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RESEARCH PAPER

Ascertaining Carcinogenicity of the Consumption of Red Meat and Processed Meat:

A scoping review of epidemiological studies

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ABSTRACT:

BACKGROUND: Today, more than ever, the consumption of red and processed meat has been largely proposed as evidence for the development of cancer in humans, especially in those populations consuming a western diet. The determination of this causation, specifically by red or processed meat, is contingent on the identification of plausible mechanisms that lead to the incidence of cancer.

PURPOSE: To critically appraise current literature underlying the epidemiological relationship of the intake of red and processed meat with the risk of cancer.

METHODS: A systematic review was conducted using literature published from 1990-2018, selected from various data sources: PubMed, Springer Nature, Science Direct, and Wiley Online Library.

RESULTS: The carcinogenicity of red meat intake was reviewed through 16 studies that met the specified inclusion criteria. Most of these studies were designed to examine the role of heterocyclic amines (HCA) and polyaromatic hydrocarbons (PAH) in relation to breast and colon carcinogenesis, haem iron as a promoter of carcinogenesis, and high fat content. Additionally, the role of sodium nitrite, nitrate and N-nitroso compounds (NOCs) and gene mutations were discussed as causative factors in developing the risk of cancer for subjects consuming both red and processed meat. Each study was graded [either 1, 2 or 3] to assess the overall study quality based on a set criterion for grading evidence for cancer prevention from the Third Expert Report of the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) grading criteria.

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Of the sixteen studies included, eight were graded as (1) providing strong evidence to support a convincing relationship, a further seven were graded as (2) supporting a convincing causal relationship but limited in amount or by methodological flaws, and one study was graded (3) as providing insufficient evidence to support a judgement that a particular lifestyle factor relating to diet (i.e., meat consumption) is unlikely to have a substantial casual relationship to cancer.

CONCLUSIONS: High meat intake (cooked and processed red meat) may increase the risk of cancer incidence. This is through various hypothesised mechanisms and pathways that have a detrimental effect on the development of the likelihood of cancer. The limitations of the study involve the risk of bias due to constraints, adjustment for confounders and recall bias in dietary assessment. Studies that have supported an association suggest changes in dietary habits with less frequent consumption of red meat; this may be a useful observation for planning a cancer preventative diet in the future.

KEYWORDS: *Diet; Carcinogenesis; Meat intake; Red meat; Processed meat; Haem iron; Carcinogens; Meat mutagens; Anti-carcinogens*

INTRODUCTION

Scale of the Problem

Cancer is clinically defined as a "set of diseases characterised by uncontrolled and unregulated cell growth leading to the invasion of surrounding tissues and spread (metastasis) to other parts of the body" (Chung *et al.*, 2005). In 2018, an estimated 18.1 million new cases were diagnosed worldwide (Bray *et al.*, 2018), with breast cancer accounting for 9.6 million (Bray *et al.*, 2018; Parkin *et al.*, 2001). Similar reports were estimated for prostate cancer cases, with approximately 1,276,106 new cases reported causing 357,989 deaths in men worldwide (3.8% of all deaths caused by cancer in men) (Figure 1).

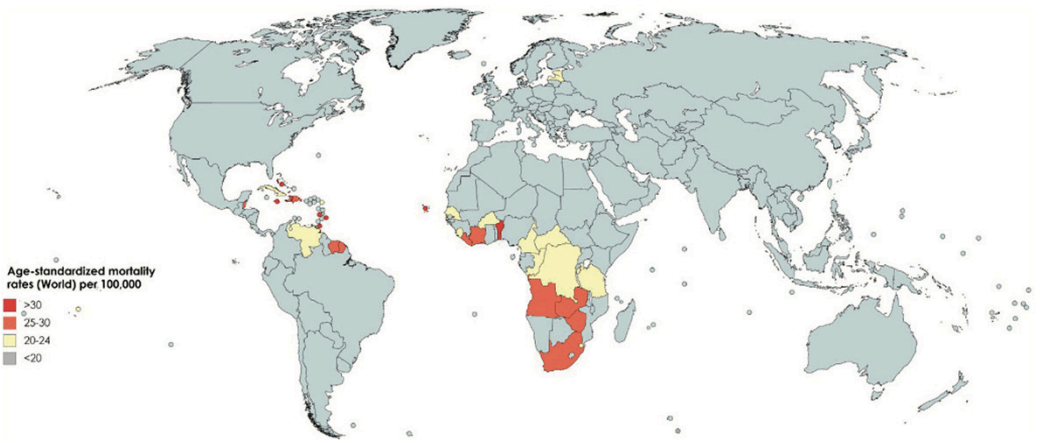

Figure 1: Map to Show Estimated Age-standardised Mortality Rates Amongst Males of All Ages for Prostate Cancer Worldwide in 2018

Source: Data obtained from Globocan 2018 (Bray *et al.*, 2018)

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Gastric cancer (GC) remains the second leading cause of cancer death in both sexes worldwide (Jemal *et al.*, 2011; Kamangar *et al.*, 2006). The distribution of GC incidence displays heterogeneity across the world. Of the estimated 1 million new cases per year, approximately 50% occur in Eastern Asia (Jemal *et al.*, 2011). Colorectal cancer (CRC) results in 60,000 deaths annually and is the third most frequently diagnosed cancer worldwide (Chan *et al.*, 2011). In 2017, The Global Burden of Disease Project estimated 11 million deaths were attributed to diet factors alone, with 913,000 of those cancer related (Hay *et al.*, 2017). The risk of cancer is dependent on environmental, lifestyle and dietary factors (Arnold *et al.*, 2015; Zhang *et al.*, 2012) with incident rates accumulating in developing countries, including Latin America, Asia and Eastern Europe (Figure 2).

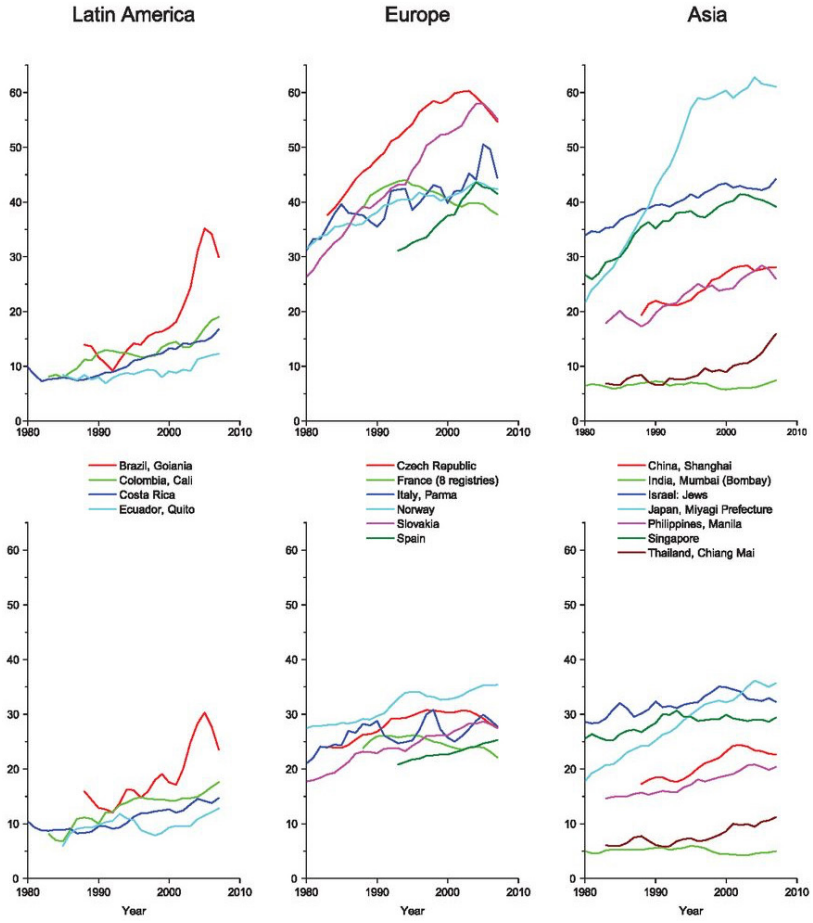

Figure 2: Incidence Trends of Colorectal Cancer (CRC) in Selected Countries, 1980-2007
Source: Torre *et al.*, 2015

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Meat Intake in Relation to the Risk of Cancer

The risk of cancer may be dependent on environmental factors, for example, the addition of dietary pattern foods into traditional dietary habits as part of broader, societal socio-economic changes (Nomura *et al.*, 1985). Dietary factors account for approximately 30% of cancers, including colorectal and breast cancer, making diet the second preventable cause of cancer (Doll and Peto, 1981; Key *et al.*, 2002). As estimated by the World Cancer Research Fund (WCRF), a third of common neoplasms can be prevented by a change in lifestyle and dietary habits (Latino-Martel *et al.*, 2016). Being able to reach a diversified palate and diet should be a key modifiable risk factor in the primary prevention of cancer (Latino-Martel *et al.*, 2016).

At a global level, the average per capita consumption of total meat is continuing to rise as a result of both average individual incomes and population growth (FAO, 2017). Processed food products are perceived to be microbiologically safe (Luiten *et al.*, 2015; Monteiro *et al.*, 2017), but are lacking in both vitamin and fibre density (Fiolet *et al.*, 2018). Notably, meat is a key source of both water and fat, and consists of 20-35% protein, providing all essential amino acids (lysine, threonine, methionine, phenylalanine, tryptophan, leucine, isoleucine and valine) as well as adequate amounts of micronutrients (i.e., iron, zinc and selenium) (Górska-Warsewicz *et al.*, 2018). However, the World Cancer Research Fund (WCRF) report published in 2007 raised considerable alarm about the cancer risks associated with red and processed meats, concluding that they are a combining cause of cancer (Marmot *et al.*, 2007).

In addition to health consequences, it has been identified that red and processed meat consumption is strongly connected with environmental concerns, including high greenhouse gas emissions (GHG), global diversity loss and pollution of water and lands (Tilman and Clark, 2014). It is estimated that livestock is responsible for approximately 14.5% of GHG emissions, causing an adverse impact on climate change (De Haan, 2006). Meeting the global challenge of consuming less meat could reduce GHG emissions whilst still meeting dietary requirements for well-being (Macdiarmid *et al.*, 2012; Yip *et al.*, 2013; Soret *et al.*, 2014; Biesbroek *et al.*, 2014). To achieve a reduction in GHG emissions, it is urgent that dietary habits change. One of the 10 universal guidelines for healthy nutrition is limiting the intake of red meat to less than 500g per week (equivalent to 70g prepared/d) with very little, if any, processed meat; these guidelines are a result of the "convincing evidence" for an association with an increased risk of colorectal cancer (CRC) (Marmot *et al.*, 2007).

Possible Mechanisms by which Meat Could Increase the Risk of Cancer

A number of potential mechanisms and relevant pathways have been suggested in promoting carcinogenesis through the consumption of meat. One mechanism proposed is exposure to carcinogens (i.e., heterocyclic amines (HCAs) and/or polycyclic aromatic hydrocarbons (PAHs) as a result of high-temperature cooking that may promote the proliferation of cancerous cells. Other

causative factors include haem iron as a promoter of carcinogenesis (Santarelli *et al.*, 2008; Marmot *et al.*, 2007), and high saturated fat content and dietary cholesterol. Additionally, it is suggested that sodium nitrite, nitrate and N-nitroso compounds (NOCs) and genetic mutations in specific subtypes (i.e., colon and rectal subtypes) contribute to the development of the risk of cancer for subjects consuming both red and processed meat. If the primary mechanisms are established, it may be possible to alleviate the cancer load by modifying the processes that lead to carcinogenic formation. A summary of possible approaches is illustrated below (Figure 3).

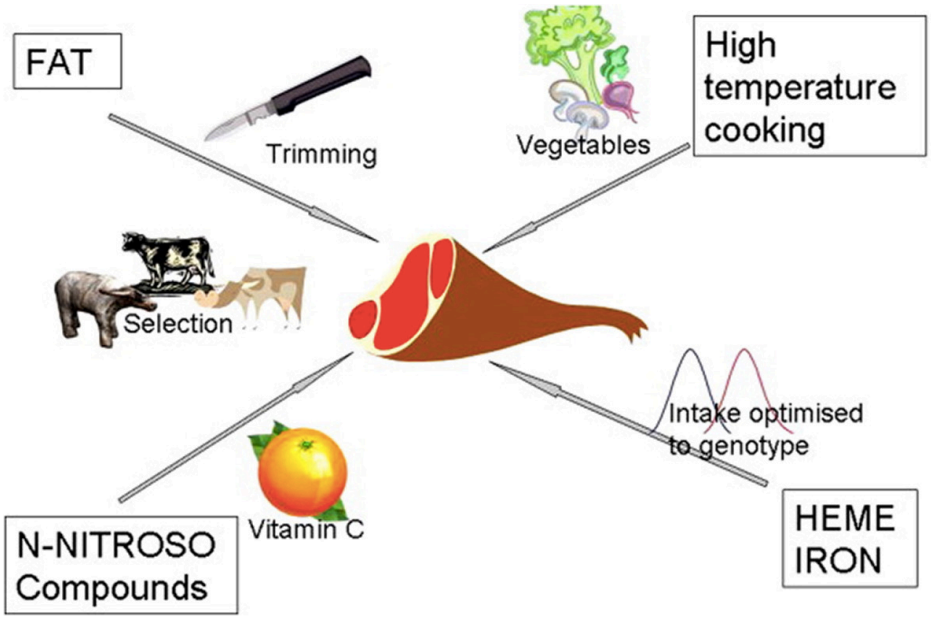

Figure 3: Key Mechanisms Hypothesised to Increase Cancer Risk and Possible Approaches to Reduce Cancer Risk From Red and/or Processed Meat

Note: Possible approaches include the inclusion of dietary components (i.e., anti-carcinogens) as part of a diversified palate to protect against potential cancer risks.

Source: Ferguson, 2010

RESEARCH AIMS AND OBJECTIVES

Aims: The following systematic review aims to critically appraise existing literature to ascertain the relationship between meat [red and processed] intake and carcinogenesis through relevant mechanisms and suggested pathways.

In order to achieve this overall aim, the key objectives for this systematic review are:

- **Primary Objective:** To identify potential carcinogenic compounds in red and processed meat and their mechanism of action based on current scientific literature.

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- **Secondary Objective:** To situate the health risks associated with red and processed meat intake within the context of its potential benefits in order to better assess the overall impact on human health and well-being.
- **Third Objective:** To devise key mechanism(s) underlying the epidemiological relationship of meat [red and processed] consumption with cancer incidence in order to outline recommendations to solve or at least minimise the problem.

METHOD

Selection of Studies

A systematic search was conducted for publications on red and processed meat and cancer risk using electronic databases: PubMed, Springer Nature, Science Direct, and Wiley Online Library. The following key words were used: Diet; Cancer; Meat intake; Red meat; Processed meat; Haem iron; Carcinogenesis; Carcinogen compounds; N-nitroso compounds; Anti-carcinogens. The initial search was broad to include all appropriate publications. The inclusion and exclusion criteria on which the search was based are displayed in Table 1 below.

Table 1: Study Inclusion and Exclusion Criteria

Inclusion	Exclusion
Range of studies: i.e., epidemiological, ecological, observational, meta-analyses and RCTs	Subjects <18
Conducted from 1990s-2018	Conducted before the 1990s
Published in the English language	Not published in English language/Abstract-only publications
Short-term and long-term studies included	Non-human/Animal studies
Studies based worldwide	Studies with a different topic and no cancer outcome
Potential carcinogen compounds (i.e., nitrite, nitrate, haem iron, heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs) and N-nitroso compounds (NOCs))	Non-carcinogenic compounds

Source: Compiled by authors

A flow diagram was used in regard to the study selection for both red meat (Figure 4) and processed meat (Figure 5) separately following the inclusion and exclusion criteria illustrated above. In total, 16 studies were identified for analysis. Of this, ten studies were included to analyse for red meat and six studies were included for processed meat.

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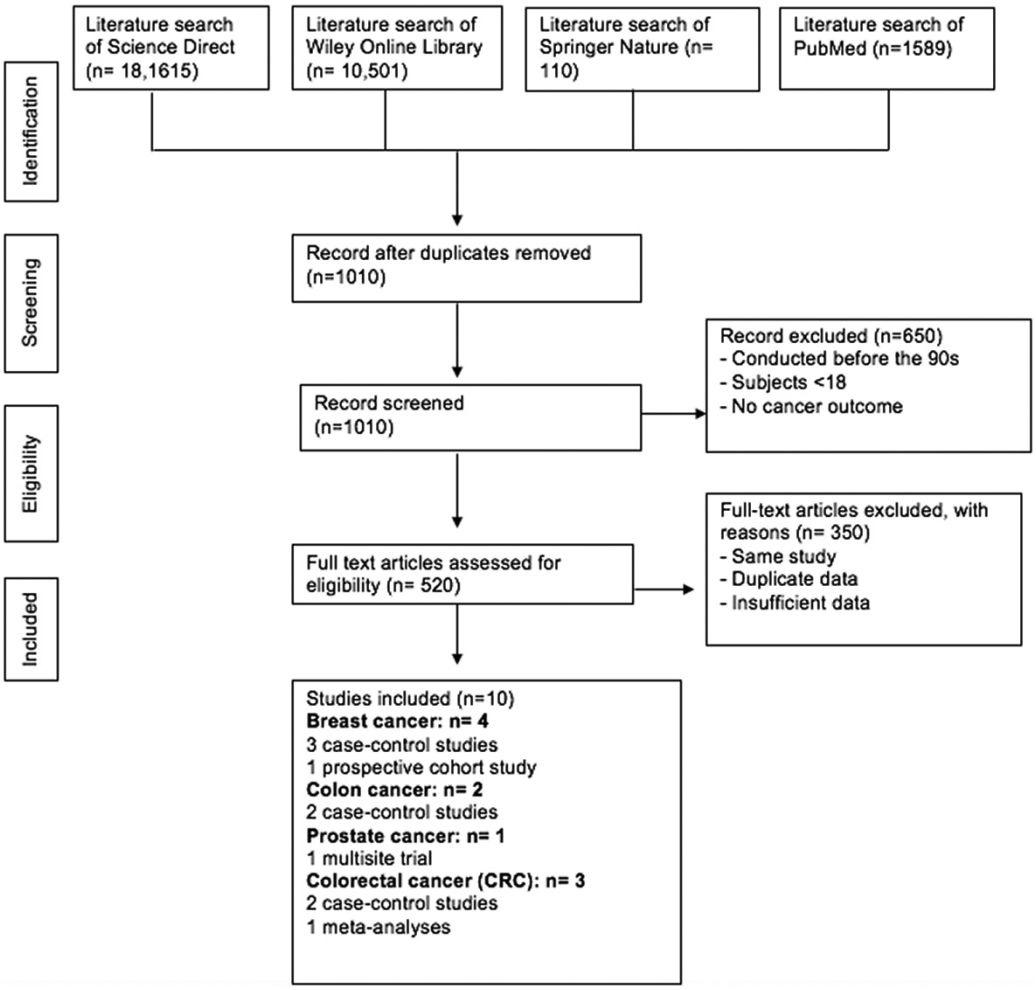

Figure 4: Flow-chart of Red Meat Study Selection

Source: Constructed by authors

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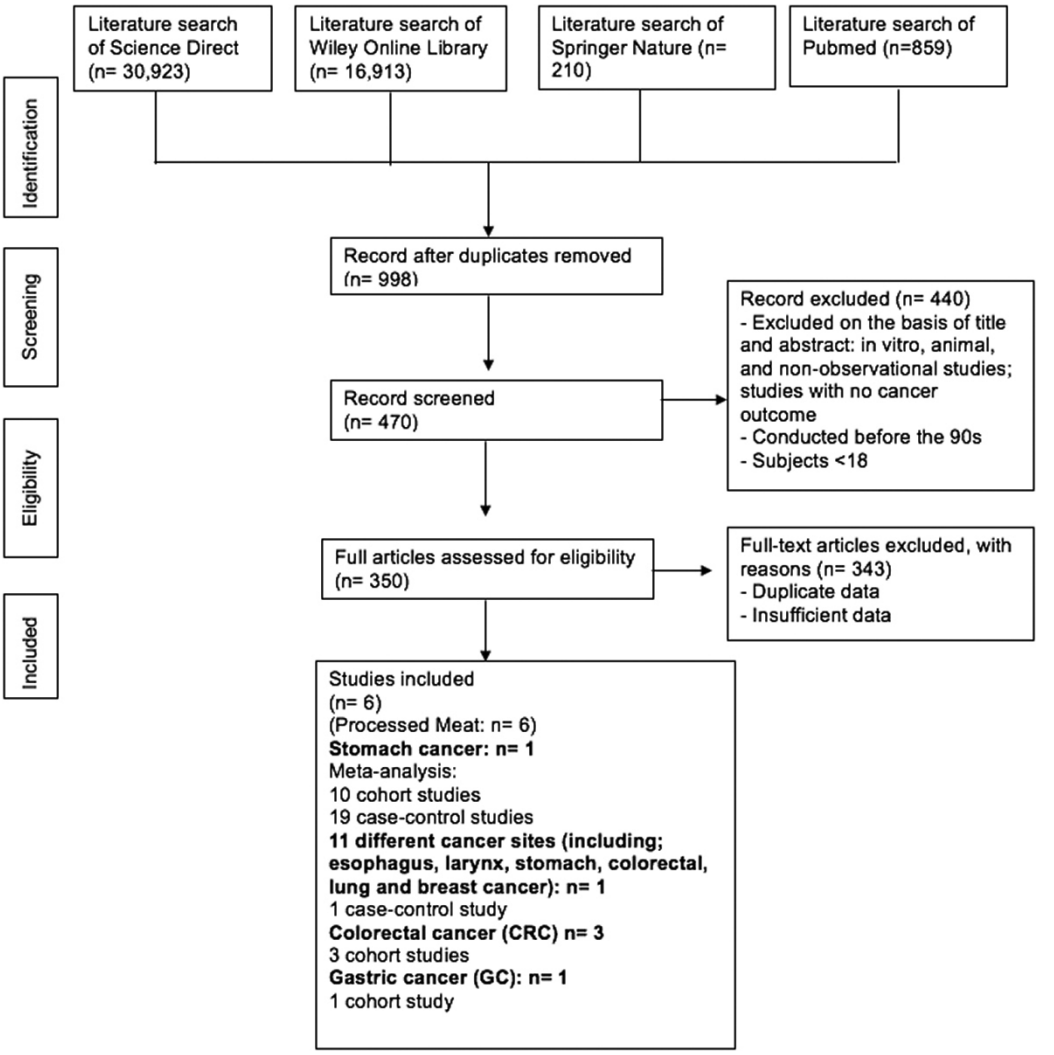

Figure 5: Flow-chart of Processed Meat Study Selection

Source: Constructed by authors

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Data Interpretation/Analysis

Each study was critically appraised according to its aims, objectives, method and outcomes. The applied score (either 1, 2 or 3) was based on the quality of the study. A defined scoring system was created and adapted to assess the overall study quality based on a set criterion for grading evidence for cancer prevention from the Third Expert Report of the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) grading criteria (Demeyer *et al.*, 2008). The grading criteria were slightly modified by selecting three definitions of WCRF/AICR grading criteria and numerically labelled 1-3 to assess study design quality (Table 2).

Table 2: Study Design Quality Grading Criteria

Score	Explanation	Type of Study
1	Evidence is strong enough to support a judgement of a convincing or probable causal (or protective) relationship.	A score of 1 was given to studies with an acceptable design, an adequate number of participants, high significance (P = <0.05), minor flaws, long follow-up period (>5 years) and lower likelihood of bias. A score of 1 was also given to studies strong enough to support a judgement of a convincing or probable causal (or protective) relationship. Type of studies included prospective, case-control.
2	Evidence is inadequate to support a probable or convincing causal (or protective) relationship. The evidence may be limited in amount or by methodological flaws, or there may be too much inconsistency in the direction of effect (or a combination), to justify making specific public health recommendations.	Given to studies with an acceptable design, but where evidence is inadequate to support a probable or convincing causal relationship. A score of 2 was also given to studies that were limited by methodological flaws such as low sample size, only one gender tested, dietary data collection. A score of 2 was also awarded to studies where quality control could have been improved (e.g., more information on how data were collected) and likelihood of bias. Type of studies included case-control (subject to bias).
3	Evidence is strong enough to support a judgement that a particular lifestyle factor relating to diet is unlikely to have a substantial causal (or protective) relationship to cancer outcome.	Studies that lacked clearly defined aims and objectives, had missing data, methodological flaws and a short follow-up time period (<5 years) and did not support a relationship or causal factor in relation to cancer outcome. Type of study included cohort.

Source: Adapted from Demeyer *et al*., 2008

RESULTS

Results were divided into two parts: Part I (Table 3) focuses on appraising published literature concentrating on red meat and carcinogenicity; Part II (Table 4) concentrates on appraising published literature focused on processed meat and carcinogenicity.

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Part I

Table 3: Summary of Studies Selected of Red Meat and Cancer Risk (n = 10)

Author, Year, Study	Aims and Objectives	Method	Outcomes (95% CI) (RR = Relative Risk) (HR = Hazard Ratio) (OR = Odds Ratio)	Critical Review (+ = Strength) (- = Weakness)	Score (1-3)
Dai *et al.*, 2002	Aimed to evaluate the association of breast cancer risk with consumption of animal foods (i.e., meat) in a population with a traditionally low risk of breast cancer.	Retrospective study, data used from the Shanghai Breast Cancer Study (population-based case-control study) consisting of Chinese women in Shanghai (25-64). 1,459 cases included and 1,556 age-frequency-matched controls Red meat included: pork, beef, and lamb; white meat included poultry.	Increasing intake of red meat associated with a moderately elevated risk of breast cancer risk (P = 0.002). Stratified analyses concluded that the positive association with red meat was restricted to those who used deep-frying cooking methods, particularly those who used deep-fried foods to well-done (OR, 1.92; 95% CI, 1,20-2.83 for the highest *versus* lowest quintile; *P* for trend, 0.002) Positive association of breast cancer risk with red meat intake was more pronounced among women with a high body mass index (BMI) compared to those without this risk factor (P = 0.01)	**Strength:** + Provides an opportunity to compare the association of the type of oil used (i.e., non-hydrogenated soybean oil) and breast cancer risk by cooking method. + Recall bias by treatment is unlikely as a rapid case-reporting system was used to complete an in-person interview for nearly half of the cases to those were interviewed before any treatment. The positive association with well-done meat intake was stronger in this subset than others (e.g., deep-fried) suggesting a small potential differential recall bias. + Study is population-based and had a high response rate, therefore minimising potential selection bias. + Large sample size, providing adequate statistical power to investigate potential interactions. **Weakness:** - FFQ used: Misclassification errors (differential and non-differential) in exposure assessment: due to cancer diagnosis and treatment, diets of cases may have changed, and current diet may influence the recall of usual diet.	**1**
Butler *et al.*, 2003	Aimed to examine the association between meat intake with colon cancer in terms of cooking method, doneness, and levels of heterocyclic amines (HCAs), benzo(*a*) pyrene, and mutagenicity.	Population based case-control study of colon cancer in North Carolina (1996-2000). Included 701 African American (274 cases, 427 controls) and 957 white (346 cases, 611 controls) participants 150-item FFQ used to measure dietary intake over the year prior to diagnosis.	Association strongest for pan-fried red meat (OR = 2.0, 95% CI: 1.4, 3.0). Associations with meat intake by doneness were strongest for well-/very well done red meat (OR = 1.7, 95% CI: 1.2, 2.5). The strongest association for individual HCAs was reported for 2-amino-3,4,8-trimethylimidazo[4,5-f] quinoxaline (DiMelQx) across all levels of exposure (OR 1.8-2.0). P = <0.01	**Strength:** + Ethnically diverse population included. + One of the largest studies of colon cancer among African Americans, who have a higher CRC incidence and mortality than whites in United States. **Weakness:** - Misclassification of exposure (study did not incorporate meat doneness photographs in their exposure assessment. - Potential sources of bias (i.e., differential recall bias) that could result in OR biased towards or away from the null value. - Selection bias- indicated by an overall response rate (number interviewed/number eligible) of 61%, with a 16% greater response among cases than controls.	**2**

De Stefani *et al.*, 1997	To study how the intake of meat causes the risk of breast cancer through the formation of heterocyclic amines.	Hospital-based case-control study conducted in Uruguay involving 352 patients with breast cancer and 382 controls.	A high intake of fried meat associated with an increased risk of breast cancer than broiled (grilled) meat (OR = 2.71; P<0.001) that only showed a marginal increase in risk. However, was associated with a significant reduction in risk for the uppermost quartile of consumption (OR, 0.42)	**Strength:** + Study provides support to the carcinogenic effect of heterocyclic amine exposure in breast cancer. Previous studies on other cancer sites (colon and lung) are only partially supportive as suggested exposure of heterocyclic amines was due to the cooking method (frying or broiling), whereas the current study combined both the cooking method and estimated content of heterocyclic amines in the diet. **Weakness:** - However, patients were hospitalised, therefore effect of the disease may be modified by the usual diet, which leads to the under- or over-estimation of results.	**2**
Cross *et al.*, 2005	Aimed to examine whether meat intake or meat-related mutagens, particularly PhIP, was associated with prostate cancer risk.	Prospective cohort study Conducted in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, an RCT/ Multisite study. During follow-up, a total of 1,338 prostate cancer cases among 29,361 men ascertained Diet was assessed using a 137-item FFQ and a detailed meat-cooking questionnaire linked to database for BaP and the HCA 2-amino-3,8-dimethylimi- dazo[4,5-b] quinoxaline (MeIQx), 2-amino-3,4,8-trimethylimi- dazo[4,5-f] quinoxaline (DiMeIQx), and PhIP.	>10 g/d of very well-done meat, compared with no consumption, was associated with a 1.4-fold increased risk of prostate cancer and a 1.7-fold increased risk of incident disease No association with MeIQx and DiMeIQx, The highest quintile of PhIP was associated with a 1.2-fold increased risk of prostate cancer (highest versus lowest quintile RR, 1.22; 95% CI, 1.01-1.48; *P* = 0.04) and incident disease (highest versus lowest quintile RR, 1.28; 95% CI, 1.01-1.61; *P* = 0.01).	**Strength:** + Detailed information on screening procedures that could be used to control for screening frequency. + Detailed information on meat and meat-cooking practices that enabled the determination of HCA and BaP intake. **Weakness:** - Measurement errors using FFQ. - Although questionnaire used was very detailed, authors did not consider marinating or flipping of hamburgers, both of which can affect the formation of HCAS and BaP. - Although considered a large number of potential confounders, cannot be certain that all confounding variables were identified as prostate cancer is a disease with a few known risk factors.	**1**

(continued)

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Table 3: Summary of Studies Selected of Red Meat and Cancer Risk (n = 10) *(continued)*

Author, Year, Study	Aims and Objectives	Method	Outcomes (95% CI) (RR = Relative Risk) (HR = Hazard Ratio) (OR = Odds Ratio)	Critical Review (+ = Strength) (- = Weakness)	Score (1-3)
Larsson *et al.*, 2005	Aimed to prospectively examine whether the association of red meat consumption with cancer risk varies by subsite within the large bowel.	Population based prospective study using 61,433 subjects from The Swedish Mammography cohort aged 40-75 years without any form of cancer at baseline in 1987-1990.	Significant positive association between red meat consumption and risk of distal colon cancer (p for trend = 0.001) but not of cancers of the proximal colon (p for trend = 0.95) or rectum (p for trend = 0.32). Weak inverse association of poultry consumption with colorectal cancer risk (RR = 0.75, 95% CI 0.55-1.02) compared to women who rarely or never consumed poultry	**Strength:** + Supports the idea that a high consumption of red meat increases the risk of colorectal cancer as it was observed that increased risk may be distal colon specific related. + Population-based design: Results can be generalised. + Specific sites within the colon were examined separately and the Swedish Cancer Register system made it possible to identify all CRC incident cases that occurred in the cohort. **Weakness:** - Meat consumption self-reported by questionnaire: Misclassification of exposure inevitable that may cause bias towards the null. - Inability to control for physical activity.	**1**
Sørensen *et al.*, 2008	Aimed to investigate the relationship between polymorphisms in NAT1 and NAT2 and risk of CRC	Meta-analyses of 160,725 individuals aged 50-64 among a cohort of 57,000 members were assessed from the Diet, Cancer and Health (DCH) prospective follow-up study.	Higher risk in those frying their meat brown to dark (RR =1.36; 95% CI 1.04-1.77) than light to light brown. There were no statistically significant interactions between the different meat types and *NAT1 or NAT2* in relation to risk of CRC (*p* for interaction >0.30 for all analyses).	**Strength:** + Prospective nature: low risk of recall and selection bias as both cases and their comparison group were selected from same cohort. + Low likelihood of information loss: Meat consumption was used as a continuous variable rather than categorical resulting in a higher statistical power. **Weakness:** - Dietary assessment used- FFQ used over the preceding year within 12 possible categories ranging from never to 8 times or more per day.	**2**

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Norat *et al.*, 2005	Aimed to investigate the risk of colorectal cancer (CRC) associated with red and processed meat consumption	Prospective study (EPIC): Followed large Western European population that includes half a million subjects from 23 centres from 10 European countries: The European Prospective Investigation into Cancer and Nutrition (EPIC). Baseline 1992-2000 Follow up 1998-2002 478,040 subjects (men and women) included in analysis. Diet measured between 1992 and 1998 by country-specific validated questionnaires.	There were no significant effects of intake of red meat, total red meat or poultry on CRC risk. Subgroup analysis: No significant difference in CRC risk for highest vs. lowest intake of meat from beef/veal, pork or lamb, but a significant trend for pork (p for trend = 0.02) and for lamb (p for trend = 0.03)	**Strength:** + Findings support the hypothesis that CRC is positively associated with high consumption of red and processed meat and inversely associated with the intake of fish. **Weakness:** - Measurement errors of food intake lead to the attenuation of the disease risk estimates; attempted to correct for this measurement error by adjusting for self-reported total energy intake. - Study assumed no correlation of errors produced by 24-hour diet recall and the dietary questionnaire. However, in practice, individual errors of dietary measurements (24-hour recall and questionnaire) tend to be positively correlated. This would lead to an underestimation of the de-attenuation factor and therefore would bias the hazard ratio estimates towards the null value of 1.	2
Kallianpur *et al.*, 2008	Aimed to evaluate the association between dietary iron intake from various food sources and breast cancer risk, as well as interactions between dietary iron and fat intake.	Case-control study using data collected from a large cohort of women who participated in the Shanghai Breast Cancer Study	Animal-derived (largely haem) iron intake was positively associated with breast cancer risk (P<0.001; OR = 1.49 in the highest vs. lowest quartile). Intake of animal-derived fats associated with increased risk (OR = 1.34). A significant interaction between iron and fat from animal sources was observed (P<0.001).	**Strength:** + Significant increases were found with a high daily intake from animal sources and primary breast cancer. + Results supported by recent studies. + Potential of selection bias exists in study but is unlikely to have affected the results as the overall high participation rates were high among both cases and controls in study. + Carefully adjusted for antioxidant vitamin and isoflavone intake and regular use of vitamin supplements, as well as for known breast cancer risk factors. + Population-based design. + Large sample size and participation rate minimised potential for selection bias. + Study had sufficient power to investigate interactions between animal-derived iron and fat, for which a biologically plausible mechanism exists. **Weakness:** - Cannot exclude the possibility of confounding variables by other dietary factors; did not analyse the effects of different cooking methods.	**1**

(continued)

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Table 3: Summary of Studies Selected of Red Meat and Cancer Risk (n = 10) *(continued)*

Author, Year, Study	Aims and Objectives	Method	Outcomes (95% CI) (RR = Relative Risk) (HR = Hazard Ratio) (OR = Odds Ratio)	Critical Review (+ = Strength) (- = Weakness)	Score (1-3)
Kabat *et al.*, 2010	Aimed to examine the association of post-menopausal breast cancer with haem iron intake	Used data from large prospective study, The National Institutes of Health, AARP Diet and Health study (NIH-AARP), including 116,674 post-menopausal women. During 6.5yr of follow up, 3,396 breast cancer cases were found	HR for the highest compared with the lowest quintiles of intakes of total iron, iron from meat, iron from red meat, and haem iron all close to unity and no increasing trends with increasing intakes (HR = 1.01) (95% CI: 0.89, 1.14; P for trend = 0.97)	**Strength:** + A strength of the study was that a linked database was used to estimate exposure from meat and haem iron. Also, a detailed questionnaire was used to assess the intakes of types of meat and preparation. **Weakness:** - Intakes were based on FFQs that were subject to measurement error. An association may have not been found as quantitative information on supplemental intakes of iron (i.e., dosage, frequency, and duration) was not collected.	**2**
Lin *et al.*, 2004	Aimed to examine the association of intakes of different types of fat and fatty acids with risk of CRC	Prospective study using data from the Women's Health Study (Randomised trial) including 37,547 healthy US women aged >45 years Intakes of dietary fat and its food sources were assessed at baseline by 131-item FFQ	Intake of total fat was unrelated to risk of colorectal cancer (p for trend = 0.64) Intake of red meat was inversely associated with risk of colorectal cancer (RR = 0.66; P for trend = 0.05) Positive association between intake of fried foods and CRC risk (RR = 1.86; P for trend = 0.01)	**Strength:** + Prospective nature: Avoided selection and recall biases associated with case-control studies. + Information on a wide range of potential risk factors for CRC; this enabled authors to control for variables in analyses. **Weakness:** - Self-reporting methods subject to measurement errors (i.e., underreporting of overall intake), which may result in attenuation risk estimates. - Measurement error due to random within-person variation may be inevitable: Only assessed food and nutrient intake once at baseline. - Limited number of cases in data; low statistical power for conducting stratified analyses. - Many nutrients were tested in present study; findings may be subject to chance.	**2**

Source: Constructed by authors

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Cooking Methods, Doneness and Heterocyclic Amines (HCAs)

Heterocyclic amines (HCA) and/or polycyclic aromatic hydrocarbons (PAH) are amongst the carcinogens found in red and processed meat. The formation of these carcinogens varies by the type of meat, cooking method and "doneness" level (rare, medium, or well done). The presence of HCAs and PAHs compounds in fried/grilled meat can induce DNA damage and enhance the risk of cancer (Figure 6).

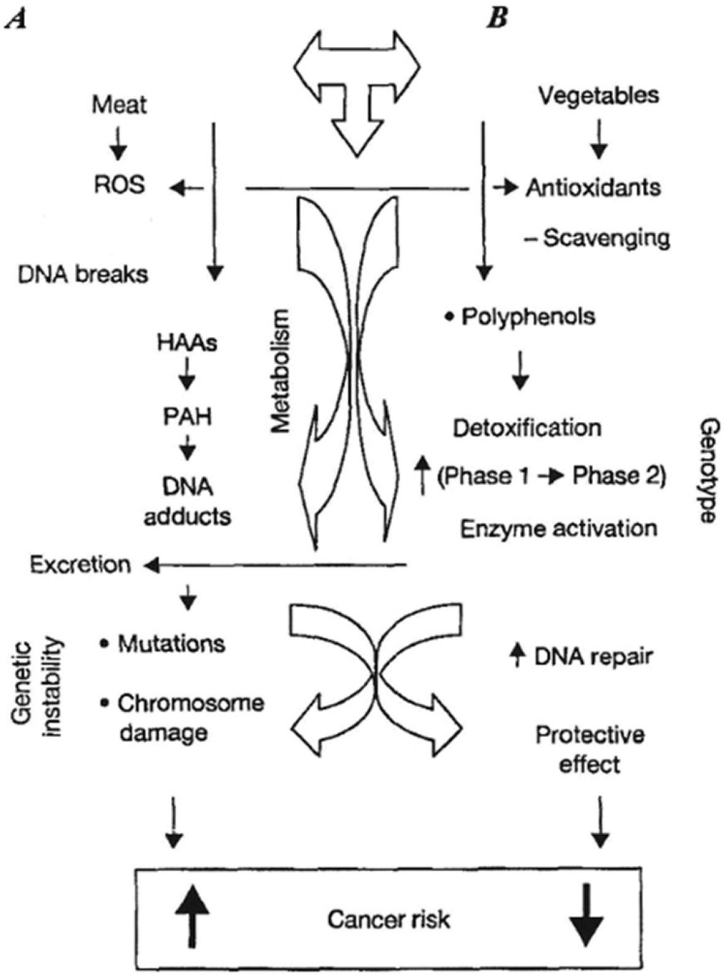

Figure 6: Consumption of Fried/grilled Meat Inducing DNA Damage and Enhancing Cancer Risk Due to HCAs and PAHs

Source: Kapiszewska, 2006

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High cooking temperatures cause amino acids and creatine to react to form a variety of HCAs (Figure 7). The most common HCAs, 2-amino-1-methyl-6-phenyl-imidazo[4,5-b]pyridine (PhIP), and 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) (Baghurst, 1999), and the most common PAH compound, benzo[*a*]pyrene (B[*a*]P), have been identified as possible human carcinogens (Baghurst, 1999; IARC, 1993; Layton *et al.*, 1995; Nagao and Sugimura, 1993). This may contribute to the development of colorectal cancer (CRC) (Joshi *et al.*, 2015). A retrospective study examined the association of total meat intake and degree of browning by deep-frying with breast cancer risk in a population-based case-control consisting of Chinese women in Shanghai (Dai *et al.*, 2002). Stratified analyses found that the positive association with red meat intake was primarily restricted to those who used deep-frying cooking methods compared to well-done (OR, 1.92; P for trend = 0.002), therefore signifying a stronger risk of breast cancer with deep frying methods (Dai *et al.*, 2002).

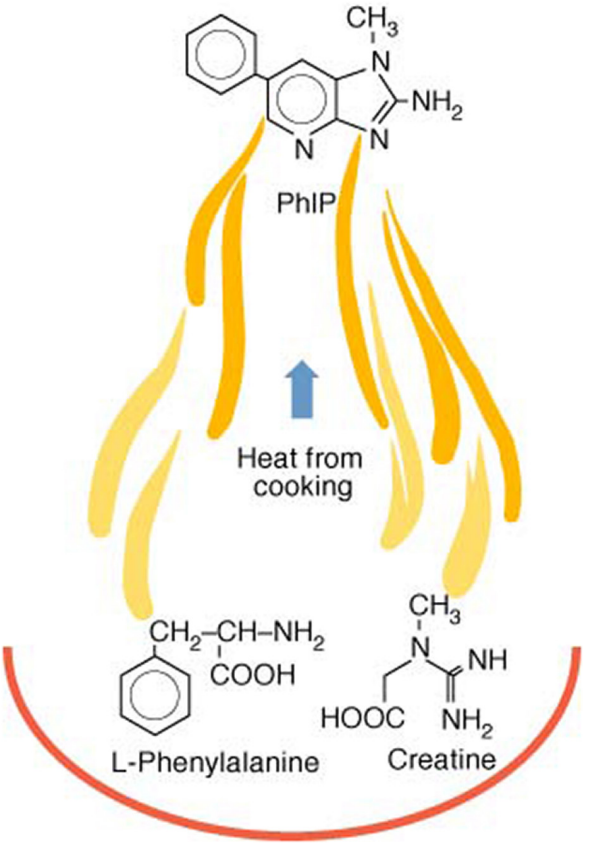

Figure 7: Diagram Demonstrating How Heat From High Temperature Cooking Forms HCA Compounds

Source: Felton and Knize, 2008

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Similarly, moderate associations were reported in a population-based, case-control study of African Americans and whites in the North Carolina Colon Cancer Study (Butler *et al.*, 2003). The authors examined the association between colon cancer and meat intake categorised by level of doneness, cooking method, and estimated levels of HCAs, B[*a*]P and mutagenicity. As observed previously, pan-fried meat had the strongest association for individual HCA, 2-amino-3,4,8-trimet hylimidazo[4,5-f] quinoxaline (DiMelQx) across all levels of exposure (OR, 1.8-2.0) (Butler *et al.*, 2003). The results suggest that the HCA, DiMelQx, may be amongst the aetiologically relevant compounds in cooked meat. The continual consumption of fried meat that contains a heavily browned surface has been observed to result in a 3-fold increase in the risk of CRC (De Verdier *et al.*, 1991).

In addition, a case-control study conducted in Uruguay reported a significant association of breast cancer incidence rates with the intake of fried meat compared to broiled (grilled meat) (OR, 2.71; P for trend <0.001). Broiled meat was associated with a significant reduction in risk for the uppermost quartile of consumption (OR, 0.42), offering protective exposure against breast cancer (De Stefani *et al.*, 1997). The follow-up of the same study reported a positive correlation with the risk of breast cancer with intake of total meat (P for trend <0.001) (Aune *et al.*, 2009). This may indicate that fried red meat produces a greater quantity of carcinogenic compounds (i.e., HCAs and PAHs) than broiled meat that consists of cooked vegetables in stew (De Stefani *et al.*, 1997). Similar findings were observed in subjects who fried their meat brown to dark brown in one meta-analysis (Sørensen *et al.*, 2008), and as a result were at a significantly higher risk of CRC (RR, 1.36; 95% CI, 1.04-1.77) compared to those who fried their meat light to light brown. This suggests the degree of cooking methods is detrimental in contributing to cancer risk.

The association between meat types, cooking methods, doneness, and meat mutagens and the risk for prostate cancer was prospectively examined in the follow-up of the Agricultural Health Study (n = 197,091) (Koutros *et al.*, 2008). The authors of this study reported that the intake of well/very well-done total meat was associated with a 1.26-fold overall increase in risk of advanced disease. Two of the common HCAs, 2-amino-3,4,8-trimethylimidazo-[4,5-f] quinoxaline (4,8-Di-MeIQx) and DiMelQx, were of borderline significance for prostate cancer risk when the highest quintile was compared with the lowest. The association of meat and meat mutagens, especially PhIP, and prostate cancer has been further investigated in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (Cross *et al.*, 2005). An intake of >10g/d of very well-done meat vs 0g/d was associated with a 1.4-fold increase in risk of prostate cancer and a 1.7-fold risk of incident disease (Cross *et al.*, 2005). The risk for those consuming >10 g/d of very well-done meat increased for both prostate cancer (42%) and incident disease (69%). This highlights a significant risk between meat mutagen (PhIP) and prostate cancer.

Although limited, the strongest evidence supporting an association with red meat intake was for colorectal cancer (CRC) (WHO, 2015). This is based on a considerable number of studies, many

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of whose conclusions are collated in three meta-analyses of case-control studies (Larsson *et al.*, 2006; Norat *et al.*, 2005; Sandhu *et al.*, 2001), with risk confined within the distal colon subsite. The Swedish Mammography Cohort (n = 61.443) examined whether the association of red meat consumption with CRC differs according to the subsite within the large bowel (Larsson *et al.*, 2005). A high red meat intake (>94 g/d) compared to low intake (<50 g/d) led to a 32% increase in risk of CRC. No association was found between processed meat intake or poultry intake and CRC (Larsson *et al.*, 2005). Over a mean follow-up of 13.9 years, the authors identified 234 proximal colon cancers, 155 distal colon cancers and 230 rectal cancers. A positive association was reported of red meat consumption with risk of distal colon cancer (P for trend <0.001) but not of cancers of the proximal colon (P for trend = 0.95) or rectum (P for trend = 0.32).

Similarly, in The European Prospective Investigation into Cancer and Nutrition (EPIC) study consisting of 478,040 men and women from 10 European countries, the risk of developing CRC within 10 years for a person aged 50 years was 1.71% for the highest category of red meat and processed meat intake (>160 g/d) and 1.28% for the lowest category (<20 g/d) (Norat *et al.*, 2005). The CRC hazard risk (HR) was observed to increase by 42% for highest (>80 g/d) versus lowest (<10 g/d) intake of processed meat (Norat *et al.*, 2005). A greater intake of red meat was associated with a borderline significant risk in cancer mortality (HR, 1.21; 95% CI, 1.00-1.46 per 100 g/d), thus supporting the above.

Haem Iron as a Promoter of Carcinogenesis

Another plausible mechanism suggested involves the content of haem iron as a promoter of carcinogenesis. Haem is the iron-porphyrin pigment of red meat and induces cytotoxicity of gut contents; this damages the epithelium of the colon surface (IJssennagger *et al.*, 2012). Haem also forms N-nitroso compounds (NOCs) and free iron that stimulates the production of free radicals leading to mutagenic environments in the body, resulting in a significant risk of breast cancer (Marmot *et al.*, 2007). In a large population-based case-control study using data collected from the Shanghai Breast Cancer Study, animal-derived haem iron intake was positively associated with breast cancer risk (P for trend <0.001; OR, 1.49 in the highest vs lowest quintile) after adjustment for known risk factors, antioxidant vitamin and isoflavone intake, and vitamin supplement use (Kallianpur *et al.*, 2008).

A meta-analysis of prospective cohort studies of colon cancer, in which haem intake had been estimated, indicated that the relative risk (RR) of colon cancer increased slightly for individuals with the highest consumption of haem iron (RR, 1.18) (Kim *et al.*, 2013). A large prospective study using data from the National Institutes of Health, AARP Diet and Health study (NIH-AARP) reported no upward trend with the consumption of red meat (HR, 1.01; P for trend = 0.97) (Kabat *et al.*, 2010). In support, the Nurses' Health Study and Health Professionals Follow-up Study observed no strong correlation between haem iron intake and incidence of CRC in an analysis of 2,114 incidence cases during a 22-year period of follow-up (Zhang *et al.*, 2011). Similar results were found in a

study conducted previously in which no association was observed between intake of iron, haem iron, or iron from meat and CRC incidence (Kabat *et al.*, 2007). Authors of the Shanghai Breast Cancer Study observed a significant interaction between iron and fat (P for trend <0.01) (Kallianpur *et al.*, 2008). The disparity between results makes the mechanism of haem iron as a promoter of carcinogenesis questionable.

High Fat Content

Another potential mechanism suggested that explains red meat intake and carcinogenicity has often been attributed to its high content of saturated fat and dietary cholesterol. The mechanism of action on carcinogenesis includes the secretion of bile acids; these have a non-specific irritant effect on the colonic lumen, thereby damaging the colonic mucosa, stimulating regeneration of the epithelium, hence elevating the risk of endogenous mutations (Chomchai *et al.*, 1974; Kinzler and Vogelstein, 1996; Narisawa *et al.*, 1974). Due to its involvement in metabolic alterations, such as insulin resistance, fat intake may also lead to risk of CRC due to changes in the fatty acid composition of the membranes (Giovannucci and Goldin, 1997). The fat content in meat may also increase the levels of oestrogen and androgen in plasma (Kelley *et al.*, 1992), weaken the immune system (Kelley *et al.*, 1992), and cause excessive fat accumulation (i.e., obesity), a risk factor for several different cancer sites (Marmot *et al.*, 2007).

To examine the association of different types of fat and fatty acids with the risk of CRC, a prospective study using data from the Women's Healthy Study examined the association of different types of fat intake and fatty acids with risk of CRC (Lin *et al.*, 2004). Among the 37,547 women eligible for the present study, the study found that 202 developed CRC during an average follow-up period of 8.7 years (1993-2003). However, no significant association was observed with either total fat intake with CRC risk (P for trend = 0.64), or intakes of the different types of fat and major fatty acids. However, an intake of red meat was inversely associated with risk of developing CRC (highest quintile vs. lowest: RR, 0.66; P for trend = 0.05). A positive association was also observed between the intake of fried meat and CRC risk (highest quintile vs. lowest: RR, 1.86; P for trend <0.01).

In addition, results from a multicentre prospective study conducted on 142,520 men considered the relationship between dietary fat intake and prostate cancer risk. They found no significant association (P for trend = 0.155) between dietary fat (total, saturated, mono-unsaturated (MUFA), and poly-unsaturated fat (PUFA) and the ratio of poly-unsaturated to saturated fat) and risk of prostate cancer (HR for highest vs. lowest quintile of total fat intake = 0.96) (Crowe *et al.*, 2008). There were also no significant associations (P for trend = 0.413) between prostate cancer risk and fat from red meat. Therefore, the results of current cohort studies provide little support for a mechanism of high fat content and possible cancer risk. However, intake of fried foods and/or other factors related to cooking methods/preparation may outline a possible association due to the formation of carcinogens, HCAs and PAHs, as previously mentioned.

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Part II

Table 4: Summary of Studies Selected of Processed Meat and Cancer Risk (n = 6)

Author, Year, Study	Aims and Objectives	Method	Outcomes (95% CI) (RR = Relative Risk) (HR = Hazard Ratio) (OR = Odds Ratio)	Critical Review (+ = Strength) (- = Weakness)	Score (1-3)
Aune *et al.*, 2009	Aimed to explore the association between meat consumption and risk of 11 cancers	Large hospital-based multi-site case-control study of 11 cancer sites in Uruguay (1994-2004) Included 3,539 cancer cases and 2,032 hospital controls.	High intake of processed meat was associated with increased risk of cancers of the oesophagus (OR = 1.63; P = 0.001), larynx (OR = 1.84, P = 0.001), stomach (OR = 1.62; P = 0.03), colorectal (OR = 2.15; P<0.0001), lung (OR = 1.70, P<0.0001) and breast (OR = 1.53, P = 0.08).	**Strength:** + Able to detect significant associations due to large dietary variation in the Uruguayan population and high meat intake. + Strong ORs found in study may reflect the very high meat intake in the population, compared to other populations (i.e., EPIC). + High participation rates: Minimises the potential for selective participation according to lifestyle practices. **Weakness:** - Possibility of recall/selection bias: Retrospective assessment of diet. If the controls of the cohort were to report their meat consumption in a different way from the general population, biased results would occur. - Selection of hospital controls are a potential source of bias; however, the diseases of the control selected in this study were unrelated to dietary factors and the controls were without recent changes in their diet.	**1**
Larsson *et al.*, 2006	Aimed to investigate the associations between the intake of processed meat and their content of N-nitrosodimethylamine (NDMA) with risk of stomach cancer	Meta-analysis of prospective data from the Swedish Mammography Cohort, a large population-based cohort (n = 61,443)	Higher consumption of processed meat, but not of other meats (i.e., red meat, fish and poultry) was associated with a statistically significant increased risk of stomach cancer (HR for highest vs. lowest category of total intake of all processed meats = 1.66; P for trend = 0.008) Inverse association of low and high poultry intake and risk of cancer (p for trend = 0.04) Stomach cancer risk was 2-fold higher among women in the top quintile of N-nitrosodimethylamine intake when compared with those in the bottom quintile (HR = 1.96)	**Strength:** + Dietary exposure information was collected from participants at 2 time points therefore was up to date. The repeated measures of the participants' diet and the population-based and prospective design allowed for a better estimate of long-term effects and a prevention of measurement error. + Population-based and prospective design: Prevented biased recall of dietary intake. + Availability of dietary exposure collected from participants at 2 time points. + Practically complete follow-up of the study population through linkage with computerised registers: Minimised concern that findings were affected by differential loss to follow-up. + Repeated measures of diet to obtain better estimate of long-term meat and NDMA intake and reduce measurement error. **Weakness:** - Diet assessed with self-administered FFQ: Misclassification of meat and NDMA intake attenuate any true relationship. - Observational nature of study: The possibility that an unevaluated risk factor for stomach cancer that is correlated with processed meat consumption may have had some effects on results.	**1**

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Jakszyn *et al.*, 2006	Aimed to examine the effect of dietary intake of NDMA and exogenous formation of NOCs and gastric cancer (GC)	Large prospective study of diet and cancer including 314 incident case of GC that occurred 6.6 years of follow-up in EPIC study	No association between NDMA intake and GC risk (HR = 1.00) ENOC was significantly associated with non-cardia cancer risk (HR = 1.42 for an increase of 40 µg/day) but not with cardia cancer (HR = 0.96). Data suggest a possible interaction between ENOC and H.pylori infection (P = 0.09).	**Strength:** + Methodology could be a useful tool in epidemiological studies where it is not possible to obtain direct estimations of endogenous nitrosation **Weakness:** - Use of indirect measurement of endogenous exposure; however, the correlation between iron and ENOC very high.	**2**
Cross *et al.*, 2010	Aimed to examine multiple potential mechanisms to test for the association between red and processed meat intake and CRC risk.	The National Institutes of Health (NIH)-AARP (formerly the American Association for Retired Persons) Diet and Health Study Large prospective observational cohort study (300,948 men and women) During 7 years of follow-up, 2,719 CRC cases ascertained.	High red meat intake (61.6g/1000 kcal) was significantly associated with increased risk of colon cancer (HR = 1.21, 95% CI: 1.03-1.41, p for trend <0.001), rectal cancer (HR = 1.35, 95% CI: 1.03-1.76, p for trend = 0.024) and colorectal cancer (HR = 1.24, 95% CI 1.09-1.42, p for trend <0.001) compared to low meat intake (9.5 g/1000 kcal). High processed meat intake (22.3 g/1000 kcal) compared to low processed meat intake (1.6 g/1000 kcal) was significantly associated with increased risk of colorectal cancer (HR = 1.16, 95% CI: 1.01-1.32, p for trend = 0.017), but not to colon cancer (HR = 1.11, 95% CI: 0.95-1.29, p for trend = 0.057) or rectal cancer (HR = 1.30, 95% CI: 1.00-1.68, p for trend = 0.145).	**Strength:** + The administration of a detailed meat questionnaire enabled the investigation of multiple components of meat. + Questionnaire was completed prior to diagnoses; limited recall bias and reverse causation. Attempted to minimise this error by adjusting models for total energy intake. **Weakness:** - Haem iron database limited; likely to underestimate total haem iron intake. - Possibility of residual confounding variables. - Possibility of some degree of measurement error (due to observational study design).	**1**

(continued)

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Table 4: Summary of Studies Selected of Processed Meat and Cancer Risk (n = 6) *(continued)*

Author, Year, Study	Aims and Objectives	Method	Outcomes (95% CI) (RR = Relative Risk) (HR = Hazard Ratio) (OR = Odds Ratio)	Critical Review (+ = Strength) (- = Weakness)	Score (1-3)
Brink *et al.*, 2005	Assessed the association between the intake of total fresh meat, meat products and fish with K-*ras* mutation in relation to the risk of colon and rectal cancer	European prospective case-cohort analyse- 448 colon and 160 rectal cancers that occurred during 7.3yrs of follow-up, excluding first 2.3 years, and 2,948 sub-cohort members of The Netherlands Cohort Study.	Positive association observed with wild-type K-*ras* tumours in the colon (RR for highest vs lowest quartile of consumption 0.70; P for trend = 0.09) and borderline significant trend with increased risk of rectal tumours harbouring G>A transitions observed (RR for highest vs lowest quartile of intake 2.37; P for trend = 0.07). No statistically significant associations observed between total fresh meat and risk of colon (P = 0.82) or rectum cancer (P = 0.43) with or without K-*ras* mutation. Weak association observed for tumours with a wild-type K-*ras*, including beef (P = 0.90) and colon tumours	**Strength:** + Low likelihood of selection bias due to the prospective nature of the study and high completeness of follow up. However, meat preparation (i.e., cooking method) not collected in the study that may have affected results. + One of the very few studies on meat and specific K-*ras* mutations. + Selection bias unlikely: Due to prospective design and high completeness of follow-up + Likelihood of information bias is low due to potential preclinical cancer incidence and exclusion of the first 2.3 years of follow-up. **Weakness:** - Information on cooking methods was not collected at baseline: Fresh meat generally needs further preparation; this type of meat may be an important source of these carcinogens	**1**
Goldbohm *et al.*, 1994	Examined the association of the consumption of meat with the risk of colon cancer	European (Netherlands) Prospective cohort study involving 852 men and women, aged 55-69. After excluding the cases diagnosed in the first year of follow-up, this study included 215 colon cancer cases.	No association between intake of fresh meat, beef and pork with colon cancer risk. Intake of processed meat significantly increased the risk of colon cancer (RR = 1.72, 95% CI 1.03-2.87, p for trend = 0.02) comparing an intake of >20 g/d with 0g/d. For processed meat an increased risk (RR = 1.17, 95% CI 1.03-1.33) was seen per increment of 15 g/d of total processed meat.	**Strength:** + Large sample size and high participation rate. **Weakness:** - Detection bias: In the Netherlands, mass screening of symptomless subjects for CRC does not take place. - Validity of the FFQ not very high for processed meat; the low correlation may be attributable to under-reporting. - Short follow up period, 3.3 years, subclinical disease that caused a change in dietary habits may have been present in a relatively large proportion of the cases at baseline. - Results may be affected by confounding variables or an unevaluated confounder (e.g., physical activity).	**3**

Source: Compiled by authors

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Sodium Nitrite, Nitrate and Formation of N-nitroso Compounds (NOCs)

In addition to carcinogen formation, processed meat consists of added nitrite and nitrate that are metabolised to nitrogen oxides (NO); these react with secondary amines located in the stomach to form N-nitroso compounds (NOCs), including nitrosamines found in processed meat products (e.g., bacon, sausage and ham) (Bogovski and Bogovski, 1981; IARC, 2010; Lijinsky, 1987). The involvement of NOCs in relation to colorectal tumour development is illustrated below (Figure 8).

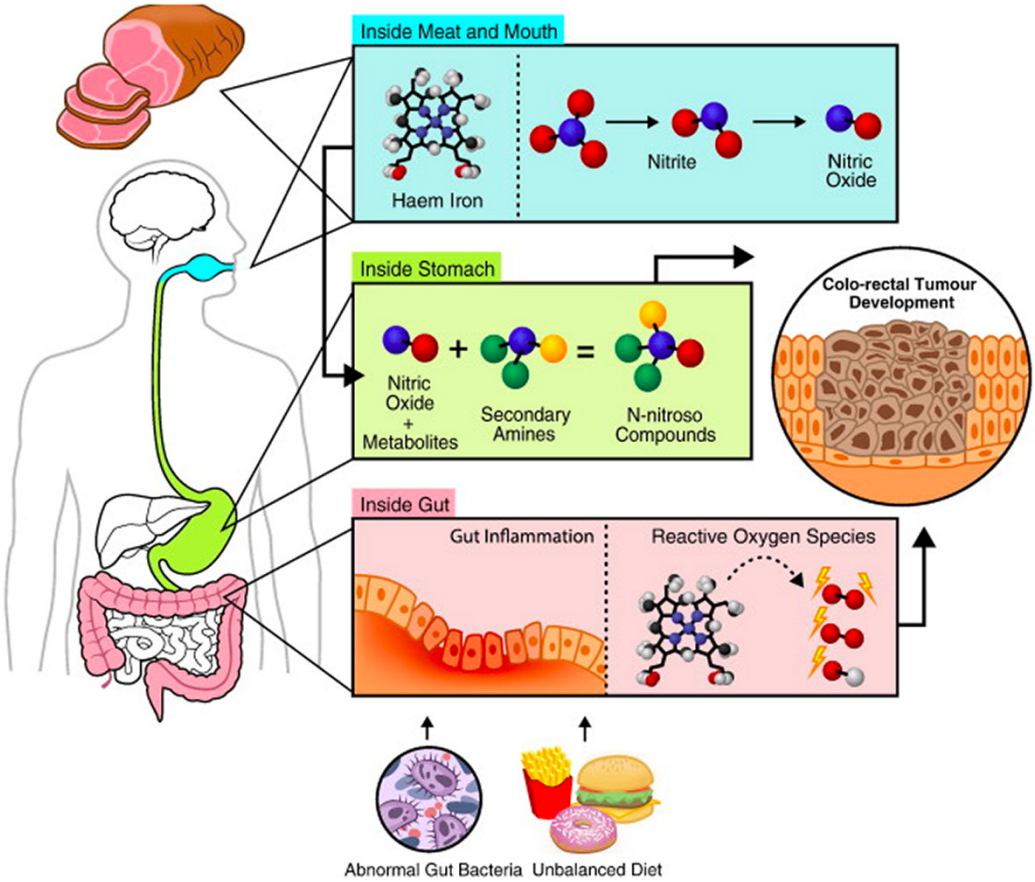

Figure 8: Potential Health Risks Associated With Meat Consumption

Source: Pegg and Shahidi, 2008

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A positive association was observed with greater intake of total meat, red and processed meat and multiple cancer risk in a large hospital-based case-control study in Uruguay (Aune *et al.*, 2009). This included a significant risk of oesophagus cancer with processed meat intake (P for trend = 0.001), larynx (P for trend = 0.001), stomach (P for trend = 0.03), colorectum (P for trend <0.001), lung (P for trend <0.001) and breast (P for trend = 0.08). Similarly, in the EPIC study, the risk of CRC was significantly associated with intake of processed meat (HR, 1.42; 95% CI, 1.09-1.85; P for trend = 0.02) for highest (>80g/d) versus lowest (<10g/d) intake (Norat *et al.*, 2005). The results suggest meat consumption is not limited to causing one cancer only but spreads the risk of multiple cancers.

The common nitrosamine found in food products is nitroso-dimethylamine (NDMA) and, together with NOCs, are strong risk factors for stomach cancer (Marmot *et al.*, 2007). Meta-analyses of prospective data from The Swedish Mammography Cohort observed a statistically significant risk of stomach cancer (HR for highest vs. lowest category of total intake of all processed meat, 1.66; P for trend = 0.008), but not of other meats (i.e., red meat, fish and poultry) (Larsson *et al.*, 2006). No significant difference was reported between low and high poultry intake and risk of cancer type, but a tendency to an inverse association was observed (P for trend = 0.04). Amongst women in the top quintile of NDMA intake, the risk of stomach cancer was associated with a 2-fold increase compared to those in the bottom quintile (HR, 1.96). The findings of this study suggest that a greater consumption of processed meat may be responsible for the positive association between dietary nitrosamines and risk of stomach cancer.

Additionally, endogenous formation of N-nitroso compounds (ENOCs) have been observed to increase in the upper gastrointestinal tract following consumption of processed meat (Lunn *et al.*, 2007). Endogenous production is substantiated by high levels of faecal output (in the order of 500 µg/day) compared with dietary intakes of only 13 µg/day (Bingham *et al.*, 1996). In a large prospective study of diet and cancer (n = 314 incident cases), dietary NDMA and ENOCs were estimated using an index of endogenous nitrosation to assess the effect of both on gastric cancer (GC) risk (Jakszyn *et al.*, 2006). No significant association was observed between NDMA intake and GC risk (HR, 1.00; 95% CI, 0.7-1.43). However, a statistical association was observed with endogenous nitrosation and non-cardia cancer risk (HR, 1.42; 95% CI, 1.14-1.78 for an increase of 40 µg/day) but not with cardia cancer (HR, 0.96; 95% CI, 0.69-1.33). The results indicate that endogenous exposure is likely to be the major contributor to the overall burden of human exposure to NOC. However, additional cohort studies with more cases and years of follow-up are needed to confirm these findings.

Moreover, haem iron, found primarily in animal-based foods (i.e., meat) can react with PUFA in the gut, resulting in reactive oxygen species (ROS) that can cause DNA damage and alter normal cell division (Pegg and Shahidi, 2008). In a large prospective cohort study, compared to low processed meat intake (1.6 g/1000 kcal), a high intake of processed meat (22.3 g/1000 kcal) was significantly associated with CRC (HR, 1.16; P for trend = 0.017) but not to colon cancer

(HR, 1.11; P for trend = 0.057) or rectal cancer (HR, 1.30; P for trend = 0.145) (Cross *et al.*, 2010). The potential mechanisms for this risk included haem iron (P for trend = 0.022), nitrate from processed meat (P for trend <0.001) and heterocyclic amine (HCA) intake (HR, 1.19; P for trend <0.001 for MelQx) and (HR, 1.17; P for trend <0.001 for DiMelQx) (Cross *et al.*, 2010). This suggests a potential relationship between meat [red and processed] and CRC risk, independent of its nitrate/nitrite content.

Gene Mutations

Mutations in the Kirsten-*ras* (K-*ras*) gene are the most common abnormality of oncogenes in human tumours (Porta *et al.*, 2003), including colorectal adenomas (Zauber *et al.*, 2003) and carcinomas (Andreyev *et al.*, 1998; Brink *et al.*, 2003). The K-*ras* gene encodes the p21 *ras* protein; a guanine nucleotide binding-protein that engages in transmitting growth-stimulating signals from membrane-bound tyrosine kinases through a group of downstream regulators to the nucleus (Egan, 1993). When a specific mutation occurs in the K-*ras* gene, the *ras* protein is locked in its active status; this contributes to cell proliferation and metastasis through a signalling pathway (Figure 9).

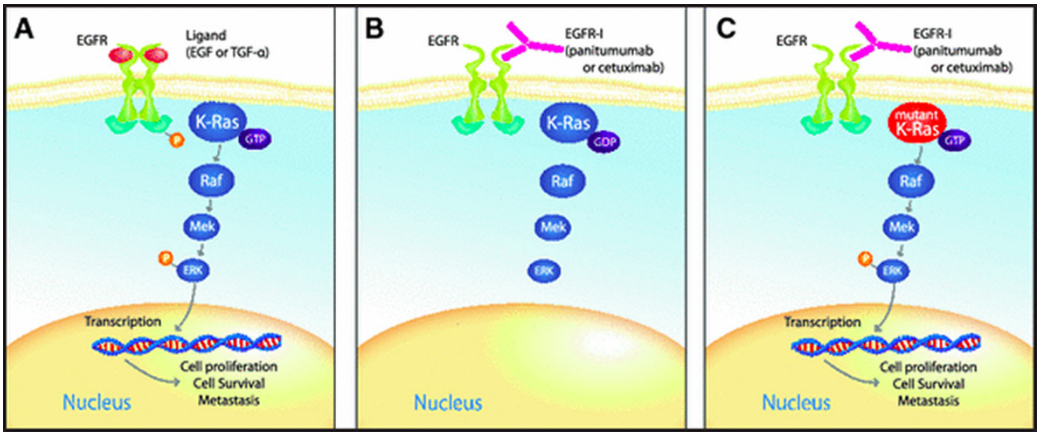

Figure 9: Signalling Pathway of K-*ras* Protein

Notes: **A** The ligands epidermal growth factor receptor (EGFR) causes phosphorylation of the tyrosine kinase domain. K-*ras* uses a guanosine triphosphate (GTP) bound conformation and activates ERK leading to the transcription of genes associated with cell proliferation, survival, and metastasis. **B** Inhibition of EGFR by the EGFR-I panitumumab leads to K-*ras* becoming guanosine diphosphate (GDP) bound, which inhibits downward signalling. **C** K-*ras* becomes mutated and harbours a guanosine triphosphate (GTP) bound conformation, which results in activation of the *Ras* pathway

Source: Khambata-Ford *et al.*, 2007

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Additionally, it has also been suggested that environmental carcinogens (i.e., N-nitroso compounds (NOCs)) that are endogenously derived from processed meat may induce (specific) K-*ras* mutations in tumour sites such as the colon (Figure 10). A large cohort study with 448 incident colon and 160 incident rectal cancer patients reported no statistically significant associations between total fresh meat and the risk of colon (P for trend = 0.82) or rectal cancer (P for trend = 0.43), with or without the K-*ras* mutation (Brink *et al.*, 2005). For meat products, however, a statistically significant association was observed with wild-type K-*ras* tumours in the colon (RR for highest vs lowest quartile of consumption, 0.70; P for trend = 0.09), and a borderline significant trend with K-*ras* tumours in the rectum acquiring G>A transitions (RR for highest vs lowest quartile of intake, 2.37; P for trend = 0.07). The findings suggest that consumption of cured meat products (i.e., beef, pork and others) appear to be associated with colon or rectal tumours with a wild-type K-*ras* gene, proposing that they may apply their actions in colon or rectal cancer through a pathway independent of a mutation in the K-*ras* gene.

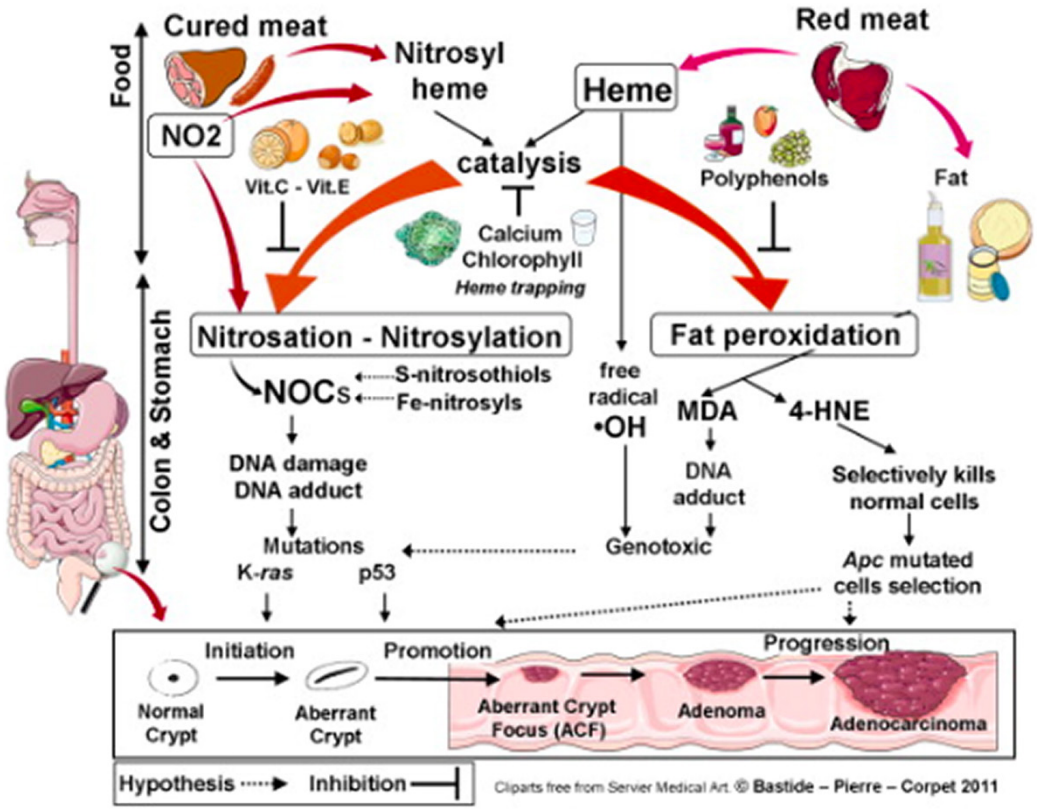

Figure 10: Catalytic Effect of Haem Iron and N-nitrosation and Consequences for the Development of Colorectal Cancer (CRC)

Source: Bastide *et al.*, 2011

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In support, the risk of CRC in both men and women was positively associated with the intake of processed meat in the Netherlands prospective cohort study women (RR, 1.17 per increment of 15 g/day; 95% CI, 1.03-1.33) (Goldbohm *et al.*, 1994). The risk significantly increased post-consumption for >20g/d processed meat (RR, 1.72; 95% CI, 1.03-2.87; P for trend = 0.02) in comparison to 0g/d. The results appeared to be due to one of the five questionnaire items on processed meat, which consisted of mainly sausages. While this study does not support a role of fresh meat in the aetiology of colon cancer in this population, it does suggest an involvement of NOCs in relation to CRC risk. However, this particular mutagenic pathway is not yet sufficient to draw clear conclusions.

DISCUSSION

The purpose of this systematic review was to ascertain the carcinogenicity of the intake of meat [red and processed] through relevant mechanisms and suggested pathways. After conducting the literature search and refining the studies against the set criteria, most reported a positive association between the intake of red and processed meat and carcinogenicity. Based on the WCRF/AICR grading criteria, 7 of the 16 studies were graded high quality (1), 8 were graded as inadequate in providing a causal relationship, flawed by methodological errors (i.e., bias), but had an acceptable study design (2), and 1 study was graded as poor quality with methodological errors (3).

Cooking Methods, Doneness and Heterocyclic Amines (HCAs)

Cooking method and doneness clearly affect the mutagen and carcinogenic levels of meat (Sinha *et al.*, 2001). Epidemiological studies have demonstrated that cooking methods of meat may be positively associated with breast cancer, particularly among women who deep-fried red meat to well-done (Butler *et al.*, 2003; Dai *et al.*, 2002; De Stefani *et al.*, 1997). Conversely, other studies have reported no association between meat type or specific cooking methods with cancer risk (Koutros *et al.*, 2008) as well as other case-control (De Verdier *et al.*, 1991; Lyon and Mahoney, 1988) and prospective (Knekt *et al.*, 1994; Koutros *et al.*, 2008; Pietinen *et al.*, 1999) studies of colon cancer. The inconsistencies between studies may be attributed to the variations in cooking methods/dietary assessment methods across study populations. The most commonly used cooking method in Chinese and other ethnic populations is the use of high-temperature cooking. However, this has rarely been studied and may account for the positive associations reported (Dai *et al.*, 2002). In comparison, within Finnish populations, meat is typically cooked at low temperatures and consumed as mixed dishes (Knekt *et al.*, 1994; Pietinen *et al.*, 1999).

Additionally, variances in cooking methods may be explained by the temperature of the cooking oil used for deep-fried cooking, typically in the range of 240-270°C. Deep fried cooking oil has the potential to produce fumes containing mutagenic compounds (i.e., 1,3-butadiene, benzene, acrolein, and formaldehyde) (Shields *et al.*, 1995). It may also generate non-volatile hazardous compounds (i.e., hydroperoxides, *trans* fatty acids, and aldehydes) (Goburdhun *et al.*, 2001).

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Both hydroperoxides and aldehydes are endogenous reactive chemicals that have carcinogenic potential (Gupta and Lutz, 1999; Linn, 1998). In one cohort (Cross *et al.*, 2005) and case-control (De Stefani *et al.*, 1997) study, fried meat was strongly associated with breast cancer risk, whereas broiled meat only showed a marginal increase in risk. The risk estimates for broiled meat may arise due to the presence of cooked vegetables in stew, which is the richest source of this food item in this population (De Stefani *et al.*, 1997). Previous studies in other cancer sites, mainly colon and lung, were partially supportive of such an association (Deneo-Pellegrini *et al.*, 1996; Lyon and Mahoney, 1988; Schiffman and Felton, 1990). Amongst the studies, the exposure of HCA was detected by the cooking method (frying or broiling) or through doneness levels. However, controls of one case-control study were selected from the same hospital as the cases and reported similar places of residence and levels of education (De Stefani *et al.*, 1997). Therefore, this sample could be considered members of the same (secondary) population base and results cannot be generalised to a wider population (Wacholder *et al.*, 1992).

It has also been proposed that grilling/barbecuing meat products (e.g., beef) in comparison to other cooking methods, results in the highest heterocyclic amine (HCA) content (Sinha *et al.*, 1999). However, other studies have suggested no association (De Stefani *et al.*, 1997), this may be as a result of subjects questioned only about the grilling and barbecuing methods together in one question. One explanation could be due that in North Carolina, barbecuing is a slow-roasting method with a vinegar-based marinade, unlike the charred meat surfaces termed "barbecued" in other regions (Butler *et al.*, 2003). Similarly, authors of a large cohort study failed to gather information on cooking methods to estimate dietary exposure of HCAs and PAHs (Norat *et al.*, 2005). Nonetheless, to correct for food measurement errors, the authors attempted to adjust for total energy intake and body weight, because adjustment for self-reported total energy intake is proposed to partly correct for measurement error (Willett, 2001).

From meat-derived HCA estimates, the strongest association reported was for DiMelQx with colon cancer (Butler *et al.*, 2003). However, misclassification of HCA exposure may have occurred from not accounting for other sources of exposure, such as the addition of marinades (Salmon *et al.*, 1997) or the use of a microwave to defrost that may weaken the formation of HCA (Felton *et al.*, 1994). Also, the authors did not consider meat doneness in their exposure assessment (Butler *et al.*, 2003). In comparison, in one study, meat samples cooked at home were photographed and sent in for HCA quantification; after comparing doneness levels by self-reporting in contrast to independent assessment of the photographs, the authors concluded that showing meat doneness photographs to each subject of their study resulted in a less subjective definition of meat doneness, and a greater classification of HCA levels into more representative categories (Keating *et al.*, 2000). However, a strength of the North Carolina study was its population-based study design; this, coupled with a very high response rate and sample size, minimised the likelihood of selection bias and allowed sufficient statistical power to investigate potential interactions (Butler *et al.*, 2003).

Furthermore, in one study, 2-amino-1-methyl-6 phenylimidazo[4,5-b] pyridine (PhIP) intake was associated with a 22% elevated risk for prostate cancer and 28% higher risk for incident disease (Cross *et al.*, 2005). Previous cohort studies have yielded conflicting results for red meat intake and prostate cancer risk, with some studies suggesting a positive association (Gann *et al.*, 1994; Giovannucci *et al.*, 1993; Le Marchand *et al.*, 1994; Veierød *et al.*, 1997), whereas others have found no association (Hirayama, 1979; Hsing *et al.*, 1990). Although the use of a validated questionnaire (i.e., FFQ) includes very detailed questions on meat intake and meat-cooking practices (Cross *et al.*, 2005), the authors did not consider marinating of meat or flipping of hamburgers (De Stefani *et al.*, 1997), both of which can affect the formation of HCAs and BaP (Salmon *et al.*, 1997; Tran *et al.*, 2002). Nevertheless, this study does give support to experimental observations and, if confirmed in further studies, PhIP would be the first chemical carcinogen associated with prostate cancer in human studies.

In addition, the biological mechanism relating red meat intake and colon cancer remains speculative. It was suggested that the risk of colorectal cancer (CRC) was confined to the distal colon in a large population-based prospective study of Swedish women (Larsson *et al.*, 2005). In support, a case-control study conducted in Hawaii suggested CRC risk to be confined to the proximal colon in men but not in women (Le Marchand *et al.*, 1997). Whilst it has been suggested that the exposure to HCAs/PAHs exerts carcinogenic effects, the levels of HCAs in cooked white meat (i.e., fish and poultry) are as high or exceed the levels in cooked red meat (Sinha *et al.*, 1995; Skog *et al.*, 1997). Therefore, this biological mechanism is unlikely to explain the positive association of red meat, but not of white meat, with risk of cancer at any subsite within the colon. Subsites within the colon should be considered individually to signify a potential mechanism existing.

In addition, differences in N-acetylation status may account for the significance in risk of red meat consumption with CRC (Chan *et al.*, 2005; Chen *et al.*, 1998; Lilla *et al.*, 2006; Ognjanovic *et al.*, 2006; Sørensen *et al.*, 2008). Higher levels of HCA-DNA adducts have been found in NAT1 and/or NAT2 fast acetylators compared to slow acetylators (Ambrosone *et al.*, 2007). Conversely, one study reported no interactions between the consumption of fried red meat and polymorphisms in NAT1/NAT2 fast acetylators for CRC (Sørensen *et al.*, 2008). The inconsistency between findings can be explained by differences in study design as previous studies have considered meat as a categorical variable (i.e., daily intake or servings) (Keating *et al.*, 2000), whereas meat consumption was studied as a continuous variable in one meta-analysis, resulting in minimum loss of information and higher statistical power (Sørensen *et al.*, 2008).

Reducing the Formation and/or Tutagenicity of HCAs and PAHs

The identification of differences in cooking method and doneness related to carcinogen formation are useful in informing the public on "less dangerous" meat preparation methods. HCAs are a key factor in the production of genetic mutations in the diet (Ferguson *et al.*, 2004). In this context, the addition of anti-carcinogens in the diet consumed at the same time as usual dietary habits may scale

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down the likelihood of DNA interactions and mutations. Similarly, green tea has been identified as an inhibitor of HCA-induced colonic lesions that may be relevant to CRC. Epigallocatechin-3-gallate (EPCG) is the most abundant catechin in tea and has been researched for its anti-carcinogenic benefits in human health and disease (Carter *et al.*, 2007).

Haem Iron as a Promoter of Carcinogenesis

Moreover, it has been suggested that haem iron increases cell proliferation in the mucosa, through lipoperoxidation and/or cytoxicity of faecal water (Sesink *et al.*, 1999). The mechanism of haem iron as a promoter of carcinogenesis has been studied in The Nurses' Health Follow-up Study (Zhang *et al.*, 2011). No strong correlation was observed between consumption of haem iron and incidence of CRC in an analysis of 2,114 cases during a long follow-up period of 22 years. In comparison, authors of the Iowa Women's Health Cohort (Lee *et al.*, 2004) reported a positive association of haem iron with proximal, but not distal colon cancer, but only when zinc intake was included in the model. The effect of zinc can be explained by the trace mineral's ability to inhibit oxidative processes; zinc ions may possibly replace redox active molecules and activate the synthesis of metallothionein, a sulfhydryl-rich protein that protects against free radicals (Lee, 2018). However, at a molecular level, iron can substitute for zinc and cause metal-induced DNA damage and carcinogenesis, suggesting a close relationship between these two nutrients (Conte *et al.*, 1996; Sarkar, 1995). In this particular cohort, information regarding cooking methods were not collected; this is a key limitation (Zhang *et al.*, 2011) as haem iron can be partially converted to non-haem iron depending on the type and extent of the cooking method (Zhang *et al.*, 2011; Sinha *et al*., 2005). Other dietary factors, including alcohol intake, may influence results as previous studies have reported a positive association between haem iron intake and colon cancer in women drinking 20g of alcohol per week (Larsson *et al.*, 2005). Therefore, the positive association of haem consumption and CRC risk remains questionable.

In addition, authors of cohort studies that have used a detailed questionnaire to assess intake of meat consumption, preparation and doneness, in addition to a linked database to estimate exposure to iron from meat and haem iron, have reported no correlation between haem iron intake from total meat [red and processed] and post-menopausal breast cancer (Kabat *et al.*, 2007; Kabat *et al.*, 2010). The insignificance of results may be attributed to quantitative information on supplemental intakes of iron (i.e., dosage, frequency and duration) not being considered. In favour, authors of one case-control (Kallianpur *et al.*, 2008) and cohort study (Kato *et al.*, 1999) carefully adjusted for regular use of vitamin supplements, antioxidant and total iron intake and found a positive association of total iron intake with cancer risk, suggesting the importance of obtaining all quantitative information on intakes of iron. Also, members of the AARP cohort were only assessed in midlife; it is likely that iron intake particularly during adolescence when the breasts are developing, may affect the risk of developing breast cancer (Kabat *et al.*, 2010).

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To determine whether iron intake contributes to the development of cancer risk, repeat measurements should be considered and information on the use of supplements containing iron obtained. Additionally, in-depth research is required to support the role of zinc or haem iron intake and CRC risk (Lee *et al.*, 2004). A constructive approach to ensure adequate iron intake may be to check the levels in the bloodstream and adjust dietary intake accordingly.

High Fat Content

As hypothesised previously, the content of saturated fat and dietary cholesterol may enhance the risk of CRC through various alterations developing the risk of exogenous mutations (Kinzler and Vogelstein, 1996; Preston-Martin *et al.*, 1990). One case-control study successfully investigated interactions between animal derived iron and fat, for which a biological mechanism exists (Kallianpur *et al.*, 2008). Conversely, using data from the Women's Health Study, a prospective study found no association between total fat intake and CRC risk (Lin *et al.*, 2004). Findings are consistent with other prospective cohort studies (Bostick *et al.*, 1994; Flood *et al.*, 2003; Giovannucci *et al.*, 1994; Goldbohm *et al.*, 1994; Willett *et al.*, 1990).

The disparity in results suggests that the inverse association with red meat may be attributed to factors other than fat content, such as the formation of HCAs and PAHs (Bandera *et al.*, 2007; Giovannucci and Goldin, 1997). However, information regarding meat doneness was only collected for one food item (beef or lamb as a main dish) as opposed to all items in one prospective (Lin *et al.*, 2004) and case-control (Augustsson *et al.*, 1999) study, therefore causing an attenuation in significance. Also, since the cohort of the Nurses' Health Study (Willett *et al.*, 1990) was relatively younger (aged 34-59 years) than most other cohorts (Lin *et al.*, 2004), it is possible that age may modify the association. This is supported by a meta-analysis that reported a higher risk of colon cancer with animal fat intake in women aged <50 years but not in those ≥50 years (Howe *et al.*, 1997). Although authors of the Women's Health Study found no difference in risk by age in this cohort, additional studies of modification of the effect by age, with larger numbers of cases, are warranted.

On the other hand, it has been suggested that the content of *trans*-fat in fried foods contributes to the risk of cancer incidence through the disruption of the phospholipid cell membrane and associated enzymes and receptors (Kinsella, 1981; Lin *et al.*, 2004). Although the risk of *trans*-fat intake with CRC is not yet clear, one (Slattery *et al.*, 2001) of two case- control studies (McKelvey *et al.*, 1999; Slattery *et al.*, 2001) observed a significant risk of colon cancer in women with a higher intake of *trans* unsaturated fat, therefore supporting the likelihood of cancer incidence.

Sodium Nitrite, Nitrate and Formation of N-nitroso Compounds (NOCs)

Amongst dietary factors, processed meat consists of meat preserved by salting, smoking, or the addition of nitrites and/or nitrates that may heighten the risk of stomach cancer (Marmot *et al.*, 2007). However, this conclusion was based only on case-control studies that are more susceptible to

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systematic bias than prospective studies (Aune *et al.*, 2009). An existing prospective study reported a significant risk of stomach cancer with processed meat consumption, whereas no associations were observed for red meat consumption (Larsson *et al.*, 2006). Conversely, other studies have been less supportive of an association between processed meat intake and stomach cancer (Galanis *et al.*, 1997; Knekt *et al.*, 1999; McCullough *et al.*, 2001; Nomura *et al.*, 1990). The disparity of results may be attributed to diets based on a single assessment in prospective studies; this could lead to the misclassification of long-term average processed meat intake and attenuate the extent of a potential association (Larsson *et al.*, 2006).

Additionally, processed meat is a key source of nitrosamines, contributing to approximately 80% of total intake in the Swedish diet (Larsson *et al.*, 2006; Österdahl, 1988). In this study, the common nitrosamine in foods, nitroso-dimethylamine (NDMA) was associated with a 2-fold higher risk in women in the highest quintile versus those in the lowest quintile. This finding is consistent with those from four case-control studies, in which a 1.4- to 7-fold increase in stomach cancer risk was observed for high NDMA (De Stefani *et al.*, 1997; González *et al.*, 1994; La *et al.*, 1995; Pobel *et al.*, 1995). Conversely, one case-control study (Risch *et al.*, 1985) and one small Finnish cohort study (Knekt *et al.*, 1999) of 9,985 individuals (including 68 cases) reported no positive association for NDMA intake. The results may be attributed to the type of dietary assessment used (i.e., FFQ) (Larsson *et al.*, 2006). Some misclassification of meat and NDMA intake is inevitable, and random misclassification would attenuate the risk by cancer subsite and by histological subtype of stomach cancer. However, the authors did use a repeated measure of diet and were therefore able to obtain a more accurate estimate of long-term meat and NDMA intake (Larsson *et al.*, 2006).

Reducing meat (red and processed) intake may be a key modifiable risk factor for several types of cancer, including breast cancer (Aune *et al.*, 2009). Findings are consistent with two previous meta-analyses of meat consumption and breast cancer risk, with one based on 22 case-control studies and 9 cohort studies (RR, 1.17) (Boyd *et al.*, 1993; 2003). However, biased results may occur if the controls of the studies were to report their meat consumption in a different way from the general population (Aune *et al.*, 2009). As the mean intake of red meat (145.5 grams per day (g/d) was found to be similar to the estimated mean intake of 145 g/d (168 g/d and 122 g/d among men and women, respectively) in dietary surveys from the same region, selection bias is unlikely to be of concern (Aune *et al.*, 2009).

Furthermore, the positive association of processed meat intake and colorectal cancer (CRC) may be due to the conversion of nitrate/nitrite to carcinogenic N-nitroso compounds (NOCs), including nitrosamines (Cross *et al.*, 2010). In this cohort study however, the exposure of nitrate from drinking water was not considered. Other epidemiologic data on the varying exposures in relation to colorectal neoplasia is limited, but nitrate and nitrite intake from processed meat (Ward *et al.*, 2007), as well as individual NOCs (Knekt *et al.*, 1999), have been positively associated with colorectal neoplasia. In addition, the authors observed a positive association for two HCAs,

MeIQx and DiMeIQx, and mutagenic activity, but not for PhIP and B[*a*]P (Cross *et al.*, 2010). Data regarding the role of HCAs in colorectal neoplasia are unclear, as other studies have found a positive association for MeIQx, but not other HCAs (Ferrucci *et al.*, 2009; Nowell *et al.*, 2002). Additionally, some studies have concluded that B[*a*]P intake increases the risk of colorectal adenoma (Sinha *et al.*, 2005). Therefore, future research is sought to strengthen this association.

In support of the NOC-related mechanism, a large prospective study reported a positive association of non-cardia gastric cancer (GC) with ENOC exposure, but not with dietary NDMA (Jakszyn *et al.*, 2006). Despite the low number of non-infected cases in this study, it has been suggested that infection with Helicobacter pylori (H. pylori) increases Nitric Oxide production (NO) from macrophages in response to bacterial overgrowth (González *et al.*, 2003; 2006), thus increasing the availability of NO in infected individuals (P for trend = 0.09) (Jakszyn *et al.*, 2006). Vitamin C has been acknowledged to offer protective effects against the infection by enhancing mucosal immune response, neutralising free radicals and inhibiting cell proliferation and H.pylori growth (Zhang and Farthing, 2005). However, due to the low number of cases studied, cohort studies with a larger distribution of cases are required to ascertain the findings as well as clarification of the mechanisms of action of these compounds and their potential interactions with H.pylori and vitamin C levels (Jakszyn *et al.*, 2006).

Gene Mutations

The risk of specific point mutations in the K-*ras* oncogene in colon and rectal tumours has been attributed to the consumption of processed meat (Brink *et al.*, 2005). In this prospective study, no association was observed either overall or after K-*ras* mutation status was considered. For cured meat products, however, there was a positive association with wild-type K-*ras* tumours in the colon and a positive correlation with G>A transitions in the K-*ras* gene in rectal tumours. Findings are consistent with earlier results of meat intake and CRC in the NLCS, that is, an association was not observed for total fresh meat and different types of fresh meat; however, a positive association was observed in those consuming processed meat (Goldbohm *et al.*, 1994). Despite the significance of results and high completeness of follow-up of cancer incidence observed that made information and selection bias unlikely, the follow-up period was relatively short, 3.3 years (Goldbohm *et al.*, 1994). Consequently, subclinical diseases that alter following a change in dietary habits may have been present in a relatively large proportion of the cases at baseline. Also, methods of meat preparation were not obtained at baseline and, as known, in this study's population (i.e., the Netherlands), meat is typically pan-fried/stewed and the variability in consumption of alternative foods, including specific vegetables, is likely to modify the effects of meat consumption (Hirayama, 1986; Lee *et al.*, 1989; Manousos *et al.*, 1983). Studies with longer follow-up periods (>5 years) are warranted to study effect modification in a relatively homologous population.

In addition, N-nitroso compounds (NOCs) may induce G4A transitions in human colonic tissue (Bingham *et al.*, 2002; Hughes *et al.*, 2001). In the NLCS study, when the absence or

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presence of K-*ras* mutations was considered, a positive association was observed between high meat intake and colon tumours harbouring a wild-type K-*ras* gene (Brink *et al.*, 2005). Similarly, in a sub-group analysis of specific point mutations in the K-*ras* gene, an association was observed with processed meat intake with rectal tumours harbouring a G4A transition. Although the association was not significantly significant, the results are in accordance with existing biological evidence (Bingham *et al.*, 2002; Hughes *et al.*, 2001; Jacoby *et al.*, 1992; Topal, 1988; Zarbl *et al.*, 1985). It remains unclear as to why the association is limited to the rectum and not the colon in this particular cohort (Brink *et al.*, 2005). A plausible explanation to explain differences in tumour site may be due to the duration of contact with, and concentration of, dietary carcinogens such as nitrosamines. The slow colonic transit in the rectum may also increase the exposure time of the rectum. Conversely, results may be due to chance finding, considering no association was observed between total meat intake and rectal cancer overall nor with K-*ras* mutation status. Therefore, additional aetiological insight into the underlying mechanisms is recommended to clarify this issue.

Critical Review of this Systematic Review

The strengths of this systematic review consist of its comprehensive search strategy. With an acceptable number of studies and study participants, there was adequate statistical power to detect significant associations in the main review with findings consistent with existing literature. However, limitations of this systematic review are of note. One of these is the differences in quality of study design, most of which is mentioned in detail above; whilst the majority of studies produced significant results, they are limited by methodological flaws including poor quality and low statistical power. In addition, only published studies in the English language were included, therefore a potential for selection bias exists because non-English language and abstract-only publications were excluded and unpublished data may have been missed. Further investigations are warranted to confirm the risk of meat (red and processed) intake and cancer, especially as the majority of literature was based on case-control studies that are subject to bias (i.e., selection and recall). Lastly, additional research underlying the geographical and inter-individual variations in diet and lifestyle exposures is warranted to assess their relative contributions to cancer risk.

CONCLUSIONS

In conclusion, the overall association derived from this systematic review of red and processed meat consumption with cancer risk appears to be positive. There is evidence that this risk may be attributed to hypothesised mechanisms and/or relevant pathways that generate carcinogens rather than a function of meat *per se*. The majority of studies examined the role of heterocyclic amines (HCA) and polyaromatic hydrocarbons (PAH) in relation to breast and colon carcinogenesis, haem iron as a promoter of carcinogenesis, high fat (saturated and *trans*-fat) and dietary cholesterol content of meat. Additionally, the role of sodium nitrite, nitrate and N-nitroso compounds (NOCs)

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and genetic alterations in the K-*ras* oncogene in colon and rectal cancer subtypes were discussed as causative factors in developing cancer risk for subjects consuming both red and processed meat. The identification of possible mechanisms allows for potential approaches in limiting consumption of red meat and if any, processed meat. Additionally, the adoption of a sustainable diet not only benefits individuals nutritionally but helps lessen the high environmental impact of meat production and climate change on a global scale. However, cancer carcinogenesis is a complex multifactorial process; therefore it is unlikely that determinants of cancer types work in isolation from one another. Only a limited number of studies included attempted to examine the effect of meat consumption independent of genetic, dietary and associated factors, and further research therefore is required to ascertain intake of meat (red and processed) with cancer risk.

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CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

AUTHORS' CONTRIBUTIONS

Reema Roda designed and carried out the study. This included the literature review, data collection, data analysis and creating the manuscript. Ihab Tewfik advised Reema regarding the study protocol, design and the approval of the final version of the manuscript.

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