4.3 Meat, poultry, fish, and eggs

MEAT, POULTRY, FISH, EGGS, AND THE RISK OF CANCER

In the judgement of the Panel, the factors listed below modify the risk of cancer. Judgements are graded according to the strength of the evidence.

	DECREASES RISK		INCREASES RISK	
	Exposure	**Cancer site**	**Exposure**	**Cancer site**
Convincing			**Red meat[1]**	**Colorectum**
			Processed meat[2]	**Colorectum**
Probable			**Cantonese-style salted fish[3]**	**Nasopharynx**
Limited — suggestive	Fish	Colorectum	Red meat[1]	Oesophagus Lung Pancreas Endometrium
	Foods containing vitamin D[4 7]	Colorectum	Processed meat[2]	Oesophagus Lung Stomach Prostate
			Foods containing iron[4 5]	Colorectum
			Smoked foods[6]	Stomach
			Grilled (broiled) or barbecued (charbroiled) animal foods[6]	Stomach
Substantial effect on risk unlikely	None identified			

1 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
2 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
3 This style of preparation is characterised by treatment with less salt than typically used, and fermentation during the drying process due to relatively high outdoor temperature and moisture levels. This conclusion does not apply to fish prepared (or salted) by other means.
4 Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3).
5 Although red and processed meats contain iron, the general category of 'foods containing iron' comprises many other foods, including those of plant origin.
6 The evidence is mostly from meats preserved or cooked in these ways.
7 Found mostly in fortified foods and animal foods.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

These animal foods are sources of protein and micronutrients. The amount and nature of the fat content of meat, poultry, and fish depends on methods of rearing, processing, and preparation, as well as the type of animal.

Production and consumption of red meat and processed meat generally rise with increases in available income. Consumption of beef and products made with beef is still increasing, notably in China and other middle- and low-income countries. In many countries, poultry is now also intensively reared and consumption has increased greatly. Much fish is now farmed.

In general, *the Panel judges* that the evidence on red meat and processed meat is stronger than it was in the mid-1990s. Epidemiological evidence on other methods of preserving and preparing meats and other animal foods is sparse; the overall evidence remains suggestive, at most. The evidence on poultry, fish, and eggs is generally insubstantial.

The Panel judges as follows:

The evidence that red meats and processed meats are a cause of colorectal cancer is convincing. Cantonese-style salted fish is a probable cause of nasopharyngeal cancer. This finding does not apply to any other type of fish product. Cantonese-style salted fish is also subject to fermentation.

There is limited evidence suggesting that fish, and also foods containing vitamin D, protect against colorectal cancer. There is limited evidence suggesting that red meat is a cause of cancers of the oesophagus, lung, pancreas and endometrium; that processed meat is a cause of cancers of the oesophagus, lung, stomach and prostate; and that foods containing iron are a cause of colorectal cancer. There is also limited evidence that animal foods that are grilled (broiled), barbecued (charbroiled), or smoked, are a cause of stomach cancer.

Red meat can be relatively high in animal fats. For a discussion of the role of animal fats on cancer, see chapter 4.4 and Chapter 7. Meat can also be energy dense. For discussion on the role of energy-dense foods on weight gain, overweight, and obesity, and the role of weight gain, overweight, and obesity in the risk of some cancers, see Chapters 6 and 8.

The strongest evidence, corresponding to judgements of 'convincing' and 'probable', shows that red meat and processed meat are causes of colorectal cancer, and that Cantonese-style salted fish is probably a cause of nasopharyngeal cancer. *The Panel also notes* limited evidence suggesting that red meat and processed meat are causes of other cancers.

It is generally, though not universally, agreed that humans evolved as omnivores, and that healthy diets usually include foods of plant and of animal origin — including meat, poultry, fish, and eggs, as well as milk and other dairy products.

Most people who do not eat meat, flesh, or any food of animal origin do so for religious or ethical reasons. Impoverished communities eat little flesh and meat is reserved for feasts. Partly because meat-eating is a sign of prosperity and partly because many people enjoy eating meat, poultry, and fish, production and consumption generally rise as available income increases. Consumption of beef is, for example, now increasing very rapidly in China, and consumption of 'burgers' made from beef is increasing worldwide.

Early reports concerned with nutritional deficiencies identified meat, poultry, and fish as good sources of protein, iron, and other nutrients, and eggs as a 'complete food', especially for children. By contrast, in the second half of the 20th century, reports on meat, poultry, fish, and eggs tended to focus on red meat as a source of fat and saturated fatty acids and on eggs as a source of dietary cholesterol in the causation of coronary heart disease. These reports promoted poultry and fish as better choices than red meat, either because they contain less fat and saturated fatty acids or, in the case of oily fish, they contain unsaturated fats identified as protective. Little attention has been given to flesh from wild animals and birds, despite this being known to have a different nutritional profile — lower in total fat and higher in unsaturated fatty acids. On the other hand, since the mid-1990s more attention has been given in epidemiological studies to processed meat as a cause or possible cause of cancers of some sites.

For discussion of the role of red meat and processed meat in energy-dense foods and drinks, the effect of energy-dense foods and drinks on weight gain, overweight, and obesity, and the role of weight gain, overweight, and obesity in the risk of some cancers, see Chapters 6 and 8.

In this Report, methods of production, preservation, processing, and preparation (including cooking), that are solely or mainly to do with meat and other animal foods, are included here. Processed meat as a category is included here. The mineral iron is also covered here, although it is also found in plant foods.

4.3.1 Definitions and sources

Meat and poultry

In this Report, meat includes all animal flesh apart from fish and seafood. Meat can be further classed as either red meat, which generally refers to flesh from animals that have more red than white muscle fibres (in this Report, beef, goat, lamb, and pork), or poultry, which usually has more white than red muscle fibres (from birds such as chickens, guinea fowl, and turkeys). Meat can also be categorised by dividing it into meats from skeletal muscles or the internal organs (offal, such as the brain, liver, heart, intestines, and tongue). Meat can also be divided according to whether the animal was domesticated or wild. Most meats consumed around the world today are from domesticated animals. 'Wild' meats, that is from non-domesticated or free-ranging species, are a significant source of protein and energy among some populations. Some non-domesticated animals, such as deer or buffalo, are also farmed. However, the evidence presented in this chapter applies only to meat from domesticated animals. Some meats are processed in various ways (box 4.3.1).

Fish

This Report uses the culinary definition of fish, which includes shellfish. There are more than 27 000 species of salt and freshwater fish; many more crustaceans, bivalves, and cephalopods can also be eaten. Fish and shellfish are the only foods that, globally, are still obtained in significant quantities from the wild. But many species are on the verge of commercial extinction and aquaculture is increasing worldwide. For instance, more than a third of the salmon eaten worldwide is farmed. Like meat, fish is also processed, for instance by drying, salting, and smoking.

Eggs

Eggs are the ova of animals and in this Report mean only

Box 4.3.1 Processed meat

What is 'processed meat'? The question is important because, as shown here, the evidence that processed meat is a cause of colorectal cancer is convincing.

In the broad sense of the word, most meat is processed — cooking is a process. But as commonly used, the term 'processed meat' refers to meats (usually red meats) preserved by smoking, curing, or salting, or by the addition of preservatives. Meats preserved only by refrigeration, however they are cooked, are usually not classified as 'processed meat'.

There is no generally agreed definition of 'processed meat'. The term is used inconsistently in epidemiological studies. Judgements and recommendations are therefore less clear than they could be.

Ham, bacon, pastrami, and salami are processed meats. So are sausages, bratwursts, frankfurters, and 'hot dogs' to which nitrites or nitrates or other preservatives are added (box 4.3.2). Minced meats sometimes fall inside this definition, often if they are preserved chemically, but not always. The same point applies to 'hamburgers'. Given the importance of this issue, transnational burger caterers should specify the methods they use to process their products.

those of birds; because they are generally eaten before they have been fertilised, they do not contain an embryo. Eggs are eaten both on their own and as an ingredient in a variety of baked goods, sauces, and other composite foods. Chicken eggs are most commonly eaten, although people also eat duck, ostrich, and quail eggs. Fish eggs (roe) and turtle eggs are not included here.

4.3.2 Composition

Meat and poultry

Meat contains around 20–35 per cent protein by weight. The fat content by weight ranges from less than 4 per cent in lean poultry to 30–40 per cent in fatty meat from domesticated, farmed animals. About 50 per cent of the fatty acids in lean meat are monounsaturated fatty acids, while saturated fatty acids make up around 40–50 per cent (see chapter 4.4.2). Poultry contains a lower proportion of saturated fatty acids (30–35 per cent) and a higher proportion of polyunsaturated fatty acids (15–30 per cent compared with 4–10 per cent).[1] There are differences between meats from domesticated animals and wild meats. Wild animals are typically more mature, leaner, and contain a greater variety of aromatic compounds than farmed animals. They will have received no medication and their diets will have been uncontrolled. Wild animals are not only lower in fat, but also have a higher proportion of polyunsaturated fatty acids than farmed varieties and a lower proportion of saturated fatty acids.

Two iron-containing components of muscle tissue, myoglobin and cytochromes, give meat its red colour. It also contains relatively high levels of B vitamins, particularly B6 (pyridoxine) and B12, as well as vitamin D, and provides readily absorbable iron, zinc, and selenium. Eating red meat increases levels of *N*-nitroso compounds in the body (box 4.3.2), which may be partially due to its high haem content (box 4.3.3). If meat is cooked over an open flame, at high temperatures, and charred or 'well done', heterocyclic amines or polycyclic aromatic hydrocarbons can be formed (box 4.3.4).

Vitamin D is a fat-soluble vitamin that plays a critical role in calcium and bone metabolism and in controlling cell differentiation. Low levels may lead to osteomalacia or, in children, rickets and possibly osteoporosis, with increased fracture risk. Most vitamin D is derived from the action of sunlight on the skin. Foods such as milk or fat spreads (see chapter 4.9) may be fortified, and then become the major dietary source of vitamin D; natural sources include sardines and other oily fish, meat, and eggs.

Fish

Fish has similar levels of protein to meat. It has a fat by weight content of between 0.5 per cent in low-fat fish such as cod or skate to as much as 20 per cent in oily fish such as Atlantic salmon or eels. Fat from fish contains lower levels of saturated fatty acids (around 20–25 per cent) than meat.

Fish oils from saltwater fish contain long-chain n-3 fatty acids (see chapter 4.4.2). Wild fish have a lower fat content than farmed fish, with a higher proportion of n-3 fatty acids. Only marine algae and phytoplankton produce these fatty acids, so the fish that feed on them are the primary dietary sources. These fatty acids are essential to the development and function of the brain and retina; they also reduce inflammation, blood clotting, and cholesterol production. The body

Box 4.3.2 Nitrates, nitrites, and *N*-nitroso compounds

Nitrate occurs naturally in plants; levels vary between species and with different soil conditions and the amount of fertiliser used. In high-income countries, vegetables account for 70–97 per cent of dietary nitrate intake.[2] Between 5 and 20 per cent of the nitrate in diets is converted by the body into nitrite, a substance that is also found in some vegetables (notably potatoes). Nitrite is used to preserve processed meats (it is extremely toxic to bacteria) and gives cured meats their recognisable colour and flavours. The addition of nitrite and nitrate to food is regulated and monitored in most countries.

Nitrite can react with the degradation products of amino acids to form *N*-nitroso compounds (nitrosamines or nitrosamides). These may be formed in meat during the curing process or in the body (particularly in the stomach) from dietary nitrite (or nitrate).

Several *N*-nitroso compounds are known human or animal carcinogens.[3] There is concern that nitrite, from processed meats for example, nitrates in vegetables, and preformed nitrosamines may be involved in carcinogenesis, particularly in the stomach (see Chapter 2). Dietary nitrates and nitrites are probable human carcinogens because they are converted in the body to *N*-nitroso compounds.[3]

Box 4.3.3 Foods containing iron

Iron deficiency is the most common and widespread nutritional disorder in the world. It is most common among children and premenopausal women, and results in iron deficiency anaemia.

Haem iron is found only in foods of animal origin, such as meat and meat products, fish, and blood products. Non-haem iron is found in plant foods, such as lentils, beans, leafy vegetables, tofu, chickpeas, black-eyed peas, figs, and apricots. The amount of dietary iron needed to meet the body's requirements depends on its bioavailability from the diet. This varies with the diet, as well as factors related to the consumer such as their iron status. Iron from animal sources is better absorbed than iron from plant sources, but non-haem iron absorption is enhanced when the body's iron status is low, or when iron-rich foods are eaten together with vitamin-C rich foods or with meat.

Iron has a central role in metabolism. It is involved in oxidative metabolism within cells and is a component of a number of enzymes. Free iron can also catalyse the generation of free radicals, which cause oxidative damage to specific cell components including DNA, protein, and membrane lipids. Iron metabolism and transport are strictly regulated to reduce the likelihood of cells being exposed to free iron and so to oxidative damage; most iron in living tissues is bound to proteins, such as transferrin and ferritin, which prevent its involvement in free-radical generation. Also see chapter 4.10.

Box 4.3.4 Heterocyclic amines and polycyclic aromatic hydrocarbons

Heterocyclic amines are formed when muscle meats such as beef, pork, fowl, and fish are cooked. High cooking temperatures cause amino acids and creatine (a chemical found in muscles) to react together to form these chemicals. So far, 17 different heterocyclic amines have been identified as being formed by cooking muscle meats and which may pose a cancer risk (also see Chapter 2).

Temperature is the most important factor in the formation of these chemicals. Frying, grilling (broiling), and barbecuing (charbroiling) produce the largest amounts because these cooking methods use very high temperatures. Oven roasting and baking involve lower temperatures, so meats cooked in this way are lower in heterocyclic amines, but gravy made from meat drippings contains substantial amounts. Meats that are partially cooked in a microwave oven before being cooked by other higher-temperature methods also have lower levels of these chemicals.[4]

Polycyclic aromatic hydrocarbons (PAHs) are a group of over 100 different chemicals formed when organic substances like tobacco or meat are burnt incompletely. Grilling (broiling) and barbecuing (charbroiling) meat, fish, or other foods with intense heat over a direct flame results in fat dropping on the hot fire; this produces PAHs that stick to the surface of food. The more intense the heat, the higher the level of contamination; using wood creates more PAHs than charcoal. Cereals contaminated with PAHs are also a common source of these chemicals in the diet. Levels in cereals are considerably lower than in grilled meats, but their overall contribution to diets is larger.[5] Taken together, cereals and meat and meat products account for more than 50 per cent of dietary levels of these chemicals. Intakes are thought to be relatively high in Europe, particularly in northern Europe, although measures are only available from a few, generally high-income, countries.[6]

can convert alpha-linolenic acid (found in plant foods and essential in the diet) to eicosapentaenoic acid and docosohexanoic acid, which are found in fish oils, but the rates of conversion are low.

Fish contain lower levels of B vitamins, iron, and zinc than meat and poultry, but oily fish are a source of retinol and vitamin D. Fish are also a source of calcium if the bones are eaten with the flesh, for example, when canned.

Fish and shellfish have the potential to accumulate pollutants that are washed into rivers and oceans, and these tend to accumulate in their fat. These pollutants can include heavy metals and organic compounds, some of which are known carcinogens. Farmed fish are exposed to veterinary medicines, and some environmental toxins may reach high concentrations in their food. But farmed fish are less likely than wild fish to become contaminated with environmental pollutants. The balance of risks and benefits of eating fish at various stages of the life course needs to be determined. Also see chapter 4.9.

Eggs

Eggs, like meat, poultry, and fish, contain all the essential amino acids needed by humans. A typical large hen's egg has roughly equal weights of protein and fat, with 60 per cent of the energy coming from fat. A typical large shelled egg contains 6 g protein; 1 g carbohydrate; 4.5 g fat (2.0 g monounsaturated, 0.5 g polyunsaturated, and 1.5 g saturated fatty acids); and about 200 mg cholesterol. It also contains retinol, folate, thiamin, riboflavin, vitamin B12, vitamin D, and iron. The yolk's colour comes from carotenoids, and contains all of the fat and cholesterol and most of the iron, thiamin, and retinol. The white is 90 per cent water and is virtually fat free, containing mainly protein, with some vitamins, and traces of glucose.

In Asia, eggs containing 2–3 week old chick fetuses may occasionally be included in diets. There is no nutritional difference between these and unfertilised eggs, except that fertilised eggs contain additional calcium absorbed from the shell.

4.3.3 Consumption patterns

Meat and poultry

Globally, meat accounts for about 8 per cent of total energy availability, 18 per cent of dietary protein, and 23 per cent of dietary fat. Meat consumption is considerably higher in high-income countries (10 per cent of total energy intake compared with 7 per cent in low-income countries), and is particularly high in the USA, parts of South America, some parts of Asia, northern Europe, and most of Oceania. Consumption is particularly low in most of Africa and other parts of Asia where vegetarian ways of life are commonplace. Bangladesh has the lowest level of intake (0.6 per cent) and Mongolia the highest (28 per cent).[7]

As a general rule, meat consumption increases with economic development. Worldwide, between 1961 and 2002, meat consumption per person doubled, with pork and poultry showing the greatest increases; in Japan it increased nearly six-fold. Globally, overall energy availability increased in the same period by just 12 per cent. Consumption of meat and other animal foods from wild and undomesticated animals is low on a global basis, but these foods are important parts of diets within many middle- and low-income countries, as well as being delicacies in high-income countries.

Fish

Worldwide, fish (including shellfish) account for 1 per cent of available dietary energy; these foods are particularly important in island and coastal communities. For instance, in the Maldives, marine fish account for 15 per cent of dietary energy, but in some landlocked, low-income countries, this figure is practically zero. In general, fish consumption is highest in Asia and Oceania. Freshwater fish provide a relatively small proportion of dietary energy (0.3 per cent), but they are a more important source of dietary energy in low-income countries, and are particularly important in regions with large lakes and rivers. Salting is a traditional method of preserving raw fish throughout much of the world (box 4.3.5).

Box 4.3.5 Cantonese-style salted fish

Salting is a traditional method of preserving raw fish throughout much of the world. The freshness of the fish and the salting and drying conditions vary considerably between regions, although fish are usually dried outside, in direct sunlight. This results in varying levels of fermentation and/or insect infestation. Salted fish is a component of diets typical of Asia, Africa, and parts of the Mediterranean.

Depending on the precise conditions, salt-preserved fish may also undergo fermentation. The degree of fermentation that occurs depends on the freshness of the raw fish, the amount of salt used, the outdoor temperature, and the duration of the drying process. In general, excluding the factor of freshness, salted fish is less likely to be fermented in the northern part of China compared with the southern part of China (where nasopharyngeal cancer is more common). Cantonese-style salted fish is characterised by using less salt and a higher degree of fermentation during the drying process, because of the relatively high outdoor temperature and moisture levels.

Cantonese-style salted fish are a traditional part of the diet in southern China, Taiwan, Malaysia, and Singapore.

Eggs

Worldwide, eggs provide 1.2 per cent of available food energy. Egg consumption is highest in the Far East, North America, and Europe, ranging from nearly 3 per cent in these areas to virtually zero in many African countries; it is significantly higher in high-income countries. Preserved eggs (pickled, salted, or cured) are traditional in some cultures.

4.3.4 Interpretation of the evidence

4.3.4.1 General

For general considerations that may affect interpretation of the evidence, see chapters 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7.

'Relative risk' (RR) is used in this Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.3.4.2 Specific

Some considerations specific to meat, poultry, fish, and eggs include:

Classification. 'Fish' is a broad classification. Different fish have different nutritional profiles and biological effects, one obvious example being white fish and oily fish. These are often not distinguished in epidemiological studies.

Terminology. As yet, there is no agreed definition for 'processed meat'. Some studies count minced meat, or ham, bacon, and sausages as processed meats; others do not. See the footnote to the matrix and box 4.3.1.

Confounding. People who consume large amounts of meat and processed meats tend to consume less poultry, fish, and vegetables, and vice versa. So an apparent effect of meat and processed meat could possibly be due, at least in part, to low intakes of these other foods.

Production, processing, patterns. Practically all the evidence relates to these foods as preserved, processed, or prepared (cooked) in some way. Evidence on meat, poultry, and increasingly on fish, is practically all from these foods as produced industrially. There is very little evidence on wild animals and birds, despite the quantity and nature of their body fat, and other aspects of their nutritional profile, being different. Epidemiological evidence on specific methods of preservation, processing, and preparation/cooking of meat, poultry, and fish is mostly patchy, despite some of these being known to generate carcinogens established as such in experimental studies. Also see chapter 4.9.

4.3.5 Evidence and judgements

The full systematic literature review (SLR) is contained on the CD included with this Report.

4.3.5.1 Meat

4.3.5.1.1 Red meat

Some studies may have included processed meats in their classification of red meat intake.

Colorectum

Sixteen cohort studies[8-24] and 71 case-control studies investigated red meat and colorectal cancer.

All of the cohort studies that reported analyses of risk for the highest intake group when compared to the lowest showed increased risk (figure 4.3.1),[8-24] which was statistically significant in four (one of these was specific to rapid-acetylator genotypes).[9 10 12 18 23] Meta-analysis was possible

Figure 4.3.1 Red meat and colorectal cancer; cohort studies

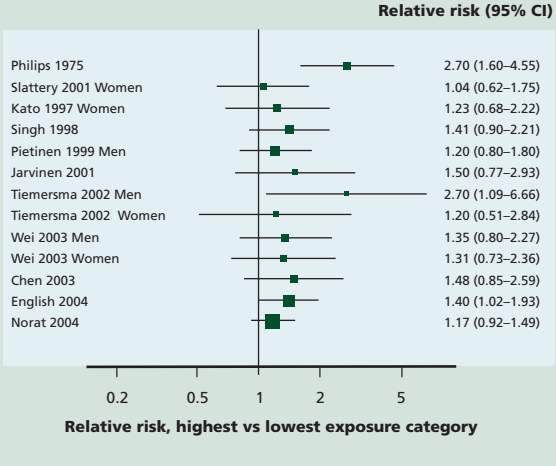


Figure 4.3.2 Red meat and colorectal cancer; cohort studies

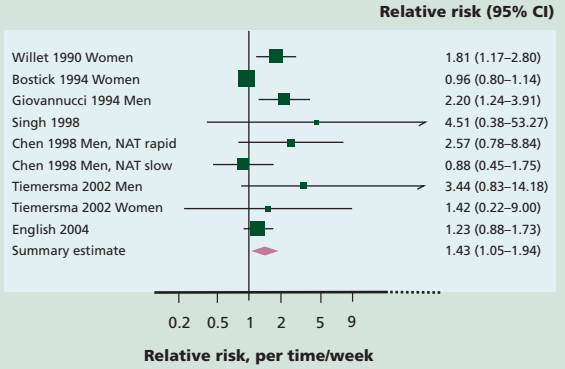


Figure 4.3.3 Red meat and colorectal cancer; cohort studies

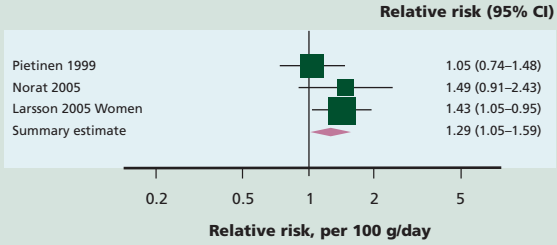
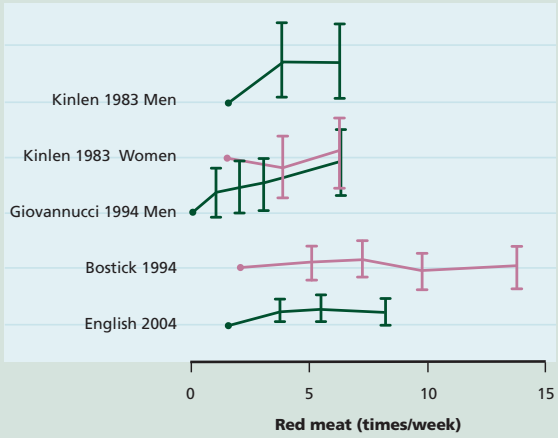


Figure 4.3.4 Red meat and colorectal cancer; cohort studies: dose response



on seven studies that measured red meat intake in 'times per week' and three studies that measured grams per day. The summary effect estimates were 1.43 (95% confidence interval (CI) 1.05–1.94) per times/week and 1.29 (95% CI 1.04–1.60) per 100 g/day, respectively (figures 4.3.2 and 4.3.3). There was moderate heterogeneity in the former analysis and low heterogeneity in the latter.

A dose-response relationship is apparent from cohort data (figure 4.3.4).

These data are supported by a recently published meta-analysis of 15 prospective studies, which reported a summary effect estimate of 1.28 (95% CI 1.18–1.39) per 120 g/day.[25]

Because of the abundant prospective data from cohort studies, case-control studies were not summarised.

The general mechanisms through which red meat could plausibly cause cancer are outlined below. In addition, dietary haem iron induces colonic cytotoxicity and hyperproliferation.[26]

A substantial amount of data from cohort and case-control studies showed a dose-response relationship, supported by evidence for plausible mechanisms operating in humans. Red meat is a convincing cause of colorectal cancer.

The Panel is aware that since the conclusion of the SLR, six cohort[27-32] and four case control studies[33-36] have been published. This new information does not change the Panel judgement (see box 3.8).

Oesophagus

Twelve case-control studies[37-50] investigated red meat and oesophageal cancer.

Eight studies reported increased risk for the highest intake group when compared to the lowest,[37-39 41-45 49 50] which was statistically significant in five.[37 41 42 45] Three studies reported non-significant decreased risk[38 40 46]; one study reported no significant effect on risk,[47 48] but did not provide further details. Most of these studies adjusted for smoking and alcohol.

The general mechanisms through which red meat could plausibly cause cancer are outlined below.

There is limited evidence, from case-control studies, some of which were poor quality, suggesting that red meat is a cause of oesophageal cancer.

The Panel is aware that since the conclusion of the SLR, one cohort study[51] has been published. This new information does not change the Panel judgement (see box 3.8).

Lung

One cohort study[52] and nine case-control studies[53-62] investigated red meat and lung cancer.

The single cohort study showed increased risk for the highest intake group when compared to the lowest, with an effect estimate of 1.6 (95% CI 1.0–2.6; p value for trend < 0.014), based on 158 cases.[52]

Seven case-control studies showed increased risk for the highest intake group when compared to the lowest,[53-58 60 61] which was statistically significant in four.[54 55 60 61] One study reported non-significant decreased risk[59] and one study showed no effect on risk.[62] All except the latter study adjusted for smoking.

The general mechanisms through which red meat could plausibly cause cancer are outlined below.

There is limited evidence, mostly from inconsistent case-control studies, suggesting that red meat is a cause of lung cancer.

Pancreas

Seven cohort studies[63-69] and four case-control studies[46 70-72] investigated red meat and pancreatic cancer.

Six cohort studies showed increased risk for the highest intake group when compared to the lowest,[63-65 67-69] which was statistically significant in one,[64] and two of the studies also had statistically significant tests for trend.[65 67] One study reported a non-significant increased risk that was very close to no effect.[66] Meta-analysis was possible on two studies, giving a summary effect estimate of 1.00 (95% CI 0.95–1.05) per 20 g/day, with no heterogeneity.[63 66] However, the two included studies were not typical. The effect estimates for the highest intake group when compared to the lowest in the other five cohort studies were 1.45 (95% CI 1.19–1.76),[64] 1.73 (95% CI 0.99–2.98; with a statistically significant test for trend),[65] 2.4 (95% CI 1–6.1; with a statistically significant test for trend),[67] 1.1 (95% CI 0.9–1.2),[68] and 1.4 (95% CI 0.4–4.8) for men and 2.7 (95% CI 0.8–8.9) for women.[69]

All of the case-control studies showed increased risk for the highest intake group when compared to the lowest,[46 70-72] which was statistically significant in three.[46 71 72] Meta-analysis was possible on three case-control studies, giving a summary effect estimate of 1.11 (95% CI 1.08–1.15) per 20 g/day, with no heterogeneity.[46 71 72]

The general mechanisms through which red meat could plausibly cause cancer are outlined below. In addition, both the secretory function of the pancreas and cell turnover within the pancreas are altered by the types of foods eaten.[73] Amino acids and fatty acids stimulate more pancreatic secretions than do carbohydrates.[74]

Evidence from cohort studies is less consistent than that from case-control studies. There is limited evidence suggesting that red meat is a cause of pancreatic cancer.

Endometrium

One cohort study[75] and seven case-control studies[46 76-81] investigated red meat and endometrial cancer.

The single cohort study showed a non-significant increased risk for the highest intake group when compared to the lowest, with an effect estimate of 1.10 (95% CI 0.70–1.73).[75]

Five case-control studies showed increased risk for the highest intake group when compared to the lowest,[46 76-79] which was statistically significant in two.[77 78] Two studies showed non-significant reduced risk.[80 81] Meta-analysis was possible on six studies, giving a summary effect estimate of 1.20 (95% CI 1.03–1.39) per 50 g red meat/day, with moderate heterogeneity.[46 76-80]

The general mechanisms through which red meat could plausibly cause cancer are outlined below.

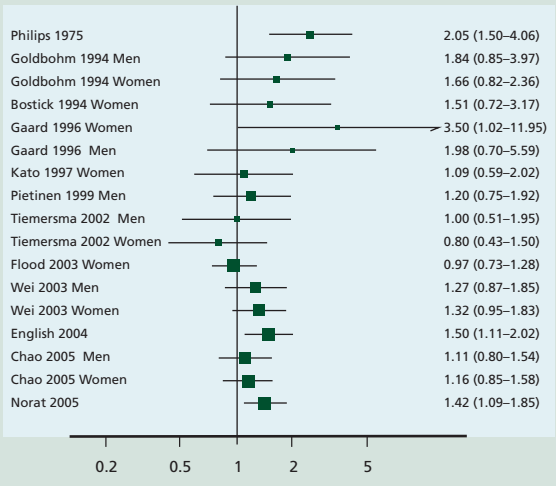
The evidence, mostly from case-control studies, is sparse. There is limited evidence suggesting that red meat is a cause of endometrial cancer.

The Panel is aware that since the conclusion of the SLR, one case-control study[82] has been published. This new information does not change the Panel judgement (see box 3.8).

General mechanisms

There are several potential underlying mechanisms for an association between red meat consumption and cancer, including the generation by stomach and gut bacteria of potentially carcinogenic *N*-nitroso compounds. Some red meats are also cooked at high temperatures, resulting in the production of heterocyclic amines and polycyclic aromatic hydrocarbons (box 4.3.4). Haem promotes the formation of *N*-nitroso compounds and also contains iron. Free iron can lead to production of free radicals (box 4.3.3). Iron overload also activates oxidative responsive transcription factors, pro-inflammatory cytokines, and iron-induced hypoxia signalling.[83]

Figure 4.3.5 **Processed meat and colorectal cancer; cohort studies**



4.3.5.1.2 Processed meat

The variation in definitions for processed meat used by different studies (see chapter 4.3.1) is likely to contribute to the observed heterogeneity.

Colorectum

Fourteen cohort studies[8-10 14-19 21 27 69 84 85] and 44 case-control studies investigated processed meat and colorectal cancer.

Twelve cohort studies showed increased risk for the highest intake group when compared to the lowest (figure 4.3.5),[8-10 14-19 21 27 69 85] which was statistically significant in three.[9 14 15 85] One study reported non-significant decreased risk and one study reported that there was no effect on risk.[84] Meta-analysis was possible on five studies, giving a summary effect estimate of 1.21 (95% CI 1.04–1.42) per 50 g/day, with low heterogeneity (figures 4.3.6 and 4.3.7). What heterogeneity there is could be explained by the disparity in category definitions between studies, as well as by improved adjustment for confounders in recent studies. A dose-response relationship was also apparent from cohort studies that measured in times/day (figure 4.3.8).

The majority of case-control studies showed increased risk with increasing intake of processed meat. Because of the abundant prospective data from cohort studies, case-control studies were not summarised.

These data are supported by a recently published meta-analysis of 14 cohort studies, which reported a summary effect estimate of 1.09 (95% CI 1.05–1.13) per 30 g/day.[25]

The general mechanisms through which processed meat could plausibly cause cancer are outlined below.

There is a substantial amount of evidence, with a dose-response relationship apparent from cohort studies. There is strong evidence for plausible mechanisms operating in humans. Processed meat is a convincing cause of colorectal cancer.

The Panel is aware that since the conclusion of the SLR, five cohort[28 30 32 86 87] and two case-control studies[36 88] have been published. This new information does not change the Panel judgement (see box 3.8).

Oesophagus

Two cohort studies[89 90] and eight case-control studies[40 41 43 44 49 50 91-94] investigated processed meat and oesophageal cancer.

Both cohort studies showed non-significant increased risk for the highest intake groups when compared to the lowest.[89 90] The effect estimates were 1.24 (95% CI 0.73–2.1)[90] and 1.6 (95% CI 0.4–6.9).[89] Both analyses adjusted for age, smoking, and alcohol.

Six case-control studies showed increased risk for the highest intake groups when compared to the lowest,[43 44 49 50 91-93] which was statistically significant in one.[93] Two studies showed non-significant reduced risk.[40 41 94]

The general mechanisms through which processed meat could plausibly cause cancer are outlined below.

Figure 4.3.6 **Processed meat and colorectal cancer; cohort studies**

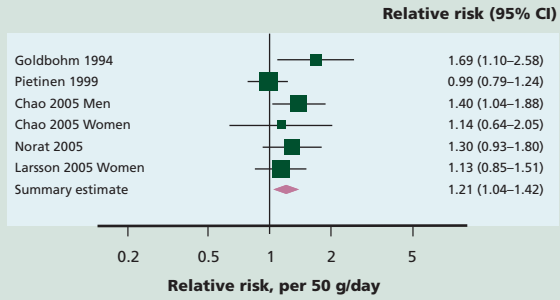


Figure 4.3.7 **Processed meat and colorectal cancer; cohort studies: dose response**

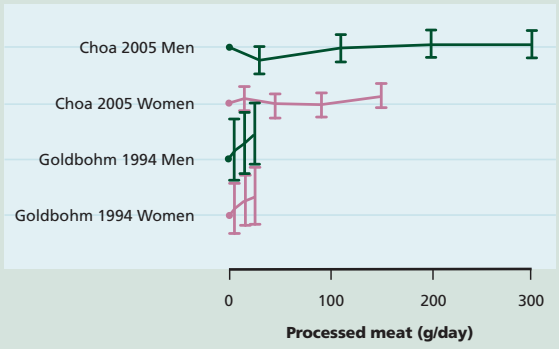
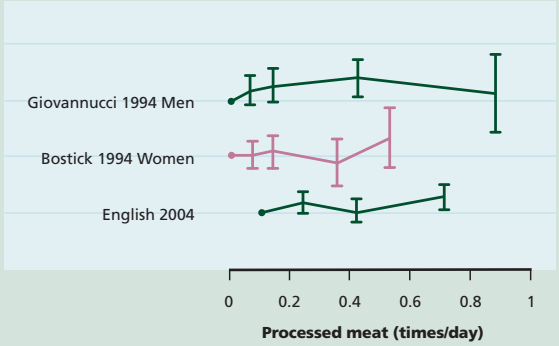


Figure 4.3.8 **Processed meat and colorectal cancer; cohort studies: dose response**



There is limited evidence, mostly from case-control studies, suggesting that processed meat is a cause of oesophageal cancer.

The Panel is aware that since the conclusion of the SLR, one cohort study[51] has been published. This new information does not change the Panel judgement (see box 3.8).

Lung

Four cohort studies[52 69 95 96] and 10 case-control studies[33 55-57 59 97-104] investigated processed meat and lung cancer.

Three cohort studies reported non-significant increased risk for the highest intake group when compared to the lowest.[69 95 96] One study reported no effect on risk.[52 95] Meta-analysis was possible on two of the studies, giving a summary effect estimate of 1.03 (95% CI 0.92–1.16) per serving/week, with no heterogeneity.[52] All four cohort studies adjusted for smoking.

Six case-control studies reported increased risk for the highest intake group when compared to the lowest,[33 56 57 59 99 100 102-104] which was statistically significant in two.[100 102] Four studies reported non-significant decreased risk.[55 97 98 101] All of the studies adjusted for smoking.

The general mechanisms through which processed meat could plausibly cause cancer are outlined below.

There is limited, inconsistent evidence suggesting that processed meat is a cause of lung cancer.

Stomach cancer

Eight cohort studies,[51 69 105-110] 21 case-control studies,[49 111-132] 1 cross-sectional study,[133] and 1 ecological study[134] investigated processed meat and stomach cancer.

Five cohort studies showed increased risk for the highest intake group when compared to the lowest,[51 106-108 110] which was statistically significant in one.[51] Two studies reported non-significant decreased risk[105 109]; and one showed no effect on risk in men and non-significant decreased risk in women.[69] Meta-analysis was possible on all eight cohort studies, giving a summary effect estimate of 1.02 (95% CI 1.00–1.05) per 20 g/day, with no heterogeneity.

Thirteen case-control studies showed increased risk for the highest intake group when compared to the lowest,[49 113 117 119-121 124-132] which was statistically significant in seven.[120 125 128-132] Three studies showed decreased risk,[118 122 123] which was statistically significant in one[118]; and one showed no effect on risk.[116] Four other studies reported no significant difference between mean intakes in cases and controls.[111 112 114 115] Meta-analysis was possible on nine studies, giving a summary effect estimate of 1.13 (95% CI 1.01–1.25) per 20 g/day, with high heterogeneity.[49 117-119 121 123 128-130]

A dose-response relationship is apparent from case-control but not cohort data.

The single ecological study reports a statistically significant correlation between increased processed meat and stomach cancer risk.[134]

The general mechanisms through which processed meat could plausibly cause cancer are outlined below.

The evidence is inconsistent. There is limited evidence suggesting that processed meat is a cause of stomach cancer.

The Panel is aware that since the conclusion of the SLR, one cohort[135] and two case-control studies[136 137] have been published. This new information does not change the Panel judgement (see box 3.8).

Prostate

Four cohort studies[138-141] and six case-control studies[142-147] investigated processed meat and prostate cancer.

All four cohort studies showed increased risk for the highest intake group when compared to the lowest,[138-141] which was statistically significant in two.[139 141] Meta-analysis was possible on all four cohort studies, giving a summary effect estimate of 1.11 (95% CI 0.995–1.25) per serving/week, with high heterogeneity. Heterogeneity was caused by varying size, not direction, of effect.

Two of these studies reported separately on advanced or aggressive cancer. Both showed increased risk with increasing intake of processed meat,[138 141] which was statistically significant in one.[141] Meta-analysis was possible on both studies, giving a summary effect estimate of 1.09 (95% CI 0.98–1.22) per serving/week, with moderate heterogeneity.

Four case-control studies showed non-significant decreased risk with increasing intake of processed meat[143-145 147]; two showed non-significant increased risk.[142 146] Meta-analysis was possible on five case-control studies, giving a summary effect estimate of 1.01 (95% CI 0.98–1.04) per serving/week, with low heterogeneity.[143-147] The general mechanisms through which processed meat could plausibly cause cancer are outlined below.

There is limited evidence from sparse and inconsistent studies suggesting that processed meat is a cause of prostate cancer.

The Panel is aware that since the conclusion of the SLR, two cohort studies[148 149] have been published. This new information does not change the Panel judgement (see box 3.8).

General mechanisms

Nitrates are produced endogenously at the low pH in the stomach and are added as preservatives to processed meats, both of which may contribute to *N*-nitroso compound production and exposure. *N*-nitroso compounds are suspected mutagens and carcinogens.[150] Many processed meats also contain high levels of salt and nitrite. Some processed meats are also cooked at high temperatures, resulting in the production of heterocyclic amines and polycyclic aromatic hydrocarbons. Red meat contains haem iron. Haem promotes the formation of *N*-nitroso compounds and also contains iron. Free iron can lead to production of free radicals (box 4.3.3).