7.2 Nasopharynx

Cancer of the nasopharynx is the 23rd most common type of cancer worldwide. About 80 000 cases were recorded in 2002, accounting for less than 1 per cent overall. In most parts of the world, this cancer is rare. It is relatively common on and near the southern Chinese littoral, and among communities who have migrated from that part of China to other countries. It is twice as common in men as in women. It is the 20th most common cause of death from cancer.

Overall, *the Panel judges* that there is a specific role for Cantonese-style salted fish in the causation of cancer of the nasopharynx.

***The Panel judges* as follows:**
Cantonese-style salted fish is probably a cause of nasopharyngeal cancer. This judgement does not apply to fish salted or fermented by any other method.

There is limited evidence suggesting that non-starchy vegetables and fruits protect against this cancer.

Other causes of this cancer include tobacco smoking and infection with the Epstein-Barr virus.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable", shows that Cantonese-style salted fish is a probable cause of this cancer.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE NASOPHARYNX

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

	DECREASES RISK	INCREASES RISK
Convincing		
Probable		**Cantonese-style salted fish[1]**
Limited — suggestive	Non-starchy vegetables[2] Fruits[2]	
Limited — no conclusion	Cereals (grains) and their products; nuts and seeds; herbs, spices, and condiments; meat; fish; shellfish and seafood; eggs; plant oils; tea; alcohol; salted plant food; Chinese-style pickled cabbage; pickled radish; pickled mustard leaf; Chinese-style preserved salted eggs; fermented tofu and soya products	
Substantial effect on risk unlikely	None identified	

1 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.
2 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.

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.

The nasopharynx is the top portion of the pharynx, the muscular cavity leading from the nose and mouth to the larynx.

Cancers in this area arise predominantly from epithelial cells, with squamous cell carcinomas being the most common. Carcinomas constitute 75–90 per cent of nasopharyngeal cancers in low-risk populations, and virtually 100 per cent in high-risk populations.[25] Nasopharyngeal squamous cell carcinomas are included here; other types are not.

7.2.1 Trends, incidence, and survival

Age-adjusted rates of nasopharyngeal cancer are decreasing in areas of high incidence, such as Hong Kong and Singapore.[25]

This cancer is predominantly a disease of low-income countries, with overall rates more than three times higher in middle- to low- than in high-income countries. Incidence is also higher in certain ethnic groups — for instance Chinese and also Malay and Filipino people living in south-eastern Asia.

Around the world, age-adjusted incidence rates range from 20–30 per 100 000 people in parts of Hong Kong and south-eastern Asia, to less than 1 per 100 000 across most of the Americas and Europe.

This cancer also occurs in northern Africa, parts of the Middle East, and Micronesia and Polynesia. However, the highest rates are among Cantonese people who live in the central region of Guangdong Province in southern China, which includes Hong Kong.[25] Migrant populations from this province carry the risk levels of the original population, but this decreases over generations.[26] Rates are approximately twice as high in men as in women.[2]

The age profile of nasopharyngeal cancer is different in areas of high compared with low incidence. Risk increases with age in most of the world, but in Guangdong Province it peaks between the ages of 45 and 54. In populations where there is a moderate incidence of this cancer, risk peaks in young adults.[25] Overall 5-year survival rates are around 50 per cent.[27] Also see box 7.1.1.

There are two variants of nasopharyngeal squamous cell carcinoma: keratinising and non-keratinising. The non-keratinising variant can be further divided into differentiated or undifferentiated. In North America, the proportions of each are 25, 12, and 63 per cent, respectively. In southern China, the distribution is different: 2, 3, and 95 per cent.[27]

Box 7.2.1 Epstein-Barr virus

Most adults are infected with the Epstein-Barr virus, but relatively few will ever develop the cancers of which this virus is a contributory or necessary cause. Other factors beyond infection with the virus are needed to lead to the development of cancer. Environmental factors including some dietary factors are thought to render precancerous epithelial cells sensitive to Epstein-Barr virus infection, which then triggers malignancy.[29]

Epstein-Barr virus is a DNA virus of the herpes family. It primarily infects B lymphocytes (white blood cells that produce antibodies), though it can also infect epithelial cells. Infection usually occurs in childhood and does not usually produce symptoms, but in adults it can cause infectious mononucleosis or glandular fever. It is particularly associated with undifferentiated nasopharyngeal carcinoma, the most prevalent type.[30 31]

In nasopharyngeal carcinoma, all of the tumour cells carry viral DNA in a monoclonal form. This means that Epstein-Barr virus infection must have occurred quite early in the cancer process, before rapid growth.[32] It is not normally possible to detect Epstein-Barr virus infection in non-cancerous nasopharyngeal cells.[31]

7.2.2 Pathogenesis

Variation in the distribution of keratinising squamous cell carcinoma and the two forms of non-keratinising carcinoma in North America and southern China, together with the different age profiles in the two regions, suggests that different disease paths may occur in high-incidence populations.

Patches of dysplasia are the first recognisable precancerous lesions; latent infection with the Epstein-Barr virus (see box 7.2.1) leads to severe dysplasia. The subsequent genetic and chromosomal changes in these lesions lead to invasive carcinoma.[28]

7.2.3 Other established causes

(Also see chapter 2.4 and 7.1.3.1.)

Tobacco use. Smoking tobacco is a cause of nasopharyngeal cancer.

Occupational exposure. Occupational exposure to formaldehyde is also a cause of this cancer.[33-35]

Infectious agents. Epstein-Barr virus infection is a cause of nasopharyngeal cancer (see box 7.2.1).[30] It may be necessary but is not a sufficient cause.

7.2.4 Interpretation of the evidence

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

7.2.4.2 Specific

Considerations specific to cancer of the nasopharynx and to Cantonese-style salted fish, include:

Classification. The term 'salted' is an incomplete and perhaps misleading term, given that the fish is also fermented. See the footnote of the matrix for this section, and also 7.2.5.3.

Confounding. It is not possible to exclude a genetic component. Those at highest risk are Cantonese-speaking communities living in or originally from Guangdong Province.

Production, preservation, processing, preparation. The method of salting or the type of fish salted varies between regions. The presence of nitrates and nitrosamines (see box 4.3.2) in the fish also varies.

7.2.5 Evidence and judgements

In total, 74 publications were included in the SLR for nasopharyngeal cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are to be found in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.2.5.1 Non-starchy vegetables

(Also see chapter 4.2.5.1.)

Five case-control studies and two ecological studies investigated non-starchy vegetables; a further four case-control studies investigated green vegetables. Preserved vegetables were excluded from all categories. Nearly all of the studies showed decreased risk with increased intake.

This is a wide and disparate category, and many different plant food constituents are represented that could contribute to a protective effect of non-starchy vegetables. These include dietary fibre, carotenoids, folate, selenium, glucosinolates, dithiolthiones, indoles, coumarins, ascorbate, chlorophyll, flavonoids, allylsulphides, flavonoids, and phytoestrogens, some of which are potentially antioxidants. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage. It is difficult to unravel the relative importance of each constituent and it is likely that any protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

The evidence on non-starchy vegetables is sparse but generally consistent. There is limited evidence suggesting that non-starchy vegetables protect against nasopharyngeal cancer.

7.2.5.2 Fruits

(Also see chapter 4.2.5.2.)

Six case-control studies investigated general fruits and a further five case-control studies investigated citrus fruits. Preserved fruits were excluded from all categories. Most of the studies for general fruits and all of the studies for citrus fruits showed a decreased risk.

This is a wide and disparate category, and many different plant food constituents are represented that could contribute to a protective effect of fruits. These include dietary fibre, carotenoids, folate, selenium, glucosinolates, dithiolthiones, indoles, coumarins, ascorbate, chlorophyll, flavonoids, allylsulphides, flavonoids, and phytoestrogens, some of which are potentially antioxidants. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage. It is difficult to unravel the relative importance of each constituent and likely that a protective effect may result from a combination of influences on several pathways involved in carcinogenesis. In addition, some components of citrus fruits have been shown directly to inhibit Epstein-Barr virus activation.[36]

The evidence, from case-control studies only, is sparse. There is limited evidence suggesting that fruits protect against nasopharyngeal cancer.

7.2.5.3 Cantonese-style salted fish

(Also see chapter 4.3.5.3.1.)

One cohort study and 21 case-control studies of adult diets were examined. The single cohort study and most of the case-control studies showed increased risk with higher intake. Meta-analysis showed a 28 per cent increased risk per time eaten per week (figure 4.3.9). There is some heterogeneity, not all readily explained. Childhood diet data implicate an increased risk with early-life exposure.

Cantonese-style salted fish is dried in natural conditions outdoors. As prepared on the southern Chinese littoral, it is characterised by treatment with less salt than used on the northern littoral; it is also subject to fermentation during the drying process in the warm, damp climate of southern China.

The high content of nitrate and nitrosamines may account for some of the increased risk associated with salted fish intake. Nitrosamines are known mutagens and animal carcinogens that induce gene mutation. The direct role of nitrosamines in the carcinogenic process is supported by the increased risk for nasopharyngeal cancer development in people who have a variant allele of CYP2E1. This enzyme is expressed in the nasopharynx and is involved in the metabolic activation of nitrosamines to carcinogenic adducts.[37] Additional evidence has suggested a component of salted fish may contain Epstein-Barr virus-activating substances, although the specific agents of action have not been identified.[38]

Evidence from several case-control studies is consistent and shows a dose-response effect. There is evidence for plausible mechanisms. Cantonese-style salted fish is probably a cause of nasopharyngeal cancer.

7.2.5.4 Other exposures

Other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: cereals (grains) and their products; nuts and seeds; meat; fish; shellfish and seafood; eggs; herbs, spices, and condiments; tea; alcohol; plant oils; salted plant foods; Chinese-style pickled cabbage; pickled radish; pickled mustard leaf; Chinese-style preserved salted eggs; and fermented tofu/soya products.

7.2.6 Comparison with previous report

7.2.6.1 General

See 7.1.6.1, and box 3.8.

7.2.6.2 Specific

The previous report judged the evidence that Cantonese-style salted fish is a cause of nasopharyngeal cancer to be convincing. No further cohort studies have been conducted since the mid-1990s.

7.2.7 Conclusions

The Panel concludes:

Cantonese-style salted fish is probably a cause of nasopharyngeal cancer. This does not apply to fish salted or fermented by any other method.

There is limited evidence suggesting that non-starchy vegetables, and also fruits, protect against this cancer.