meat; limit red meat and any foods high in salt'.[36]

The Food-based Dietary Guideline for SA that refers to the consumption of meat[37] recommends that no more than 560 g of red meat should be consumed on a weekly basis. This equates to a daily intake of 80–90 g. However, there are no guidelines or recommendations regarding the consumption of processed meat.

Avoidance of red and processed meat

Due to the relationship between the consumption of processed meat, and in certain studies a combination of red and processed meat referred to as total meat intake,[18,23] and the development of colon cancer, the question that arises is: Should vegetarian diets not be actively promoted as part of public health messages that promote health? In shaping this decision, consideration should be given to the fact that vegetarian diets versus those that include meat have different health-related advantages and disadvantages. The IARC evaluation did not directly compare the health risks associated with following a vegetarian diet compared with eating meat. In addition, a comparison of this nature is difficult because vegetarians can differ from non-vegetarians in ways other than just the consumption of meat.[15] However, data from the Adventist Health Study showed that non-vegetarians had an increased risk for colorectal cancer when compared with vegetarians.[38] It should, however, be remembered that red meat is a source of high biological value protein and micronutrients such as vitamin B6, B12, iron (free iron and haem iron), selenium and zinc.[1,2,15,20] In addition, the nature and content of fat in red meat varies according to breed, age, gender, feed and the cut of meat.[2, 20] To facilitate optimal health, non-vegetarian consumers should be educated to choose lean cuts of meat and consume them in moderate amounts as per the eighth Food-based Dietary Guideline of SA: 'Fish, chicken, lean meat and eggs can be eaten daily'.[37]

Conclusion

A recent review by the IARC that investigated the relationship between consuming red and processed meat and the development of colon cancer sparked renewed global interest when red meat was labelled as a probable cause, while processed meat was classified as carcinogenic. Although the factors that

contribute to the development of cancer are multifactorial, the local incidence of colon cancer as well as meat consumption patterns should be assessed on a regular basis as a transitional developing country like South Africa which is characterised by urbanisation, nutrition transition and the adoption of a Westernised lifestyle. Another factor that could affect the eating habits of SAs is food prices. As processed meats are generally more affordable than red meat and chicken, local food-based dietary guidelines should also be reviewed on a regular basis to ensure that they are evidence based and in line with the changing eating habits of SAs.

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