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Review

# Meat and cancer

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ABSTRACT

An increasing literature associates high intake of meat, especially red meat and processed meat with an increased risk of cancers, especially colorectal cancer. There is evidence that this risk may not be a function of meat per se, but may reflect high-fat intake, and/or carcinogens generated through various cooking and processing methods. The cancer risk may be modulated by certain genotypes. Cancers associated with high meat consumption may be reduced by the addition of anticarcinogens in the diet, especially at the same time as meat preparation or meat consumption, or modification of food preparation methods. Meat contains potential anticarcinogens, including omega-3 polyunsaturated fatty acids, and conjugated linoleic acid (CLA). Red meat, in particular, is an important source of micronutrients with anticancer properties, including selenium, vitamin B6 and B12, and vitamin D. Adjusting the balance between meat and other dietary components may be critical to protecting against potential cancer risks.



**Contents**



## 1. Introduction

Meat is a primary source of water and fat, and contains between 20% and 35% protein, providing all essential amino acids (lysine, threonine, methionine, phenylalanine, tryptophan, leucine, isoleucine and valine), as well as good amounts of various micronutrients (National Health & Medical Research Council, 2006). It is an easily absorbable source of iron, zinc and selenium, as well as containing good levels of vitamins B6 and B12, and vitamin D, and significant amounts of omega-3 polyunsaturated fatty acids. Thus, it is a valuable source of some key nutrients. However, the publication in 2007 of the (World Cancer Research Fund/American Institute for Cancer Research, 2007), raised considerable alarms about the cancer risks associated with red and processed meats, in concluding that they are a convincing cause of colorectal cancer (CRC). The summary of this report stresses that people should be eating an upper limit of 500 g of cooked red meat per week, and avoiding

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processed meats. This same conclusion has been reinforced by the recent publication of the policy document (World Cancer Research Fund/American Institute for Cancer Research, 2009). If the conclusion is true and the recommendations are strictly followed, human consumption of this nutrient source could be substantially reduced or largely prevented.

The conclusions of the report are controversial. For example, Boyle, Boffetta, and Autier (2008) drew a different conclusion from the presented data, disputing that the evidence linking meat consumption to colorectal cancer was convincing, and concluding that there was no substantive evidence for associating many forms of cancer with specific dietary practices, including meat consumption. It would also seem possible that the data reflect confounding factors.

This brief review considers some of the relevant literature, with emphasis on where a cancer hazard might be arising and how such a possible risk, if real, could be minimised.

## 2. Meat intake in relation to the risk of cancer

The main cancer type that has been associated with high meat consumption is CRC, based on a considerable number of studies, many of whose conclusions are collated in three meta-analyses of case–control studies (Larsson & Wolk, 2006; Norat, Lukanova, Ferrari, & Riboli, 2002; Sandhu, White, & McPherson, 2001). Sandhu et al. (2001) concluded that a 12–17% increased risk of CRC was associated with a daily increase of 100 g of all meat or red meat, and a 49% increased risk associated with a daily increase of 25 g of processed meat. Similar conclusions were drawn by Norat et al. (2002), who calculated that those individuals in the highest quartile of red meat consumption had a 1.35-fold increased risk of CRC, while those in the highest quartile of processed meat intake had a 1.31-fold increased risk. Larsson and Wolk (2006) drew similar conclusions, in attributing a 1.28-fold increased CRC risk for the highest as compared with the lowest red meat intake, and 1.20-fold increased risk for processed meat. However, the reviews concluded that there was no significant association between total meat intake and CRC risk.

The European Prospective Investigation into Cancer and Nutrition (EPIC) included 478,040 men and women from 10 European countries, and considered CRC formation some time after the collection of dietary information. All subjects were free of cancer at enrolment, at which time they provided information on diet and lifestyle (Norat et al., 2005). Approximately 5 years later, the same group showed a statistically significant increase in CRC risk that was positively associated with the intake of red and processed meat. A high intake was considered as >160 g/day, while low intake was <20 g/day. The high intake group had a risk 1.35-fold as compared with the lower intake group, although the confidence interval did not exclude the null hypothesis. By 10 years, the risk of development of colorectal cancer for a study subject aged 50 years was 1.71% for the highest category of red and processed meat intake, and 1.28% for the lowest category of intake. The association with CRC was stronger for processed than for unprocessed red meat.

Bandera, Kushi, Moore, Gifkins, and McCullough (2007) summarised current evidence relating endometrial cancer to dietary intake of animal products. Their meta-analysis, mainly based on case–control studies, showed an increased endometrial cancer risk of 1.26 per 100 g/day of total meat, 1.51 per 100 g/day of red meat and 1.03 per 100 g/day of poultry. They concluded that endometrial cancer risk is enhanced by high meat consumption, particularly of red meat. Our own New Zealand data suggested that differences between cancer risk of different ethnic group might be partly explained by different patterns of meat consumption (Ferguson, 2002).

The most convincing evidence on meat association with cancer is from processed meat. It is thus important to characterise what this actually means. The common use of this term refers to meats preserved by the addition of preservatives, or by smoking, curing, or salting. This class generally includes ham, bacon, smoked chicken, pastrami, and salami. Since this term is used inconsistently in epidemiological studies, the data are highly variable. The European data, which is most convincing, includes sausages, bratwursts, frankfurters, and hot dogs, all of which have nitrites, nitrates or other preservatives added.

Diet is difficult to measure accurately, especially in separating out effects of individual foods and food components, given the multiple correlations that exist between the different elements (Boyle et al., 2008). The effect of confounding factors is well illustrated by the recent pooled analysis of 13 prospective studies on renal cell cancer reported by Lee et al. (2008). Their analysis included 530,469 women and 244,483 men, who had completed a validated food frequency questionnaire at study entry. Follow-up times of up to 7–20 years allowed comprehensive examination of the influence of meat, fat, and protein intakes on risk of renal cell cancer. Lee et al. (2008) described statistically significant positive associations between intakes of total fat, saturated fat, monounsaturated fat, polyunsaturated fat, cholesterol, total protein, and animal protein and this cancer. However, after adjusting for body mass index, fruit and vegetable intake, and alcohol intake, the associations were no longer statistically significant.

It is also possible that the relationship between cancer risk and disease formation seen in some studies is reflecting a dietary pattern rather than revealing effects of meat per se. For example, De Stefani et al. (2008) considered a Western dietary pattern as one that is characterised by high levels of red meat, fried eggs, potatoes and red wine. This pattern was associated with a significantly increased risk of bladder cancer (OR 2.35, 95% CI 1.42–3.89).

## 3. Possible mechanisms by which meat could increase the risk of cancer

There are a number of possible mechanisms for a link between meat consumption and CRC. These include the promotion of carcinogenesis by high-fat intake, the production of carcinogenic heterocyclic amines (HCAs) and/or polycyclic aromatic hydrocarbons (PAHs) during cooking, the formation of carcinogenic *N*-nitroso compounds (NOCs) either within meat per se or as a result of endogenous processes, and the promotion of carcinogenesis by haem iron (Santarelli, Pierre, & Corpet, 2008; World Cancer Research Fund/American Institute for Cancer Research, 2007). It is also suggested that the high energy density of meat increases the likelihood of obesity, itself a major risk factor for cancer (World Cancer Research Fund/American Institute for Cancer Research, 2007). If the primary mechanisms could be established, it may be possible to reduce the cancer load by changing the processes that lead to carcinogen formation, in preference to banning red or processed meats. A summary of such possible processes is shown in Fig. 1.

### 3.1. High-fat intake

This hypothesis suggests it is not the meat per se, but high-fat diets that promote carcinogenesis. One mechanism suggested for this is via insulin resistance or fecal bile acids (Santarelli et al., 2008). Epidemiological studies, such as those of Lin, Zhang, Cook, Lee, and Buring (2004), have related CRC risk in women to dietary fat and fatty acids intake. Although fat intake from meat has been suggested to explain a link between CRC and meat intake, experimental studies have shown inconsistent results, and epidemiological studies have failed to confirm a link (Santarelli et al., 2008).

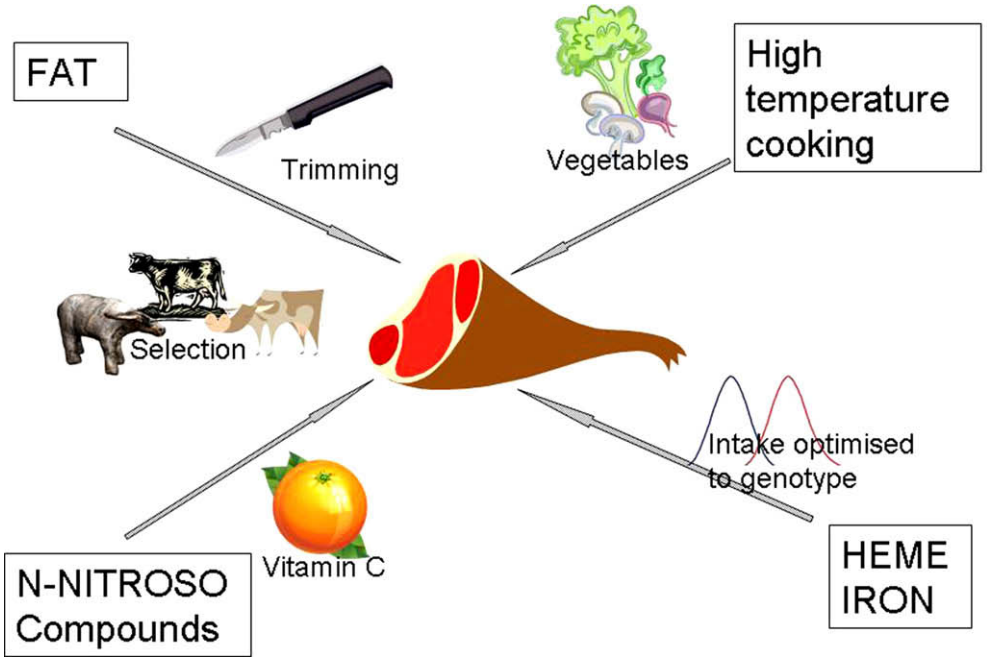


**Fig. 1.** Possible approaches to reducing cancer risk from meat. Four major mechanisms are hypothesised to be involved in the cancer risk associated with high intake of meats. The high-fat content of meat is currently being widely addressed by breeding practices, and trimming of various cuts of meat. The mutagenicity of compounds associated with high-temperature cooking of meats can be reduced by cooking or eating these at the same time as a high intake of fruits, vegetables and cereals. The efficacy of formation of NOC is reduced by high levels of vitamins C or E. The co-carcinogenic effects of heme iron are apparent at high overall dietary iron levels, and may respond to optimising overall iron intake according to genotype.

However, it needs to be noted that the nature and content of fat is determined by a number of factors including the breed, feeding conditions, and manner of preparation of the meat. Poultry may have as low as 4% fat, while fat content of domesticated, farmed animals may be as high as 30–40%. Monounsaturated fatty acids make up to 50% of the fat in lean meat, with saturated fatty acid content being 40–50% (World Cancer Research Fund/American Institute for Cancer Research, 2007). Poultry has a lower saturated fatty acid content than red meats.

Cross and co-workers prospectively investigated the association between meat and fat intakes, as estimated using a validated food frequency questionnaire, and small intestinal cancer. The study subjects were close *t* 500,000 men and women enrolled in the NIH-AARP Diet and Health Study. The data revealed no clear associations between red or processed meat intake and tumours of the small intestine. However, they found a 3.18-fold increased risk for carcinoid tumours of the small intestine in those individuals with a high saturated fat intake. On this basis, they suggested that the positive associations for meat intake previously reported in such studies may be partly explained by saturated fat intake. This does not hold across all cancers, however. For example, Crowe et al. (2008) conducted a multicenter prospective study of 142,520 men to consider the relationship between dietary fat intake and prostate cancer risk in the EPIC study. There was no significant association between dietary fat (total, saturated, monounsaturated, and polyunsaturated fat and the ratio of polyunsaturated to saturated fat) and risk of prostate cancer.

Schulz et al. (2008) identified a food pattern in which high consumption of processed meat, fish, butter and other animal fats, and margarine, and low consumption of bread, and fruit juices explained much of the total variation in dietary fatty acid intake (SFA, MUFA, *n*-3 PUFA, *n*-6 PUFA). They studied 15,351 female subjects in the Potsdam arm of the EPIC study, to conclude that high-fat intake, but no specific type of fat, enhanced the risk of breast cancer.

The high-fat content of many meats is part of the reason that these have a high energy density. In this context, it is noteworthy that several studies such as that of Goodman et al. (1997), have related cancer, in this case endometrial cancer, to obesity. This would also be a major conclusion of the World Cancer Research Fund/American Institute for Cancer Research (2007, 2009) documents. It is well recognised that obesity and body size generally is a balance between too high a kilojoule intake, and too little energy expenditure through physical activity.

### *3.2. Heterocyclic amines and polycyclic aromatic hydrocarbons formed during high-temperature cooking of meat*

Heterocyclic amines (HCAs) are produced during high-temperature cooking of meat, especially grilling, frying and barbecuing, for extended times. Such high cooking temperatures cause amino acids and creatine to react to form a variety of HCAs (Felton & Knize, 2006; Ni, McNaughton, LeMaster, Sinha, & Turesky, 2008; Sugimura, Wakabayashi, Nakagama, & Nagao, 2004). These latter authors identified the HCAs in common meat items, cooked according to common practice. 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) was abundant in well cooked chicken and bacon, while 2-amino-1,7-dimethylimidazo[4,5-g]quinoxaline was the most abundant HCA in very well done pan-fried beef and steak, and in beef gravy.

Most of the current evidence of risk from such compounds depends upon association of cancer risk with very well cooked meats, likely to have high HCA levels. Koutros et al. (2008) prospectively examined the association between meat types, meat cooking methods, meat doneness, and meat mutagens and the risk for prostate cancer in 197,017 person-years of follow-up in the Agricultural Health Study. They reported no association between meat type or specific cooking method and prostate cancer risk. However, the intake of well or very well done total meat was associated with a 1.26-fold overall increased risk of prostate cancer and a 1.97-fold

increased risk of advanced disease. Risks associated with the two heterocyclic amines 2-amino-3,4,8-trimethylimidazo-[4,5-f]quinoxaline and 2-amino-3,8-dimethylimidazo-[4,5-b]quinoxaline were of borderline significance for increased prostate cancer risk when the highest quintile was compared with the lowest. We associated a 1.68-fold increased risk of prostate cancer with the consumption of very well cooked red meats (Norrish, Ferguson, Knize, Felton, & Jackson, 1999). This study also quantified some of the key HCAs in New Zealand meats. The spectrum was not identical to those published from other countries. This may be because animals in that country tend to be pasture fed, while American practices often involve grain feeding because of harsher climatic conditions.

Alaejos, Gonzalez, and Afonso (2008), reviewed the data on HCAs to conclude that there is not sufficient scientific evidence to support the hypothesis that human cancer risk associated with meat consumption is specifically due to the intake of HCAs in the diet. However, this conclusion fails to recognise the importance of other carcinogens, co-carcinogens and anticarcinogens in the diet, and genetic susceptibility to HCAs. Goodenough, Schut, and Turesky (2007), described an accurate and sensitive liquid chromatography-electrospray ionisation/multi-stage mass spectrometry (LC-ESI/MS/MS($n$)) technique for the characterisation and quantification of DNA adducts of the dietary mutagen, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP). This technique will be important in helping to better establish the role of these compounds in cancer risk in subsequent studies.

Polycyclic aromatic hydrocarbons (PAHs) are produced from the incomplete combustion of organic compounds and are an important component of environmental pollution. Thus, these are found in well cooked meats and fish, as well as poorly washed and prepared foods (Kazerouni, Sinha, Hsu, Greenberg, & Rothman, 2001; Phillips, 1999; Santarelli et al., 2008). Indeed, they are found in varying amounts in many common food items. Data on PAHs in heavily cooked meat would support these being a cancer risk factor, but again it is difficult to be certain that the risk is unequivocally associated with a single group of compounds (Santarelli et al., 2008).

This latter group of chemicals may be particularly prevalent in processed meats. For example, Garcia-Closas, Castellsague, Bosch, and Gonzalez (2005) detected them in smoke produced by the burning of several different woods. During traditional smoking processes, the PAHs are transferred into a range of meats, such as chorizo sausages with collagen and tripe casings.

### 3.3. Formation of N-nitroso compounds

NOCs are produced by the reaction of nitrite and nitrogen oxides with secondary amines and *N*-alkylamides (Lijinsky, 1999). NOCs are present in certain processed meats, including bacon, smoked fish and smoked cheeses, and can be formed endogenously after consumption of red and processed meat (Santarelli et al., 2008). A Finnish cohort study of CRC risk in 9985 adult men and women found a significant positive association with intake of *N*-nitrosodimethylamine (NDMA), including a relative risk between highest and lowest quartiles of intake of 2.12 (Knekt, Jarvinen, Dich, & Hakulinen, 1999). Cured meats and sausages were good sources of NDMA in this community. The study as a whole associated a relative risk of 1.84 of CRC among individuals with a high intake of cured meat and sausages. Processed meat, and specifically endogenous formation of NOCs resulting from that, was implicated as a major cause of gastric cancer (Jakszyn et al., 2006). However, a re-evaluation of the data made a more convincing link between *Helicobacter pylori* contamination and gastric cancer risk. There was also an interaction between plasma vitamin C and ENOC ($P < 0.02$). Jakszyn et al. (2006), suggested that ENOC formation may account for their previously reported association between red and processed meat consumption and gastric cancer risk.

Mitacek et al. (2008) tested the hypothesis that the dietary intake of nitrate, nitrite, and nitrosodimethylamine (NDMA) in North and Northeast Thailand was the cause of the high rate of the liver and gastric cancers in these regions. They comprehensively sampled fresh and preserved Thai foods, and analyzed their NDMA contents from 1988 to 1996 and 1998 to 2005. They also administered food frequency questionnaires. From these data, they calculated intakes of nitrate, nitrite, and NDMA in four regions of Thailand, and showed a strong positive association between these with the trends in liver and stomach cancer age-standardised incidence rates (ASR) in those same geographic regions.

The probability of NOC formation is affected by other dietary components, including haem iron, which may catalyse the formation of NOCs from natural precursors in the gut (Santarelli et al., 2008). Given that red meats are a richer source of haem iron than white meats, such an effect might go part way towards explaining why the epidemiological correlations are more convincing with red as compared with white meat.

### 3.4. Heme iron as a promoter of carcinogenesis

Huang (2003) reported a strong association between iron overload and cancer risk in humans. This report suggested that this was suggestive evidence that iron is a carcinogenic metal. However, it may be more likely to have co-carcinogenic effects. There is evidence that heme iron increases cell proliferation in the mucosa, through lipoperoxidation and/or cytotoxicity of fecal water (Sesink, Termont, Kleibeuker, & Van der Meer, 1999). Nitrosation might increase the toxicity of heme in cured meat products.

## 4. Possibilities of reducing the cancer risk of meat and meat products

For each of the mechanisms implicated in cancer formation, there is an approach to reducing any cancer threat.

### 4.1. Modifying fat composition

The selection of meat will affect its' fat content. It seems that wild animals are overall lower in fat, with a lower proportion of saturated fatty acids and higher proportion of polyunsaturated fatty acids as compared with farmed animals. In general, as identified for pork Olivares, Daza, Rey, and Lopez-Bote (2009), the selection of animals according to genotype, and diet they are fed on will profoundly influence not only the total fat concentration in the meat, but also the nature of the fats. Obvious modulations include dietary fat intake, but controlling the intake of other nutrients such as vitamin A will also have an influence.

The fat content of meat has decreased in recent years, with new breeds coming onto the market, and different trimming processes. To provide our own local figures, the average adult New Zealander gets 35% of their energy from fat, of which beef and veal make up 6%, lamb and mutton 2%, sausages and processed meats 5%, pies and pasties 5% (Russell, Parnell, & Wilson, 1999). Of the nutrients considered to have detrimental effects, saturated fatty acids (SFA) provide around 50% of the fatty acids found in meat, while t*rans* fatty acids (TFAs) make up only a small component (National Health & Medical Research Council, 2006). The rest is mainly made up of monounsaturated fats, with small amounts of polyunsaturated fatty acids (PUFA), including small amounts of omega-3 PUFA, which are likely to be beneficial in cancer prevention. Data from Australia show that meat, poultry and game contribute 43% to the overall intakes of omega-3 PUFA, of which 22.3% is from beef and 5.9% from lamb (Howe, Meyer, Record, & Baghurst, 2006).

Conjugated linoleic acid (CLA) refers to mixtures of positional and geometric conjugated isomers of linoleic acid, of which the principle dietary form is the *cis*-9, *trans*-11 isomer (Pariza, Park, & Cook, 2000). The highest levels of dietary CLA are found in the meat and milk from ruminant animals. In animal studies, CLA inhibits carcinogenesis, possibly through modulating immune function (Pariza et al., 2000; Philpott & Ferguson, 2004). However, human data are inconclusive. Removal of visible fat and cooking methods will also be important for reducing this possible source of cancer hazard.

### 4.2. Reducing the formation and/or mutagenicity of HCAs and PAHs

HCAs become DNA alkylating agents and can induce mutations in DNA following activation by various metabolising enzymes (Felton & Knize, 2006; Turesky, 2002, 2007). This, they are a key factor in mutagenesis of the diet (Ferguson & Philpott, 2008). In this context, either preparing meat in the presence of other mutation modulating agents, or ensuring that it is consumed at the same time as potential antimutagens and anticarcinogens (Ferguson, Karunasinghe, & Philpott, 2004) may be a constructive way to reduce the possibility of DNA interactions and mutation. For example, we have evidence that a diet high in dietary fibre sources such as wheat bran may reduce potentially carcinogenic effects of HCAs through modifying their absorption and excretion (Kestell, Zhao, Zhu, Harris, & Ferguson, 1999). Carter et al. (2007) identified white tea, green tea, epigallocatechin-3-gallate, and caffeine as inhibitors of HCA-induced colonic lesions that may be relevant to CRC. Other micronutrients and phytochemicals also have different types of antimutagenic action (Botting, Young, Pearson, Harris, & Ferguson, 1999).

One of the mechanisms by which a wheat bran diet is likely to modify mutations through HCAs is by modulating the activity of certain xenobiotic metabolising enzymes (Helsby, Zhu, Pearson, Tingle, & Ferguson, 2000). This may be an important mechanism, since it is well recognised that individual susceptibility to carcinogenesis by HCAs is affected by variation in activity of XMEs (Turesky, 2004). There are at least 15 enzymes thus involved, including cytochrome P450, glutathione *S*-transferase, UDP-glucuronosyltransferases, sulfotransferases (SULT) and *N*-acetyltransferases (NAT). As well as dietary regulation, various single nucleotide polymorphisms (SNPs) in these enzymes will modulate the metabolism, and at least theoretically, may impact cancer risk by overcooked meats (Felton & Knize, 2006).

A case–control study design considered diet and lifestyle factors for 1095 cases and 1890 controls identified through the population-based Ontario Cancer Registry (Cotterchio et al., 2008). The study also measured genetic polymorphisms in several of these enzymes, in DNA samples from most of the subjects. Although high versus low red meat intake increased CRC risk 1.67-fold, effects of genetic polymorphisms were variable. However, CYP2C9 and NAT2 variants were associated with CRC risk per se, while the CYP1B1 combined variant and SULT1A1-638G > A variant significantly modified the association between red meat doneness intake and CRC risk.

Lumbreras et al. (2008) collected data as part of a nested case–control study on bladder cancer from within the EPIC cohort. Tested separately, meat intake and NAT2 genotype were not associated with bladder cancer risk. However, those subjects with the rapid NAT2 genotype showed a significant relationship, of odds ratios 2.9, between bladder cancer risk and consumption of meat. This relationship was not present among subjects with the slow genotype, and no effects were seen of the SULT1A1 allele variants on this cancer.

Sorensen et al. (2008) considered polymorphisms of NAT1 and NAT2, in association with meat consumption and risk of colorectal cancer in a prospective study of a 57,000 member European cohort. In a nested case control study on 379 cases of CRC and 769 controls, there were no statistically significant associations between consumption of red meat, processed meat or fried meat and CRC risk, although an increased risk was associated with a preference for very well done pan-fried meat. NAT1 fast acetylators had a significantly higher risk of CRC as compared with slow acetylators, but no effect of NAT2 acetylator status.

### 4.3. Modifying N-nitroso compound formation

Most of these compounds are formed endogenously. However, the formation processes can be affected by other dietary components, and are blocked, for example, by vitamin C. Mirvish (1986) and Bartsch, Ohshima, and Pignatelli (1988) reviewed the ability of vitamins C and E to inhibit the formation of NOC in chemical systems and in nitrite-preserved meat. Vitamin C also reversed cellular transformation in an in vitro system. Mirvish (1986) also examined data in experimental animals showing that both of these vitamins led to inhibition by between 30% and 60% of many carcinogenesis experiments using a range of carcinogens. He pointed to suggestive data in humans, since diets high in vitamin C sources are negatively correlated with cancer of the stomach, esophagus, larynx, mouth and cervix.

### 4.4. Modifying the effects of haem iron

The evidence suggests there is an optimal amount of iron in the diet, and this may vary according to genotype (Ferguson, 2006). The most constructive approach to getting the right dietary iron intake may to be check the levels of this nutrient in the bloodstream and adjust dietary intake accordingly.

### 4.5. Other anticancer nutrients

Meat is also a useful source of highly bioavailable zinc, as well as providing vitamin B6, B12, vitamin D, calcium, folate and selenium (National Health & Medical Research Council, 2006; World Cancer Research Fund/American Institute for Cancer Research, 2007). Each of these may have effects in cancer protection, under various situations (Ferguson, Karunasinghe, et al., 2004; Ferguson, Philpott, et al., 2004).

## 5. Conclusions

The epidemiology is indeed supporting a conclusion that high meat intake, especially of heavily cooked red meats and processed meat, may increase the risk of certain cancers. It is important to recognise, however, that meat is an important source of nutrients, several of which have potential anticancer properties. Consideration of potential mechanisms does provide some possible approaches to maintaining a moderate intake of meat, by deliberately selecting dietary components to eat alongside this and reduce potential cancer risk.

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