7.17 Skin

Cancer of the skin in its various forms is the most common type of cancer worldwide. Around 90 per cent of all skin cancers are non-melanoma. Around 4 million cases were recorded in 2002, but it is likely that many cases are not referred, and this cancer is not included in the rankings in this Report. Around 160 000 cases of melanoma skin cancer were recorded in 2002, accounting for around 1.5 per cent of all cancers. Skin cancers are more common in high-income countries and among light-skinned people. Overall rates of this cancer are increasing. Survival rates of melanoma are high and also depend on access to treatment. Five-year survival rates for non-melanoma skin cancer are more than 99 per cent. Melanoma is the 22nd most common cause of death from cancer.

Overall, *the Panel emphasises* that the main cause of skin cancer is over-exposure to radiation from sunlight.

***The Panel judges* as follows:**
Arsenic in drinking water is probably a cause of skin cancer. There is limited evidence suggesting that retinol protects against squamous cell carcinomas of the skin, and that selenium is a cause of skin cancer. It is unlikely that beta-carotene or foods containing it have a substantial effect on the risk of non-melanoma skin cancer.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable", shows that arsenic in drinking water is probably a cause of skin cancer. It is unlikely that beta-carotene or foods containing it have a substantial effect on the risk of non-melanoma skin cancer.

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

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

	DECREASES RISK	INCREASES RISK
Convincing		
Probable		**Arsenic in drinking water[1]**
Limited — suggestive	Retinol[2]	Selenium supplements[3]
Limited — no conclusion	Potatoes; non-starchy vegetables; fruits; fish; eggs; milk; total fat; cholesterol; coffee; tea; alcohol; protein; vitamin A; retinol (foods); folate; vitamin C; vitamin D; vitamin E; multivitamins; selenium; carotenoids; beta-carotene (melanoma); alpha-carotene; lycopene; physical activity; body fatness; energy intake	
Substantial effect on risk unlikely	Beta-carotene[4] (non-melanoma)	

1 The International Agency for Research on Cancer has graded arsenic and arsenic compounds as Class 1 carcinogens. The grading for this entry applies specifically to inorganic arsenic in drinking water.
2 The evidence is derived from studies using supplements at a dose of 25 000 international units/day. Applies only to squamous cell carcinoma.
3 The evidence is derived from studies using supplements at a dose of 200 µg/day.
4 The evidence is derived from studies using supplements at doses of 30, and 50 mg/day, and from foods containing beta-carotene. See chapter 4.2.

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 skin is the outer covering of the body. There are two main types of skin cancer: melanoma and non-melanoma. Non-melanoma is more common. The most common non-melanoma tumours are basal cell carcinoma and squamous cell carcinoma, which together account for 90 per cent of skin cancers.[4] Melanomas are nearly always pigmented and usually develop from pigmented lesions such as moles. Melanoma accounts for 4 per cent of skin cancers. Other skin cancers such as Kaposi's sarcoma and cutaneous lymphomas are not included here.

7.17.1 Trends, incidence, and survival

Age-adjusted rates of both melanoma and non-melanoma skin cancers are increasing. Rates have doubled since the mid-1950s in many high-income countries, particularly those that already had high rates. This trend is restricted to countries where a high proportion of the population is fair-skinned.[137] The incidence of non-melanoma skin cancer is also increasing.[4] It is estimated that there are more than a million new cases each year in the USA alone,[314] and in Australia the reported incidence is even higher.[315]

Skin cancer is mainly a disease of high-income countries, where overall melanoma rates are more than 10 times higher than in middle- to low-income countries. Age-adjusted incidence rates range from more than 30 per 100 000 people in Australia and New Zealand to less than 1 per 100 000 across much of Africa and Asia. Rates are relatively high (around 15 per 100 000) in North America, Israel, and many northern European countries.[2] In the USA, rates are higher in white people than among other ethnic groups.[3] Non-melanoma skin cancer is the most common cancer in the world, and correlates with lighter skin colour and accumulated sun exposure.[316]

Although both melanoma and non-melanoma skin cancer incidence increases with age, melanoma causes a disproportionate number of cancers in young and middle-aged people.[317] Melanomas are most common on exposed areas of the body, and are relatively rare on areas that are usually covered by clothing.

Despite the considerably higher incidence of non-melanoma skin cancer compared with melanoma (around 20 to 1 in the USA), this less common type accounts for 79 per cent of skin cancer deaths.[318] The 5-year survival rate is between 80 and 90 per cent in high-income countries, but just over half that in middle- to low-income countries.[124] This difference is partly due to a different, prevalent type of melanoma (acral melanoma, on the soles of the feet), which has a poorer prognosis. Melanoma accounts for somewhat over 1 per cent of all cancer incidence, but only around 0.5 per cent of all cancer deaths. Non-melanoma skin cancers are almost never fatal.[319] Also see box 7.1.1.

7.17.2 Pathogenesis

The skin changes with age and is affected by hormonal influences and exposure to the sun and wind. Skin pigmentation varies between individuals and its structure also differs, depending, for instance, on whether it covers the lips, the soles of the feet, or the eyelids. All of these aspects influence skin cancer risk. Both melanoma and non-melanoma skin cancers are thought to be caused largely by UV irradiation mainly from sunlight. There is a clear relationship between accumulated sun exposure and non-melanoma skin cancer, but melanoma is more common in office workers than in outdoor workers, suggesting that damage from episodic exposure and extreme occasional sun damage (blistering sunburn) may be more important.[4] The role of sun damage is supported by the association between measures of sun sensitivity and skin cancer incidence, which is higher in people who have freckles and skin that burns without tanning, more moles, blue eyes, and red hair.[320 321]

UV-damaged cells are usually removed by apoptosis (programmed cell death, see chapter 2.5.2) in a process involving the p53 protein. However, in non-melanoma skin cancer, the p53 tumour-suppressor gene is often damaged by UVB irradiation, so faulty cells are not removed from the skin. Both UVB and UVA irradiation also have direct and indirect effects on the cutaneous immune system, lowering the skin's cell-mediated immunity,[322] which is another factor that may influence carcinogenesis.

People who have a family history of melanoma may be predisposed to this type of skin cancer, although only one major inherited mutation has been found, and less than 2 per cent of melanomas are attributable to this inherited mutation.[323]

7.17.3 Other established causes

(Also see chapter 2.4 and 7.1.3.1.)

Radiation. Over-exposure to UV radiation (mainly from sunlight) is the chief cause of both non-melanoma and melanoma skin cancers.[324] In the case of melanoma, the main cause is episodic skin exposure involving severe sunburn, particularly in fair-skinned white people.[317]

Medication. Immune suppression in organ-transplant and AIDS patients is also associated with an increased risk of skin cancer (in addition to Kaposi's sarcomas).[325]

Infection and infestation. HPV can cause squamous cell carcinomas, especially in immune-compromised people.[325]

7.17.4 Interpretation of the evidence

7.17.4.1 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'.

7.17.4.2 Specific

Considerations specific to cancer of the skin include:

Classification. Melanoma and non-melanoma cancers may have different causes; this would explain heterogeneity in studies that do not distinguish between these two types of skin cancer. Non-melanoma skin cancer cases are commonly not recorded by cancer registries, and are therefore underestimated in many reports.

Confounding. High-quality studies adjust for sun exposure and distinguish between cancer types.

7.17.5 Evidence and judgements

In total, 167 publications were included in the SLR for skin cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are in Chapters 4–6.

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

7.17.5.1 Arsenic in drinking water

(Also see chapter 4.7.5.1.1.)

Two cohort studies, 5 case-control studies, 1 cross-sectional study, and 11 ecological studies investigated arsenic in drinking water. Nearly all studies showed an association between increased arsenic and skin cancer. Two case-control studies used toenail and fingernail measurements, which are thought to be more reliable than dietary estimates. These studies both showed increased risk, which was statistically significant in one. The single cross-sectional study and all ecological studies showed increased risk, with several reporting relatively large and statistically significant effect estimates.

Soluble arsenic in drinking water induces lung cancers in experimental animal models.[71] In humans, arsenic is a chromosomal mutagen (an agent that induces mutations involving more than one gene, typically large deletions or rearrangements). It can also act as a synergistic co-mutagen. Arsenic exposure also causes chronic lung disease.[71] These mechanisms may also be applicable to skin cancer. The Joint FAO/WHO Expert Committee on Food Additives has set a provisional tol-

erable weekly intake of 0.015 mg per kg body weight.[72]

The evidence is consistent, from cohort, case-control, and ecological studies. There is robust mechanistic evidence. Arsenic in drinking water is a probable cause of skin cancer.

7.17.5.2 Retinol

(Also see chapter 4.10.6.4.1.)

Two randomised controlled trials investigated retinol supplements. Both trials included only participants at risk of developing non-melanoma skin cancer, and both gave results stratified according to this type. While neither trial reported a statistically significant association to basal cell carcinoma, one of the two studies did report a statistically significant relationship with decreased squamous cell carcinoma risk.

The mechanism of anti-tumour action of the retinoids is not completely understood, but retinol is known to bind to cell receptors with promotion of differentiation, alteration of membranes, and immunological adjuvant effects.[326]

The evidence is sparse and studies were conducted on a narrowly defined population group (people at risk of developing skin cancer). There is limited evidence suggesting that retinol supplements protect against squamous cell skin cancer.

The Panel is aware that since the conclusion of the SLR, one case-control study[327] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.17.5.3 Selenium supplements

(Also see chapter 4.10.6.4.5.)

One randomised controlled trial and one cohort study investigated selenium supplements. The trial showed a statistically significant increased risk of total non-melanoma skin cancer with daily supplementation of 200 μg selenium. Subgroup analysis indicated that this risk might differ according to cancer type, with a statistically significant increased risk for squamous cell carcinoma but not basal cell carcinoma. The single cohort study stated that there was no statistically significant association.

No plausible mechanisms for how selenium might increase risk of skin cancer have been suggested.

The evidence is sparse, and no plausible mechanisms have been identified. There is limited evidence suggesting that selenium supplements are a cause of skin cancer.

7.17.5.4 Beta-carotene (non-melanoma)

(Also see chapters 4.2.5.3 and 4.10.6.4.2)

Four randomised controlled trials and one cohort study investigated beta-carotene supplements; two cohort studies and seven case-control studies investigated dietary beta-carotene; three cohort studies and one case-control study investigated beta-carotene from food and supplements combined; and eight cohort studies and three case-control studies investigated serum or plasma beta-carotene.

All three randomised controlled trials that investigated beta-carotene supplement interventions against placebo with respect to non-melanoma skin cancer reported results very close to null. Meta-analysis of the three trials produced evidence of no association. Two trials that investigated beta-carotene supplement interventions against placebo with respect to melanoma stated that there was no association with risk.

Meta-analysis of cohort data on plasma or serum beta-carotene and non-melanoma skin cancer, and cohort data that investigated the same exposure in melanoma, showed no clear association. No clear association was shown with dietary beta-carotene.

There is strong evidence from good quality trials that consistently fail to show an effect. It is unlikely that beta-carotene has a substantial effect on the risk of non-melanoma skin cancer. It is unlikely that foods containing beta-carotene have any substantial effect on the risk of non-melanoma skin cancer.

7.17.5.5 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: potatoes; non-starchy vegetables; fruits; fish; eggs; milk; coffee; tea; alcohol; foods containing selenium; total fat; cholesterol; protein; vitamin A; retinol (foods); beta-carotene (melanoma); alpha-carotene; carotenes; lycopene; folate; vitamin C; vitamin D; vitamin E; multivitamins; physical activity; energy intake; and body fatness.

7.17.6 Comparison with previous report

Skin cancers were not reviewed in the previous report.

7.17.7 Conclusions

The Panel concludes:

Arsenic in drinking water is probably a cause of skin cancer. There is limited evidence suggesting that retinol protects against squamous cell carcinomas of the skin and that selenium is a cause of skin cancer. It is unlikely that beta-carotene or foods containing it have a substantial effect on the risk of non-melanoma skin cancer. The main cause of skin cancer is over-exposure to UV radiation from sunlight.