Review

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Potential health hazards of eating red meat

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Red meat (beef, veal, pork, lamb and mutton) consumption contributes several important nutrients to the diet, for example essential amino acids, vitamins (including B12) and minerals (including iron and zinc). Processed red meat (ham, sausages, bacon, frankfurters, salami, etc.) undergoes treatment (curing, smoking, salting or the use of chemical preservatives and additives) to improve its shelf life and/or taste. During recent decades, consumption of red meat has been increasing globally, especially in developing countries. At the same time, there has been growing evidence that high consumption of red meat, especially of processed meat, may be associated with an increased risk of several major chronic diseases. Here, a comprehensive summary is provided of the accumulated evidence based on prospective cohort studies regarding the potential adverse health effects of red meat consumption on major chronic diseases, such as diabetes, coronary heart disease, heart failure, stroke and cancer at several sites, and mortality. Risk estimates from pooled analyses and meta-analyses are presented together with recently published findings. Based on at least six cohorts, summary results for the consumption of unprocessed red meat of 100 g day^{-1} varied from nonsignificant to statistically significantly increased risk (11% for stroke and for breast cancer, 15% for cardiovascular mortality, 17% for colorectal and 19% for advanced prostate cancer); for the consumption of 50 g day^{-1} processed meat, the risks were statistically significantly increased for most of the studied diseases (4% for total prostate cancer, 8% for cancer mortality, 9% for breast, 18% for colorectal and 19% for pancreatic cancer, 13% for stroke, 22% for total and 24% for cardiovascular mortality and 32% for diabetes). Potential biological mechanisms underlying the observed risks and the environmental impact of red meat production are also discussed. The evidence-based integrated message is that it is plausible to conclude that high consumption of red meat, and especially processed meat, is associated with an increased risk of several major chronic diseases and preterm mortality. Production of red meat involves an environmental burden. Therefore, some European countries have already integrated these two issues, human health and the 'health of the planet', into new dietary guidelines and recommended limiting consumption of red meat.

Keywords: cancer, cardiovascular diseases, diabetes, environment, mortality, red meat.

Introduction

In a report on the global burden of diseases published in the *Lancet* on 5 December 2015, diet was classified as the number one risk factor for a reduction in global disability-adjusted life years [1]. Red meat is a significant portion of total dietary intake in many populations, and its consumption is increasing globally. The potentially adverse health effects of red meat consumption have been receiving increasing attention in the last few decades. Using the search term 'red meat' in PubMed, it is clear that there has been a systematically increasing annual number of red meat-related publications: only eight in 1970, 65 in 1990, 309 in 2010 and over 400 in 2015 (Fig. 1). Red meat consumption emerged in the early 2000s as a public health concern. Accumulating scientific evidence has indicated that high consumption of red meat, especially of processed meat, may be associated with an increased risk of major chronic diseases, including type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and cancer, and increased mortality risk.

Unprocessed and processed red meat

The term 'red meat' encompasses beef, veal, pork, lamb and mutton. A high concentration of myoglobin in this type of meat, which in contact with

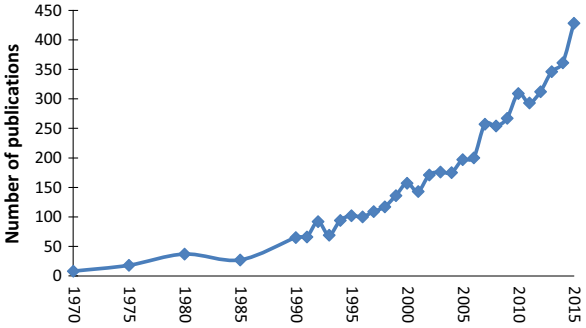

Fig. 1 *Publications on red meat during the period 1970–2015, as identified through PubMed.*

oxygen transforms to reddish oxymyoglobin, makes myoglobin-rich meats appear red. Processed red meat differs from unprocessed meat in that it undergoes treatment to extend its shelf life (curing, smoking, salting or the addition of chemical preservatives). Additives are also introduced to improve flavour, colour and quality (tenderness, juiciness and cohesiveness). Processed meat usually contains much more sodium and nitrites/nitrates than unprocessed meat [2]. Examples of processed red meat include ham, sausages, frankfurters, salami and bacon. There is large variation worldwide in the percentage of individuals consuming red meat and processed meat in various populations. Depending on the country, the proportion of red meat consumers varies from below 5% up to almost 100%, and for processed meat, the proportion ranges from 2% to 65%. Amongst those who consume unprocessed or processed red meat, the average daily intake is approximately 50–100 g per person, with high consumption considered above 200 g per person [3].

It is well known that red meat is an important source of proteins, essential amino acids, vitamins (including B12), minerals (including haeme iron and zinc) and other micronutrients [4]. However, red meat may also contain additives introduced during processing and contaminants such as polychlorinated biphenyls (PCBs); the contribution of PCBs from meat was estimated to range from 4% in Asia to 55% in North America [5]. Meat and edible offal have been estimated to contribute approximately 8% of total dietary exposure to cadmium [6]. Moreover, red meat may contain residues of antibiotics and hormones used during production [7]. The practice of cooking meat at high temperatures (e.g. pan frying and barbecuing) may lead to the production of heterocyclic amines (HAAs), which are thought to increase cancer risk in humans [8]. Polycyclic aromatic hydrocarbons (PAHs), which are considered to be carcinogenic and genotoxic, are produced during cooking at high temperatures over an open flame; grilled/barbecued meats were estimated to contribute up to 21% of the intake of benzo(a)pyrene (one form of PAHs) in the USA [9]. Exposure to high temperatures even for a short period of time can also generate in meat high levels of advanced glycation end-products (AGEs), which have been shown to increase oxidative and inflammatory processes [10].

Global changes in red meat consumption

In the last several decades, there has been a clear shift in the dietary patterns towards a high energy-dense diet, characterized by higher consumption of foods of animal origin, including red meat. The annual global production of red meat is as high as 184 million tons (cf. 109 million tons of poultry) and reflects a high per capita consumption mainly in high-income countries. However, the consumption of meat in developing countries, where almost all world population growth currently takes place, has been growing at 5–6% per annum and large part of this increase has been red meat consumption [11]. The pork consumption pattern is a good example of the dietary transition during recent decades. Americans consumed more pork than Chinese until 1997 and then this pattern reversed; during the past decade, per capita consumption of pork in the USA has been decreasing by 2% a year, whilst in China there has been a 3% annual increase. According to statistics from the US Department of Agriculture for 2011, average per capita pork consumption was 38 kg in China and 27 kg in the USA [12].

Health risks associated with red meat consumption

Scientific evidence of potential associations between unprocessed/processed red meat consumption and an increased risk of several chronic diseases (including T2DM, CVD and cancer) and of preterm mortality has been accumulating since the 1990s. Systematic reviews and meta-analyses have demonstrated that a higher incidence of several chronic diseases is related to high red and/or processed meat

consumption. Summary results from the most recent meta-analyses (2010–2015) of red meat and processed meat consumption and risk of diabetes (T2DM), stroke, coronary heart disease (CHD) and heart failure (HF) are presented in Table 1 and illustrated in Figure 2. Where a meta-analysis was not available, results from single studies are presented.

T2DM

Growing evidence indicates that high consumption of unprocessed red meat and of processed meat is associated with an increased risk of T2DM. Over the last decade, a considerable number of prospective studies have consistently shown that a diet rich in red and processed meat is associated with

Table 1 *Risk estimates from meta-analyses of cohort studies and single cohorts of the associations between unprocessed and processed red meat consumption and incidence of diabetes, cardiovascular disease and mortality*

Disease/mortality	Cohorts, *n* unprocessed/processed meat	Population	Cases	Unprocessed red meat RR (95% CI) per 100 g day^{-1}	Processed meat RR (95% CI) per 50 g day^{-1}
Diabetes					
Feskens *et al.* [13]	11/21	n.a.	n.a.	1.15 (0.99–1.33)	1.32 (1.19–1.48)
Stroke					
Kaluza *et al.* [50]					
Total	1	11 601	699	1.41 (1.04–1.92)[a]	1.24 (0.94–1.63)[b]
Total	6/6	329 495	10 630	1.11 (1.03–1.20)	1.13 (1.03–1.24)
Ischaemic	4/4	329 495	6420	1.13 (1.00–1.27)	1.15 (1.06–1.24)
Haemorrhagic	3/4	329 495	1276	1.08 (0.84–1.39)	1.16 (0.92–1.46)
Haring *et al.* [51]					
CHD					
Micha *et al.* [34]	4/5	56 311/614 062	769/21 308	0.92 (0.74–1.15)	1.42 (1.07–1.89)
Bernstein *et al.* [52]	1	84 136	3162	1.19 (1.07–1.32)	n.a.
Heart failure					
Nettleton *et al.* [53]	1	14 153	1140	1.07 (0.97–1.17)	n.a.
Ashaye *et al.* [54]	1 (men)	21 120	1204	1.02 (1.01–1.04)[c]	n.a.
Kaluza *et al.* [55]	1 (men)	37 035	2891	0.99 (0.87–1.13)	1.08 (1.02–1.15)
Kaluza *et al.* [56] (long-term diet)	1 (women)	34 057	2806	1.05 (0.92–1.21)	1.19 (1.05–1.34)
Mortality					
All cause (Larsson and Orsini [77])	9/9	1 330 352	137 376	1.09 (0.997–1.20)	1.22 (1.13–1.31)
CVD (Abete *et al.* [80])	7/6	1 674 272	44 340	1.15 (1.05–1.26)	1.24 (1.09–1.40)
Cancer (Wang *et al.* [78])	8/8	1 144 264	45 738	1.03 (0.89–1.18)	1.08 (1.06–1.11)

RR, relative risk; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; n.a., not available. [a]108 g day^{-1} vs. 14 g day^{-1}; [b]54 g day^{-1} vs. 0 g day^{-1}; [c]per serving of total red meat (unprocessed and processed) per week.

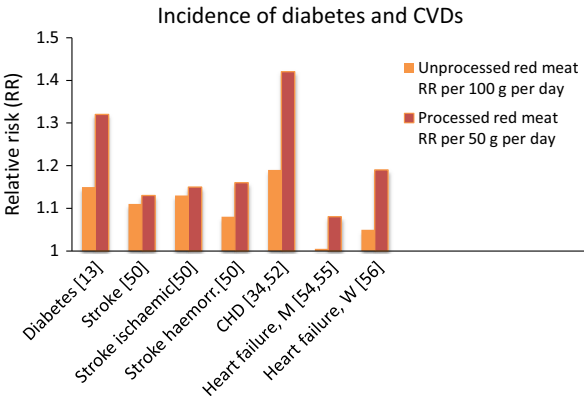

Fig. 2 *Results from meta-analyses of the associations between unprocessed red meat and processed meat consumption and incidence of type 2 diabetes and cardiovascular disease (CVD). (single studies of heart failure).*

an increased risk of T2DM. The most recent meta-analysis has shown an increased risk associated with the consumption of red meat, in particular processed meat [13]. Of interest, in a recent study, for every additional 50 g day^{-1} of processed meat consumed, fasting glucose was significantly higher; for every additional 100 g day^{-1} of unprocessed red meat consumed, both fasting glucose and insulin concentrations were significantly higher [14]. However, after adjustment for BMI, the observed associations were attenuated and no longer statistically significant. In addition, there was no modification by genetic loci that influence glucose or insulin resistance. The conclusion from a recent systematic review, although based on a small number of studies, was that a diet high in red and processed meat before pregnancy was significantly associated with an increased risk of gestational diabetes [15].

Potential mechanisms involved in T2DM development

It is not clear which components of red or processed meat contribute to the observed risk of T2DM and several components, including branched amino acids (BCAAs), saturated fatty acids (SFAs), advanced glycation end-products (AGEs), haeme iron, nitrite, nitrate and nitrosamine, phosphatidylcholine and L-carnitine, have been proposed. Possible mechanistic pathways, which might at least partly explain the observed positive association with an increased T2DM risk, are presented in Fig. 3. These pathways are briefly described below and reviewed in more detail by Kim *et al.* [16].

Branched amino acids

The BCAAs, such as leucine, isoleucine and valine, have been positively associated with insulin resistance [17, 18] and with levels of glycated haemoglobin (HbA1c) [19]. Moreover, increased BCAA plasma levels have been associated with the development of T2DM [20]. Leucine, similar to insulin, may activate the mammalian target of rapamycin complex 1 (mTORC1) and ribosomal protein S6 kinase beta1 (S6K1) resulting in serine phosphorylation of IRS-1 and IRS-2, which interrupts signalling [18].

Saturated fatty acids

Saturated fatty acids and cholesterol are present in red and processed meat and have been reported to increase insulin resistance [13]. However, given the mixed results from intervention studies, it is unclear whether SFAs specifically from red and processed meat contribute to insulin resistance.

Advanced glycation end-products

During cooking of red and processed meat, AGEs are produced. Meat is browned during roasting and barbecuing through the Maillard reaction involving the breakdown of tetrapyrrole rings in the muscle protein myoglobin [21]. Red meat and processed red meat, in particular, have the highest AGE levels per 100 g food (raw beef, 707 kU; boiled beef frankfurters, 7484 kU; broiled beef frankfurters, 11 270 kU) [22]. Of the 10–30% of AGEs absorbed in the intestine, two-thirds are retained in the body tissues and one-third is excreted in urine and/or faeces [23]. Findings from human studies indicate that diet-derived AGEs may be associated with progression to T2DM [24]. It has been shown that AGEs may increase the production of C-reactive protein (CRP), tumour necrosis factor alpha (TNF-α), vascular cell adhesion molecule-1 (VCAM-1), interleukin (IL)-1β and IL-6 by generating reactive oxygen species (ROS) [25]. A 6-week high-AGE diet in patients with T2DM increased serum levels of AGEs, CRP, TNF-α, VCAM-1 and oxidized LDL and significantly activated NF-kB [26]. It was also found that an AGE-restricted diet in patients with T2DM decreased markers of oxidative stress and inflammation and improved endothelial function and insulin sensitivity [25, 27]. However, it is still unclear whether dietary AGEs influence insulin sensitivity, as current evidence is based on low-quality studies [24].

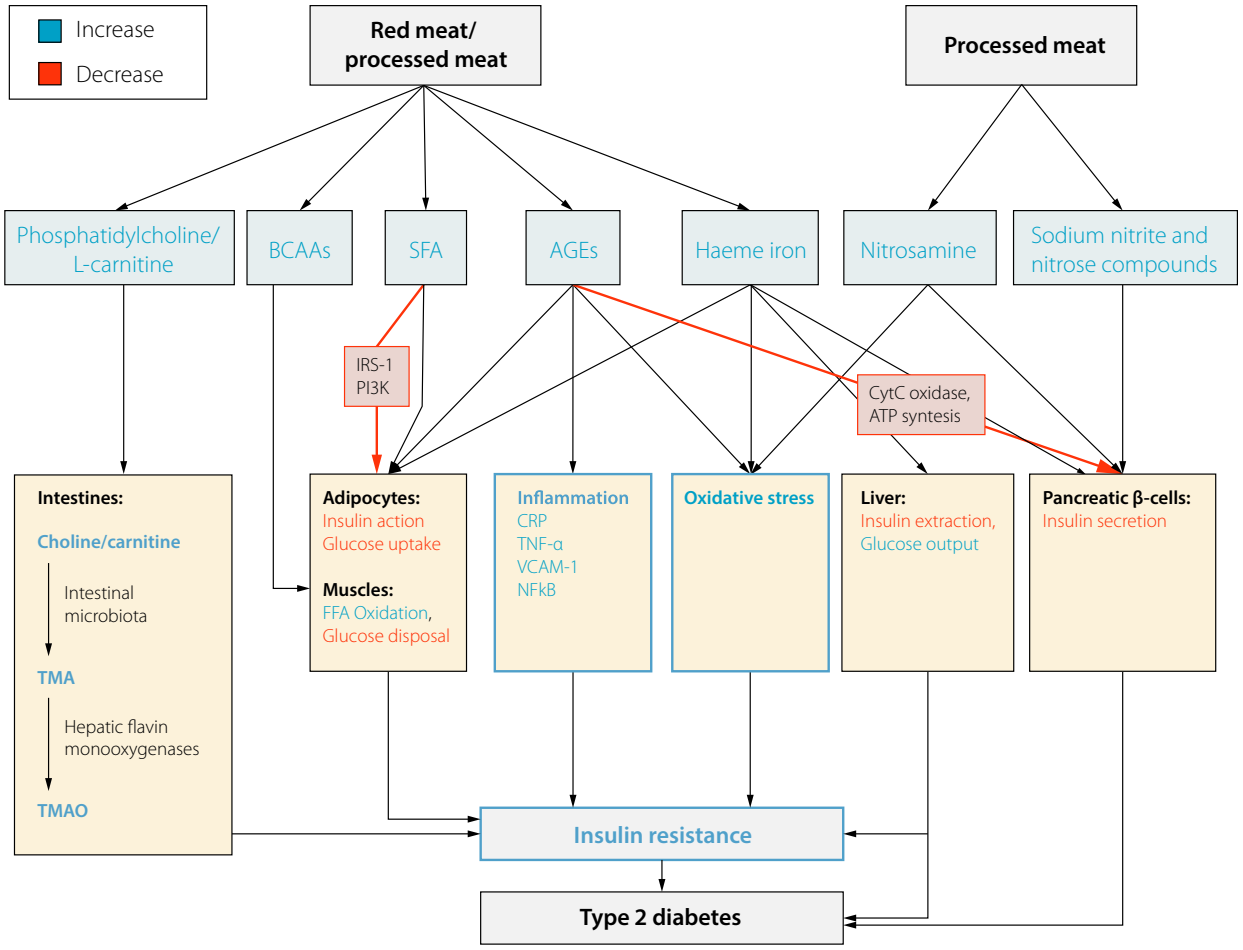

Fig. 3 *Possible mechanisms linking red and processed meat metabolites to aetiology of type 2 diabetes. Increased saturated fatty acid (SFA) intake elevates intracellular fatty acyl-CoA and diacylglyceride, which in turn results in the decreased insulin activation of insulin receptor substrate 1 (IRS-1)-associated phosphatidylinositol 3-kinase (PI3K) in muscle, leading to the decreased insulin-stimulated glucose transport activity. Elevated advanced glycation end-products (AGEs) increase the formation of nitric oxide by inducing the expression of nitric oxide synthase and, in turn, impair the glucose-stimulated insulin secretion through nitric oxide-dependent inhibition of cytochrome C oxidase and ATP synthesis (see text for further details). BCAA, branched amino acid; FFA, free fatty acid; CRP, C-reactive protein; TNF-α, tumour necrosis factor alpha; VCAM-1, vascular cell adhesion molecule-1; TMA, trimethylamine, TMAO, trimethylamine N-oxide; NF κB, nuclear factor kappaB. Modified from Kim* et al. *2015 [16].*

Iron

Red meat is the main source of haeme iron, which is more easily absorbed (25%) than nonhaeme iron (5–15%), and a raised iron concentration may contribute to increased T2DM risk via increased glucose production and decreased glucose utilization [28]. Iron, as a pro-oxidant, participates in the formation of the highly reactive ROS and may increase cellular oxidative stress, which can inhibit insulin binding [29]. ROS can damage pancreatic β-cells, impair insulin-stimulated IRS-1 tyrosine phosphorylation, decrease PI3K and inhibit the translocation of glucose transporter type 4 (GLUT4) to the plasma membrane [30]. It has been observed that iron deposition in pancreatic β-cells leads to impaired insulin secretion [31]. High hepatic iron stores interfere with hepatic insulin extraction and increased hepatic glucose output [32]. A summary result from meta-analysis of six prospective studies, including 41 091 control subjects and 4366

T2DM cases, has shown an increased risk of T2DM amongst individuals with higher serum concentrations of ferritin, a biomarker of iron stores [$RR_{summary}$ 1.66, 95% confidence interval (CI) 1.15–2.39 for the highest versus the lowest quintile; P_{trend} = 0.01) [33]. A meta-analysis of four prospective studies of the association between dietary haeme iron and risk of T2DM based on 179 689 control subjects and 9246 participants with T2DM has shown that high intake of dietary haeme iron is associated with an increased risk of T2DM ($RR_{summary}$ 1.31, 95% CI 1.21–1.43 for the highest versus the lowest quintile) [33]. Data from these meta-analyses based on observational prospective studies show that increased dietary haeme iron intake and increased stores of iron, as measured by serum ferritin concentration, are associated with a higher risk of T2DM. However, there is currently a lack of evidence from well-performed randomized controlled interventions on the impact of reduced iron stores.

Nitrite, nitrate and nitrosamine

Processed meat contains on average about 50% more nitrates than unprocessed red meat [34]. Nitrites and nitrates used in processed meat for preservation are converted to nitrosamines by binding to amino compounds within the food or in the stomach [35]. It has been shown in animal studies that nitrosamines are toxic to pancreatic β-cells, decrease insulin secretion and increase the risk of T2DM [36, 37]. Nitrosamines contribute to DNA damage and ROS generation involved in protein adduct formation, lipid peroxidation and pro-inflammatory cytokine activation [37]. By contrast, dietary nitrites and nitrates may increase nitric oxide (NO) production and improve microvascular and endothelial dysfunction, hypertension and insulin sensitivity [38]. However, NO in the presence of superoxide is transformed into a strong cytotoxic oxidant, peroxynitrite, which could potentially influence T2DM and its complications, cardiovascular and neurodegenerative diseases [39].

Sodium

Processed meat may contain on average about 400% more sodium than unprocessed red meat [34]. Salt/sodium in processed meat may be one of the factors underlying the observed increase in T2DM risk. In a prospective study, high consumption of processed meat amongst men significantly increased T2DM risk (RR 1.37, 95% 1.11–1.71 for 139 g vs. 28 g daily consumption of processed meat). After adjustment for sodium, the observed association was strongly attenuated and no longer significant; therefore, the authors concluded that sodium (more than SFAs, cholesterol, haeme iron or nitrite/nitrate) was responsible for the observed positive association with T2DM [40].The association between high salt intake and insulin sensitivity is, however, unclear, because available data are conflicting. Some studies showed an increased insulin sensitivity after severe salt restriction [41], whereas others showed no change in healthy subjects [42, 43] or reduced insulin sensitivity in hypertensive subjects [44].

Trimethylamine N-oxide from phosphatidylcholine and L-carnitine

Phosphatidylcholine and L-carnitine present in red meat have been reported to be associated with metabolic disorders and CHD [45, 46]. In the intestine, phosphatidylcholine is broken down to choline, which is transformed by the intestinal microbiota to trimethylamine (TMA), and then TMA is metabolized to trimethylamine N-oxide (TMAO) [47]. L-Carnitine is also metabolized by the microbiota to TMAO. In mice fed a high-fat diet, dietary TMAO increased fasting insulin levels and HOMA-IR and produced impaired glucose tolerance [45]. In a study investigating the association between fasting plasma TMAO concentration and incident CVD events amongst men undergoing elective coronary angiography, a high concentration of TMAO was a significant predictor of the risk of death, myocardial infarction or stroke over 3 years [hazard ratio (HR) 1.88, 95% CI 1.44–2.44 for the highest versus the lowest quartile) [46].

Endocrine disruptors

Molecules that influence the hormonal system such as dioxins, phthalates and bisphenol A may be present in plastic food packaging and consequently even in meat products. Long-term exposure to low levels of endocrine disruptors derived from red and processed meat might alter glucose metabolism, as has been observed in rats treated with a predicted 'safe' level of bisphenol A [48]. Endocrine disruptors have been shown to induce insulin resistance and impair pancreatic β-cell function [49].

In summary, red and processed meat contain several components, including natural nutrients in red meat, but also additives and preservatives,

environmental contaminants and residues from production, as well as substances created in chemical processes during cooking of meat at high temperatures, which may be linked to an increased risk of T2D.

Cardiovascular disease

Stroke

The overall findings suggest that both unprocessed and processed red meat consumption may be harmful with regard to risk of stroke. In a recent meta-analysis, results from six prospective cohorts, published between 2003 and 2012, on the association between red meat consumption and risk of stroke incidence and stroke mortality were quantitatively summarized [50]. The meta-analysis included data from 329 495 participants and 10 630 stroke cases (6420 and 1276 cases of ischaemic and haemorrhagic stroke, respectively), including men and women from the USA, Europe and Japan. There was no heterogeneity amongst the studies. Consumption of unprocessed red meat was positively associated with an increased risk of stroke; for an increase in the consumption of 100–120 g day^{-1}: $RR_{summary}$ 1.11, 95% CI 1.03–1.20 for total stroke, $RR_{summary}$ 1.13, 95% CI 1.00–1.27 for ischaemic stroke and $RR_{summary}$ 1.08, 95% CI 0.84–1.39 for haemorrhagic stroke. Consumption of processed meat was also positively associated with the increased risk; for an increase in the consumption of 50 g day^{-1}: $RR_{summary}$ 1.13, 95% CI 1.03–1.24 for total stroke, $RR_{summary}$ 1.15, 95% CI 1.06–1.24 for ischaemic stroke and $RR_{summary}$ 1.16, 95% CI 0.92–1.46 for haemorrhagic stroke. Of note, the summary risk estimates per serving were similar despite the smaller serving size (50 g) of processed meat as compared with unprocessed red meat (100–120 g).

Results from the prospective ARIC study (cohort of 11 601 adults amongst whom 699 incident strokes were diagnosed during 22.7 years of follow-up), published after the meta-analysis, further confirmed the observed positive association between red meat consumption and stroke incidence (HR 1.38, 95% CI 1.00–1.91 for 1.9 vs. 0.25 servings of total red meat per day) [51]. Specifically, the consumption of approximately one serving per day of unprocessed and processed red meat was associated with 41% (P_{trend} = 0.01) and 24% (P_{trend} = 0.04) increased risk of stroke, respectively.

Coronary heart disease

The current evidence suggests that high consumption of red meat, both unprocessed and processed, may increase the risk of CHD. However, in a recent dose–response meta-analysis of three prospective cohorts and one case–control study including 56 311 participants and 769 incident events, no association was found between the consumption of unprocessed red meat and CHD risk ($RR_{summary}$ 1.00, 95% CI 0.81–1.23 per 100 g serving/day) [34]. Following this meta-analysis, which was limited by the low number of events, results from the Nurses' Health Study (including 84 136 women and 2210 incident non-fatal myocardial infarctions and 952 deaths due to CHD) showed a statistically significantly increased CHD risk (RR 1.19, 95% CI 1.07–1.32 per serving of unprocessed red meat/day) [52]. Nevertheless, this finding needs to be confirmed in other populations.

The evaluation of processed meat consumption and incident CHD in a dose–response meta-analysis based on six studies including 614 062 participants and 21 308 events [34] indicated that each 50 g serving/day of processed meat was associated with a 42% higher risk of CHD ($RR_{summary}$ 1.42, 95% CI 1.07–1.89). In the analysis restricted to prospective studies, the risk was 44% (7–95%) higher.

Heart failure

The accumulated evidence regarding the association between red meat consumption and risk of HF is limited to four prospective cohort studies that have not been quantitatively summarized in a meta-analysis. In the first study [53] including 14 153 African-American and white participants and 1140 hospitalizations due to HF, unprocessed and processed red meat were analysed together and no statistically significant association was observed (HR 1.07, 95% CI 0.97–1.17 per serving/day). In another American cohort of 21 120 physicians, amongst whom 1204 new cases of HF were identified, high consumption of red meat (unprocessed meat and hotdogs) was associated with a statistically significantly increased risk of HF (HR, 1.02, 95% CI 1.01–1.04 per serving/day; HR 1.24, 95% CI 1.03–1.48 for the highest versus the lowest quintile) [54]. Unprocessed and processed red meats were analysed separately in only two cohorts. In a cohort of 37 035 Swedish men

amongst whom 2891 incident cases of HF and 266 deaths from HF were ascertained, the consumption of unprocessed red meat was not associated with the increased risk of HF (HR 0.99, 95% CI 0.87–1.13 for median intake of 83.2 g day^{-1} vs. 17 g day^{-1}) or HF mortality [55]. By contrast, the consumption of processed meat was statistically significantly associated with HF; for each 50 g day^{-1} increment in intake, the risk of HF increased by 8% (HR 1.08, 95% CI 1.02–1.15) and HF mortality increased by 38% (HR 1.38, 95% 1.17–1.63). The association between processed red meat and HF risk was observed for HF with and without antecedent myocardial infarction. A similar positive association with processed meat and no association with unprocessed red meat was observed in a cohort of 34 057 Swedish women, 2806 of whom were diagnosed with HF during 13 years of follow-up [56]. For each 50 g day^{-1} increase in processed red meat consumption, the risk of HF in women increased by 11% (HR 1.11, 95% CI 1.04–1.19) in analyses using only baseline assessment of meat intake and by 19% in analyses based on long-term dietary data. Overall, results from these four cohort studies suggest that there may be an increased risk of HF related to high consumption of red meat, especially processed red meat.

Figure 2 shows the magnitudes of the positive associations observed between unprocessed/processed red meat consumption and incidence of cardiometabolic diseases.

Potential mechanisms involved in CVD development

Although it is not clear which mechanisms related to the consumption of red and/or processed meat may be involved in the observed increased risk of CVD, it is likely that many of these mechanisms may be the same as those potentially related to the increased risk of T2DM (Fig. 3).

Cancer

In the last decade, concerns have been raised about the possibility that the consumption of red meat and processed meat may increase the risk of cancer. The summary of all cancer studies by the World Cancer Research Fund and American Institute for Cancer Research in 2007 concluded that the available scientific evidence was convincing that the consumption of processed and unprocessed red meat was associated with the increased risk of colorectal cancer [57]. Summary results from the most recent meta-analyses (2009–2015) based on prospective cohort studies of 11 cancer types [58–68] are presented in Table 2 and illustrated in Fig. 4. In a recent pooled analysis of 15 prospective cohort studies of prostate cancer [59], 52 683 incident cases (including 4924 cases of advanced prostate cancer) were identified during follow-up amongst 788 364 men examined within a consortium setting. For total prostate cancer, the observed associations were weak (2–4% increased risk for approximately one serving daily of unprocessed red meat or processed meat; statistically significant only for processed meat). For tumours identified as advanced stage at diagnosis (10 cohorts), a stronger positive association was observed (RR_{pooled} 1.19, 95% CI 1.01–1.40 for the consumption of ≥100 g day^{-1} vs. <20 g day^{-1} unprocessed red meat); the observed association was stronger in studies of men from North America (RR_{pooled} 1.30, 95% CI 1.07–1.57).

In October 2015, a Working Group of 22 scientists from 10 countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to evaluate the carcinogenicity of the consumption of red and processed meat [3]. They assessed more than 800 epidemiological studies that investigated cancer associations with the consumption of red meat or processed meat in many countries with diverse diets and races/ethnicities. The Working Group concluded, based on the large amount of data and the consistency of the associations across studies in different populations, that there is 'sufficient evidence in humans for the carcinogenicity of the consumption of processed meat'. Concerning red meat, chance, bias and confounding could not be ruled out with the same degree of confidence as applied to processed meat, as no clear association was observed in several of the large cohort studies. The conclusion of the Working Group was that there is 'limited evidence in humans for the carcinogenicity of the consumption of red meat' [3].These detailed assessments of more than 15 different types of cancer will be published in volume 114 of the IARC Monographs in late 2016.

Potential mechanisms involved in cancer development

Several mechanisms have been proposed to explain the observed associations between red meat consumption and cancer. It should be noted

Table 2 *Summary risk estimates from meta-analyses of cohort studies of the associations between unprocessed and processed red meat consumption and incidence of major cancers*

Cancer site	Cohorts, *n* unprocessed/ processed meat	Cases, *n* unprocessed/ processed meat	Unprocessed red meat		Processed meat	
			Servings	RR (95% CI)	Servings	RR (95% CI)
Breast						
Guo *et al.* [58]	14/12	31 552	120 g day^{-1}	1.11 (1.05–1.16)	50 g day^{-1}	1.09 (1.03–1.16)
Prostate						
Wu *et al.* [59]	15 (total) 10 (advanced)	52 683 4924	≥100 g day^{-1} vs. <20 g day^{-1}	1.02 (0.98–1.06) 1.19 (1.01–1.40)	≥40 g day^{-1} vs. <5 g day^{-1}	1.04 (1.01–1.08) 1.17 (0.98–1.39)
Lung						
Xue *et al.* [60]	6/5	n.a.	High/low	1.21 (1.14–1.28)	High/low	1.09 (0.99–1.19)
Colorectum						
Chan *et al.* [61]	8/9	4314/10 863	100 g day^{-1}	1.17 (1.05–1.31)	50 g day^{-1}	1.18 (1.10–1.28)
Gastric						
Zhu *et al.* [62]	5/9	n.a.	High/low	1.02 (0.90–1.17)	High/low	1.18 (1.00–1.38)
Oesophagus						
Qu *et al.* [63]	2/2	6499	100 g day^{-1}	1.41 (1.16–1.70)[a]	50 g day^{-1}	1.81 (1.32–2.48)[a]
Pancreas						
Larsson and Wolk [64]	11/11	6643	120 g day^{-1}	1.13 (0.93–1.39)[a]	50 g day^{-1}	1.19 (1.04–1.36)
Liver						
Luo *et al.* [65]	3/3	n.a.	High/low	1.43 (1.08–1.90)	High/low	1.01 (0.79–1.28)
Kidney						
Alexander and Cushing [66]	16/16	n.a.	High/low	1.02 (0.91–1.15)	High/low	1.19 (1.03–1.37)

Table 2 (*Continued*)

Cancer site	Cohorts, *n* unprocessed/ processed meat	Cases, *n* unprocessed/ processed meat	Unprocessed red meat		Processed meat	
			Servings	RR (95% CI)	Servings	RR (95% CI)
Bladder						
Li *et al.* [67]	5/5	4814/3927	High/low	1.08 (0.97–1.20)/	High/low	1.08 (0.96–1.20)
Ovary						
Wallin *et al.* [68]	8/8	2349	100 g week^{-1}	1.02 (0.94–1.04)	100 g week^{-1}	1.05 (0.98–1.14)

n.a, not available.
[a]Significant heterogeneity.

that mechanistic evidence is available mainly for the digestive tract. Figure 5 illustrates the potential mechanisms and signalling pathways related to the iron/haeme iron content in red meat that might be involved in colon carcinogenesis. One of the components of red meat, haeme (an iron porphyrin pigment present at 10-fold higher concentrations in red meat compared to white meat), has been ascribed a role in cancer development. Furthermore, free iron is present in red meat and in the intestinal mucosa [69]. Free ferrous iron is released from haeme and iron itself plays a role in the increased production of ROS, especially H_2O_2, which may further induce inflammation, cytotoxic effects and genetic mutations [70, 71]. Red meat consumption has been shown to initiate epigenetic changes in DNA [72] and lead to lipid peroxidation resulting in the formation of oxysterols and aldehydes, which could stimulate uncontrolled peroxidation. It also leads to the production of N-nitroso compounds (NOCs) by bacteria in the large bowel and DNA adduct formation [73]. Haeme iron in red meat under certain conditions may act as a nitrosating agent. Processed red meat preserved by the addition of nitrites and by smoking or direct fire drying may contribute even further to the production of NOCs. When beef is consumed, high levels of malondialdehyde, a known mutagen, are found in the plasma [74]. The potential mechanisms involved in the carcinogenesis of colon cancer, and in particular related to the high content of iron in red meat, have recently been reviewed in detail [75].

During the cooking of red meat at high temperature, HAAs are formed. HAAs are genotoxic and are known to be absorbed in the human gastrointestinal tract. The amounts of HAAs produced depend on the duration and temperature of the cooking method. Using high-temperature methods, such as grilling, pan frying and barbecuing, is associated with higher amounts of HAA production. However, in the context of HAA production, it should be noted that the type of cooking method rather than the type of meat cooked may be more important. HAAs are also produced during the frying of fish or chicken. Meat smoked or charred/burned over an open fire or heated surface contains polycyclic aromatic hydrocarbons (PAHs). PAHs have been shown to induce the formation of DNA adducts and interfere with apoptosis. Substantial supporting mechanistic evidence is available especially for haeme iron, NOCs and HAAs [3].

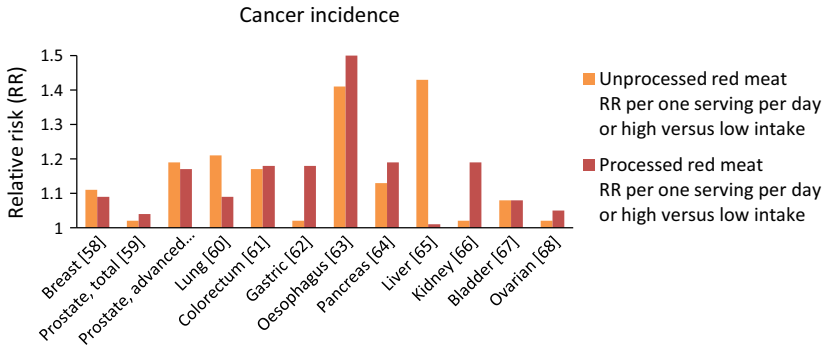

Fig. 4 *Results from meta-analyses of the association between unprocessed red meat and processed meat consumption and incidence of cancer at several sites.*

Mortality

Interestingly, in an early meta-analysis of five prospective studies from Western countries, mortality was 16–18% lower amongst occasional meat eaters, vegetarians and fish eaters, whilst regular meat eaters and vegans shared the highest mortality [76]. Summary results for mortality from the most recent meta-analyses of prospective cohort studies are presented in Table 1 and Fig. 6.

All-cause mortality

Most of the accumulated evidence from observational epidemiological studies is for all-cause mortality. The summary risk estimates in a recent meta-analysis of nine prospective cohorts evaluating mortality risk in relation to the consumption of unprocessed red meat and processed meat are based on data from 1 330 352 participants from the USA (five cohorts), Europe (three cohorts) and China (one cohort), including 137 376 all-cause deaths [77]. Processed meat consumption was statistically significantly associated with increased risk ($RR_{summary}$ 1.23, 95% CI 1.17–1.28 for the highest versus the lowest category of consumption). In a dose–response meta-analysis, the consumption of processed meat was significantly positively associated with all-cause mortality in a nonlinear fashion ($P_{nonlinearity}$ = 0.003); comparing processed meat consumption of 60 g day^{-1} vs. 10 g day^{-1}, a 22% increase in risk was observed ($RR_{summary}$ 1.22, 95% CI 1.13–1.31).

High unprocessed red meat consumption was not significantly associated with the increased all-cause mortality ($RR_{summary}$ 1.10, 95% CI 0.98–1.22 for the highest versus the lowest category of consumption). In a dose–response meta-analysis, an increase in the consumption of unprocessed red meat of 100 g day^{-1} was associated with a borderline statistically significant 9% increased risk ($RR_{summary}$ 1.09, 95% CI 0.997–1.20); heterogeneity between studies was observed. In a recent meta-analysis, the authors identified the source of the between-study heterogeneity [78]. For the US populations (four cohorts), a dose–response analysis showed that each serving per day of unprocessed red meat consumption was positively and statistically significantly associated with risk of all-cause mortality ($RR_{summary}$ 1.15, 95% CI 1.12–1.19; no heterogeneity); summaries of results from European and Asian cohorts did not show positive associations.

The combination of unprocessed and processed red meat consumption in predicting all-cause mortality was examined by Bellavia *et al.* [79] in a population-based cohort of 74 645 Swedish men and women amongst whom 16 683 deaths were documented during 15 years of follow-up. Compared with no consumption, high consumption of processed red meat (75 g day^{-1}) was associated with shorter survival (HR 1.47, 95% CI 1.13–1.90). Moderate and high intakes of unprocessed red meat were associated with shorter survival only when accompanied by a high intake of processed meat. In the analysis stratified by unprocessed and processed red meat intake, consumption of 65–100 g day^{-1} unprocessed red meat was not associated with shorter survival when the consumption of processed meat was limited to ≤20 g day^{-1} [79]). More studies are needed to replicate this finding.

CVD mortality

A recent meta-analysis of CVD mortality in relation to red meat consumption was based on data from seven prospective cohorts and in relation to processed meat on six cohorts, overall including 1 674 272 participants and 44 340 cases of CVD mortality [80]. Summary risk estimates

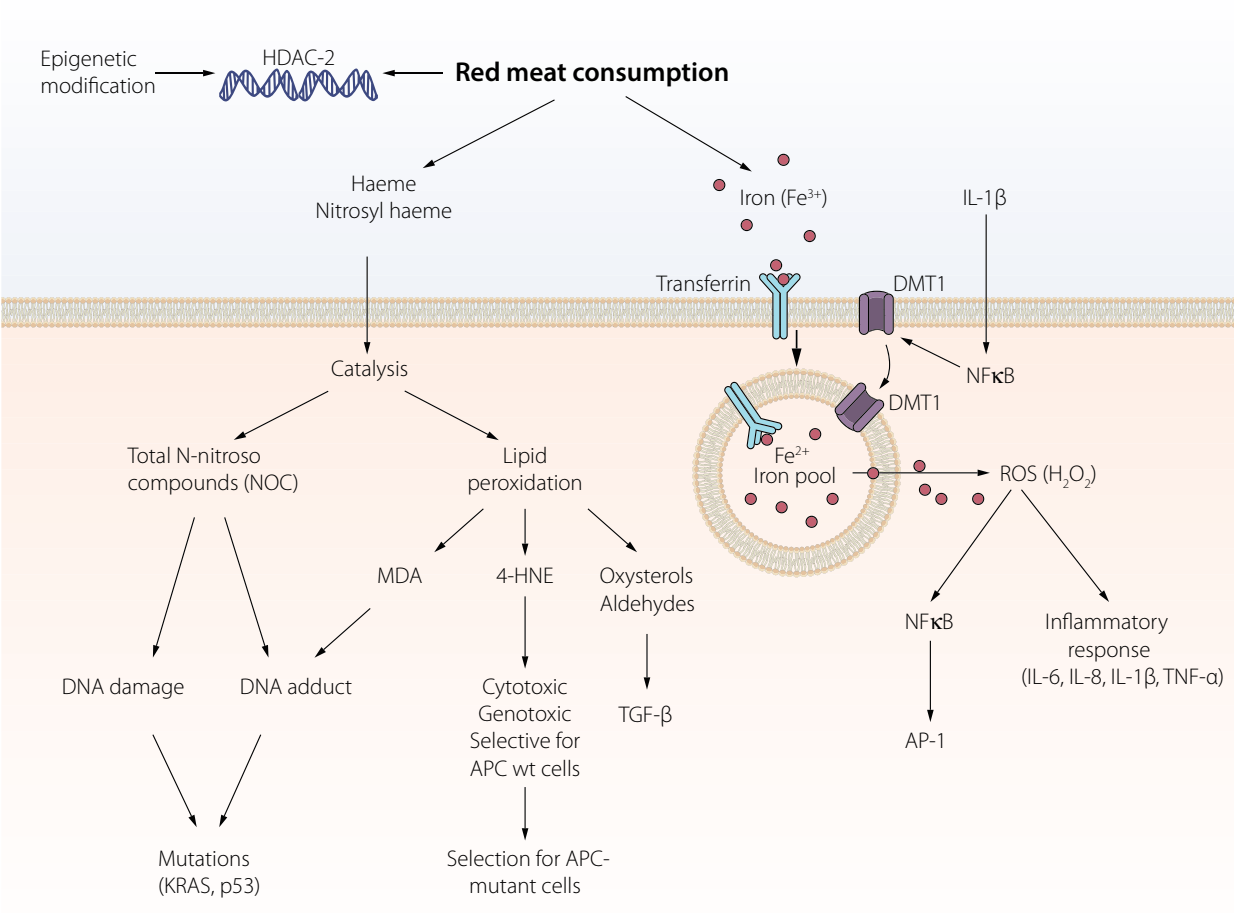

Fig. 5 *Potential mechanisms and signalling pathways involved in colon carcinogenesis related to red meat consumption. Consumption of red meat has been shown to induce epigenetic changes in host DNA. These changes occur specifically through altering the levels of histone deacetylase-2 (HDAC-2). Unprocessed and processed red meat further contain iron, haeme and nitrosyl haeme, all of which at high levels may increase the risk of colon cancer development. Both haeme and nitrosyl haeme undergo catalysis resulting in the formation of N-nitroso compounds (NOCs); these NOCs can result either in DNA damage or in DNA adduct formation. Red meat consumption specifically leads to mutations in* p53 *and* KRAS *genes, further leading to the initiation and progression of colon carcinogenesis. Alternatively, haeme catalysis can also lead to the generation of lipid peroxidation end-products, such as malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), oxysterols and aldehydes. MDA exposure can result in DNA adduct formation, leading to DNA mutations and aberrant proliferation, further contributing to the initiation of colon cancer. In addition, 4-HNE is a cytotoxic and genotoxic compound, which targets colon cells that carry a wild-type (wt)* APC *gene; this selective toxicity results in the enhancement of colon cells that carry a mutated* APC *gene, resulting in colon cancer promotion and progression. Additionally, lipid peroxidation results in the formation of oxysterols and aldehydes, which further alter hormone signalling, specifically transforming growth factor beta (TGF-β), ultimately resulting in uncontrolled proliferation that contributes to the promotion and progression of colon cancer. Another major component of red meat is iron; ferric iron (Fe^{3+}) binds to transferrin, resulting in receptor activation and endocytosis. Ferric iron is further converted to ferrous iron (Fe^{2+}) via divalent metal transporter 1 (DMT1), which then contributes to the overall iron pool of the cell. Iron has been linked to the production of reactive oxygen species (ROS), specifically H_2O_2; these reactive species can then upregulate inflammatory mediators, such as nuclear factor kappaB (NF κB), IL-6, IL-8, IL-1β and tumour necrosis factor alpha (TNF-α), leading to the promotion and progression of colon cancer. Furthermore, IL-1β signalling upregulates NFκB, which then activates DMT1 iron transporter, resulting in increased levels of ferrous iron within the cell, representing a feedback loop in iron regulation. Modified from Derry* et al. *2013 [75].*

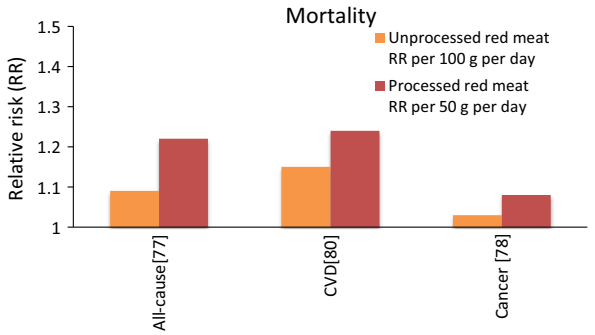

Fig. 6 *Results from meta-analyses of the association between unprocessed red meat and processed meat consumption and all-cause, cardiovascular disease (CVD) and cancer mortality.*

demonstrated that the consumption of unprocessed and processed red meat was statistically significantly positively associated with CVD mortality. In the dose–response meta-analysis, each increase in the consumption of unprocessed red meat by 100 g day^{-1} was associated with a 15% higher risk ($RR_{summary}$ 1.15, 95% CI 1.05–1.26). The summary risk estimates were higher for the US populations (four cohorts); comparing the highest with the lowest intake showed that high consumption of unprocessed red meat was associated with a 37% increased risk of CVD mortality ($RR_{summary}$ 1.37, 95% CI 1.18–1.59; no heterogeneity). Summaries of the results from two European and four Asian cohorts did not show positive associations. Each 50 g day^{-1} increase in processed meat intake was associated with a 24% increase in CVD mortality ($RR_{summary}$ 1.24, 95% CI 1.09–1.40).

Ischaemic heart disease mortality

A meta-analysis of ischaemic heart disease (IHD) mortality in relation to red meat consumption was based on data from four prospective cohorts and in relation to processed meat on three cohorts, overall including 1 674 272 participants and 1370 cases of IHD mortality [80]. Summary risk estimates based on a small number of IHD deaths did not show a statistically significant association between the consumption of red meat or processed meat and IHD mortality.

Cancer mortality

A recent meta-analysis of prospective studies of unprocessed and processed red meat consumption in relation to cancer mortality included 1 144 264 participants and 45 738 cancer deaths [78]. The summary risk estimate for the comparison of the highest versus the lowest intake of unprocessed red meat (based on eight cohorts) did not show an association with cancer mortality ($RR_{summary}$ 1.03, 95% CI 0.89–1.18). In the dose–response meta-analysis of processed meat intake, each increase in consumption by 50 g day^{-1} was associated with a statistically significant 8% increase in cancer mortality risk.

Environmental impact of red meat consumption

During the last two decades, red meat consumption has also been receiving an increasing amount of attention from nonmedical researchers because of the adverse consequences of red meat production on the environment and climate. Red meat is produced at a major cost to the environment, leading to greenhouse gas emissions, fossil energy use, water use and water quality changes as concentrated livestock operations can be major water polluters (due to animal waste products, fertilizers and pesticides) [81]. For example, greenhouse gas emissions (expressed as CO_2 equivalents per kg food) related to the production of 1 kg meat vary substantially, from 50 for lamb, 30 for beef and 10 for pork to 4 for white meat (chicken, turkey and game birds) and 2.6 for fish (6.5 for frozen fish) [82]. Changes in demand for red meat may change the environmental impact of meat production by influencing how much meat is produced. It has been estimated that global meat consumption may double from 2000 to 2050, mostly as a consequence of an increasing world population, but also partly because of increased per capita meat consumption, with much of this increase occurring in the developing world [83].

Comments

Overall, the substantial accumulated evidence from observational studies on the associations between the consumption of unprocessed/processed red meat and the risk of several chronic diseases and preterm mortality reviewed here indicates statistically significant, although weak to moderate, increased relative risks, with heterogeneity in some of the meta-analyses. Results presented in this review are based only on prospective cohorts. However, some limitations of the available evidence should be considered. The studies were based on self-reported meat intake, assessed using food frequency questionnaires

(FFQs), which may be influenced by measurement error. In future, it would be of interest to go beyond the use of FFQs by also including biomarkers or metabolomics to study the associations between unprocessed/processed red meat consumption and chronic diseases. In addition, some of the observed results in previous studies may be limited by inadequate adjustment for potential confounders. It has been suggested that higher red meat intake may be a marker of risk due to an unhealthy lifestyle, rather than a risk factor itself [84]. Indeed in some populations, it was observed that consumption of red meat and processed meat is correlated with a lower-quality diet [85]. More complete adjustment for a broad spectrum of potential confounders in future studies could help to address this potential limitation. It should be noted, however, that the recent classification of consumption of red meat (*limited evidence*) and processed meat (*sufficient evidence*) as carcinogenic, by the WHO/IARC Expert Group, was additionally based on experimental animal and mechanistic studies that supported evidence from observational studies [3].

Concerns regarding health hazards related to high red meat intake and especially processed red meat intake, both of which have been increasing during recent decades, have led to new nutrition recommendations and new dietary guidelines proposing decreased consumption of red and processed meat. So far, however, not all countries and not all health-related organizations have explicitly and quantitatively addressed this issue. The first recommendations regarding the intake of unprocessed and processed red meat, released by the World Cancer Research Fund (WCRF) and American Institute of Cancer Research (AICR) in November 2007, based on a review of cancer publications up until 2006, were specifically related to cancer prevention [57]. The general recommendation to 'limit intake of red meat and avoid processed meat' was accompanied by specific personal guidelines: 'people who eat red meat consume less than 500 g (18 oz) a week, very little if any to be processed'. These cancer-specific recommendations and quantitative guidelines were followed in 2012 by general health-related dietary recommendations in Nordic countries (Nordic Nutrition Recommendations, 2012) [86] with specific personal guidelines that also quantified intake: 'eat less red and processed meat, no more than 500 g a week. Only a small amount of this should be processed meat' [87]. Moreover, the Nordic Nutrition Recommendations considered not only public health issues but also the environmental impact of the recommended diet. The US Department of Health and Human Services and the US Department of Agriculture have released (7 January 2016) the eighth edition (2015–2020) of the Dietary Guidelines for Americans. These new guidelines do not explicitly provide recommendations regarding red meat and/or processed meat and do not quantify amounts; they also do not take into account the environmental impact of dietary patterns [88]. The most recently released (March 2016) national guidelines in the Netherlands, which are very progressive in many respects, recommend limiting the consumption of red meat, particularly processed meat [89]. The expert authors of the guidelines concluded that state-of-the-art science provides 'plausible' evidence to support these meat-related guidelines.

Conclusions

Overall, it is plausible to conclude, taking into account the available scientific evidence, that high consumption of red meat, and especially processed meat, is associated with the increased risk of several major chronic diseases and preterm mortality. Moreover, the production of red meat also involves an environmental burden. Therefore, some European countries have already integrated these two issues, human health and the 'health of the planet', into new national dietary guidelines and recommended limiting the consumption of red meat.

Conflict of interest statement

Professor Wolk was a member of the WHO/IARC Working Group evaluating the carcinogenicity of consumption of unprocessed red meat and processed meat in 2015.

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