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European Code against Cancer 4th Edition: Ultraviolet radiation and cancer☆

Rüdiger Greinert [a], Esther de Vries [b], Friederike Erdmann [c], Carolina Espina [c], Anssi Auvinen [d,e], Ausrele Kesminiene [c], Joachim Schüz [c,*]

[a] Center of Dermatology, Department of Molecular Cell Biology, Elbekliniken Stade/Buxtehude, Am Krankenhaus 1, D-21614 Buxtehude, Germany
[b] Department of Public Health, Erasmus MC/Section of Cancer Information, Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
[c] International Agency for Research on Cancer (IARC), 150 Cours Albert Thomas, 69372 Lyon, France
[d] School of Health Sciences, University of Tampere, FI-33014 Tampere, Finland
[e] STUK – Radiation and Nuclear Safety Authority, Research and Environmental Surveillance, Helsinki, Finland

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ABSTRACT

Ultraviolet radiation (UVR) is part of the electromagnetic spectrum emitted naturally from the sun or from artificial sources such as tanning devices. Acute skin reactions induced by UVR exposure are erythema (skin reddening), or sunburn, and the acquisition of a suntan triggered by UVR-induced DNA damage. UVR exposure is the main cause of skin cancer, including cutaneous malignant melanoma, basal-cell carcinoma, and squamous-cell carcinoma. Skin cancer is the most common cancer in fair-skinned populations, and its incidence has increased steeply over recent decades. According to estimates for 2012, about 100,000 new cases of cutaneous melanoma and about 22,000 deaths from it occurred in Europe. The main mechanisms by which UVR causes cancer are well understood. Exposure during childhood appears to be particularly harmful. Exposure to UVR is a risk factor modifiable by individuals' behaviour. Excessive exposure from natural sources can be avoided by seeking shade when the sun is strongest, by wearing appropriate clothing, and by appropriately applying sunscreens if direct sunlight is unavoidable. Exposure from artificial sources can be completely avoided by not using sunbeds. Beneficial effects of sun or UVR exposure, such as for vitamin D production, can be fully achieved while still avoiding too much sun exposure and the use of sunbeds. Taking all the scientific evidence together, the recommendation of the 4th edition of the European Code Against Cancer for ultraviolet radiation is: "Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds."

1. Ultraviolet radiation (UVR): sources and physical and biological properties

1.1. Introduction

UVR is part of the electromagnetic spectrum with wavelengths 100–400 nm; it is emitted by the sun and by artificial sources (e.g. sunbeds). Historically, this wavelength band has been further subdivided into three wavelength regions: UVC (100–280 nm), UVB (280–315 nm) and UVA (315–400 nm). The UV components reaching the Earth's surface comprise about 95% UVA and only 5% UVB [1]. Solar UVC is absorbed by (an intact) stratospheric ozone layer and hardly reaches the Earth's surface.

Acute skin reactions induced by UVR exposure are erythema (skin reddening) – or sunburn with increasing UVA dose – and acquisition of a suntan triggered by UVR-induced DNA damage. UVR exposure is the main cause of skin cancer, including cutaneous malignant melanoma (CM), basal-cell carcinoma (BCC) and

Abbreviations: AAD, American Academy of Dermatology; AK, actinic keratosis; ASR, age-standardised incidence rates; BCC, basal cell carcinoma; CI, confidence interval; CM, malignant melanoma; CPDs, cyclobutane-pyrimidine dimers; DT, delayed tanning; IARC, International Agency for Research on Cancer; IPD, immediate pigment darkening; MED, minimal erythemal dose; NMSC, non-melanoma skin cancer; ROS, reactive oxygen species; SCC, squamous-cell carcinoma; SPF, sun protection factor; UVI, ultraviolet index; UVR, ultraviolet radiation; US FDA, Food and Drug Administration of the United States; WHO, World Health Organization.

* Corresponding author at: IARC European Code Against Cancer Secretariat, 150 Cours Albert Thomas, 69372 Lyon Cedex 08, France. Tel.: +33 04 72 73 84 85.
E-mail address: secretariat-cancer-code-europe@iarc.fr (J. Schüz).

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1877-7821/

Box 1. European Code Against Cancer.

EUROPEAN CODE AGAINST CANCER

12 ways to reduce your cancer risk

1. Do not smoke. Do not use any form of tobacco
2. Make your home smoke free. Support smoke-free policies in your workplace
3. Take action to be a healthy body weight
4. Be physically active in everyday life. Limit the time you spend sitting
5. Have a healthy diet:
   - Eat plenty of whole grains, pulses, vegetables and fruits
   - Limit high-calorie foods (foods high in sugar or fat) and avoid sugary drinks
   - Avoid processed meat; limit red meat and foods high in salt
6. If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention
7. Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds
8. In the workplace, protect yourself against cancer-causing substances by following health and safety instructions
9. Find out if you are exposed to radiation from naturally high radon levels in your home; take action to reduce high radon levels
10. For women:
    - Breastfeeding reduces the mother's cancer risk. If you can, breastfeed your baby
    - Hormone replacement therapy (HRT) increases the risk of certain cancers. Limit use of HRT
11. Ensure your children take part in vaccination programmes for:
    - Hepatitis B (for newborns)
    - Human papillomavirus (HPV) (for girls)
12. Take part in organised cancer screening programmes for:
    - Bowel cancer (men and women)
    - Breast cancer (women)
    - Cervical cancer (women)

The European Code Against Cancer focuses on actions that individual citizens can take to help prevent cancer. Successful cancer prevention requires these individual actions to be supported by governmental policies and actions.

squamous-cell carcinoma (SCC). In 2009, the International Agency for Research on Cancer (IARC) classified solar UVR, as well as UV radiation used in tanning devices, as carcinogenic to humans (group 1) [1,2].

In the 4th edition of the European Code Against Cancer (Box 1) avoiding too much sun and not using sunbeds are recommended in order to prevent skin cancer. This recommendation is based on evidence from epidemiological studies, established causal mechanisms, the increasing skin cancer burden in the mostly fair-skinned European populations, and the modifiability of the risk factor by individual action, considering also the beneficial effects of sunlight such as vitamin D production.

1.2. UV index

The amount of solar UV irradiance measured at the Earth's surface depends on several factors. The most important ones are the time of day and season: in summer, about 20–30% of the total daily amount of UVR is received between 11 am and 1 pm, and 75% between 9 am and 3 pm (solar time, not local time) [3]. Seasonal variations in terrestrial UV irradiance at the Earth's surface, especially in UVB, are substantial in temperate regions, but less pronounced closer to the equator. Other important factors influencing UVR at the Earth's surface are geographical latitude, altitude, clouds, surface reflection and air pollution. Annual UV doses decrease with increasing distance from the equator (latitude) [3], and in general each 300 m increase in altitude increases the sun-burning effectiveness of sunlight by about 4% [4].

In order to measure the biological effects of UVR, the concept of 'minimal erythemal dose' (MED) has been developed. One unit of MED has been defined as the lowest radiant exposure to UVR that is sufficient to produce erythema with sharp margins 24 h after exposure [5]. In fair-skinned populations there is approximately a four-fold range in the MED of exposure to UVR depending on the person's skin type (Fig. 1) [6]. When the term MED is used as a unit of 'exposure dose', a representative value for sun-sensitive individuals of 200 J/m^2 is usually chosen. Measurements of many biological effects (including erythema) show that UVB is about 10^3–10^4 times more effective in inducing biological effects than UVA.

The UV index (UVI) is a standardised tool intended for the communication of the UVR intensity to the general public. It expresses the erythemal intensity of the sun as:

$$\mathrm{UVI} = k \cdot E_{\mathrm{biol}}$$

where E_{biol} represents the erythemal irradiance (in W/m^2) in the wavelength band 250–400 nm. Introduction of the constant k = 40 m^2/W converts UVI in a dimensionless number which can be used as a measure of solar UV. A UVI = 1 corresponds to an erythemal irradiance of 0.025 W/m^2.

The clear-sky UVI at solar noon is generally in the range of 0–12 at the Earth's surface, with values over 11 considered extreme.

1.3. Biological properties of UVR

1.3.1. DNA damage

The main intracellular target for UVR is DNA. A multitude of photoproducts – the ratio of which depends markedly on UV wavelength – is formed in DNA and can give rise to pre-mutagenic lesions. These photoproducts may be formed either via a direct mechanism (photon absorption in DNA) or via an indirect mechanism (excitation of other cellular chromophores which subsequently interact with DNA). Unlike UVB, UVA is only weakly absorbed by DNA. Induction of DNA damage by UVA occurs indirectly via absorption of UVA photons by endogenous photosensitisers (melanins, porphyrin, flavin groups) or exogenous photosensitisers (e.g. azathioprine, an immunosuppressive drug) [7]. These photosensitisers absorb in the UVA range and release, in a complex reaction scheme, reactive oxygen species (ROS), giving rise for example to guanine modifications, including 8-oxo-guaninine, which is an important pre-mutagenic lesion after UVA irradiation [7]. UVA can also cause the production of reactive nitrogen species (e.g. nitric acid and peroxynitrite), which can cause cellular and DNA damage [8]. UVA predominantly induces oxidation of purines and of relatively few pyrimidines, as well as a few (single-)strand breaks in DNA [9–11]. In vitro, UVA also induces double-stranded breaks in DNA of human keratinocytes and skin fibroblasts [12,13], rendering an UVA-irradiated genome prone to the production of chromosomal aberrations. UVA can also induce epigenetic changes (CpG island promoter methylation, histone methylation, etc.) in human keratinocytes through chronic exposure (200 kJ/m^2 once a week for 15 weeks), and via these modifications it can silence for example tumour suppressor p16 expression [14]. UVA can also induce the formation of cyclobutane – pyrimidine dimers (CPDs) – the most harmful pre-mutagenic lesions resulting from UVA exposure – in the genome of human skin cells; CPDs (not oxidative lesions) represent the most frequent type of DNA damage induced in human skin irradiated with UVA [15,16].

UVB is >1000 time more effective than UVA in producing CPDs (via direct photon absorption by DNA), and is therefore the main source of CPDs in human cells [17]. Irradiation of in vitro human keratinocytes with UVB (300 J/m^2) induces hundreds of thousands of CPDs in the genome [18]. If these CPDs are not repaired by cellular repair systems, or if they undergo error-prone repair during replication, they give rise to C → T or **CC → TT transitions or tandem mutations, which are considered "UV signature mutations" [19]. These types of mutation have frequently been found in tumour suppressor genes and oncogenes (e.g. p53, PTCH,

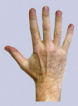
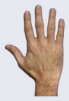
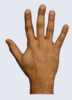
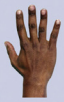
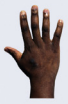
	Phenotype	UV sensitivity		Skin cancer risk
Type I 	Very fair, pale white, light coloured or red hair, often freckled	++++	Skin burns very easily, and never, or hardly ever, develops a tan	Greatest risk of skin cancer
Type II 	Fair, white skin, light hair, and blue or brown eyes. Some may have dark hair	+++	Skin burns easily, and tans slowly	High risk of skin cancer
Type III 	Light brown, light olive skin with dark hair and brown or green eyes	++	Skin does not burn easily, and develops a tan	High risk of skin cancer
Type IV 	Moderate brown, brown eyes and dark hair	+	Skin hardly ever burns, and develops a tan easily (Mediterranean skin type)	At risk of skin cancer
Type V 	Dark brown, brown eyes and dark hair	+/_	Skin never burns, naturally darker skin (Asian skin types)	Skin cancers are relatively rare, but those that occur are often detected at later, more dangerous stage.
Type VI 	Deeply pigmented dark brown to black, dark brown eyes and black hair	–	Skin never burns, naturally dark-coloured skin (Negroid skin types)	Skin cancers are relatively rare, but those that occur are often detected at later, more dangerous stage.

Fig. 1. Skin type chart: a numerical classification scheme for the colour of the skin according to the response of the different types of skin to ultraviolet radiation.

p16, RAS) which play important roles in the aetiology of skin cancer. For instance, >90% of all SCCs detected in the United States carry UV signature mutations in the p53 gene [20].

In addition to CPDs, UVB induces a second pyrimidine dimer, the pyrimidine-(6-4)-pyrimidone photoproduct ((6-4)PP), in a ratio of 3:1 (CPD:(6-4)PP) [21].

1.3.2. Immunosuppression

UVR, in addition to inducing mutations which may lead to skin cancer, also causes suppression of certain aspects of the immune system [1,22]. In human skin all the necessary cellular requirements to elicit anti-tumour immunity are present. Therefore, the development of skin cancer appears to involve failures in or suppression of immune responses [23]. For this reason, any suppression of the immune system may facilitate the development of UV-induced skin cancer. Patients with organ transplants who receive immunosuppressive medication are very prone to skin cancer [24].

Exposure to UVB suppresses the immune system by (1) inducing the production of immunosuppressive mediators, (2) damaging and triggering the premature migration of the antigen-presenting cells required to stimulate antigen-specific immune responses, (3) inducing the generation of suppressor cells, and (4) inhibiting the activation of effector and memory T cells [1].

For UVA-induced immunosuppression the production of reactive oxygen species and reactive nitrogen species alters the redox equilibrium, targeting proteins, lipids and DNA. This altered equilibrium may modulate immunocompetent cells, resulting in aberrant behaviour and migration of antigen-presenting cells, the inhibition of T-cell activation, and generation of suppressor cells [25]. In experimental systems and in human skin, UVR can induce immunosuppression locally and systemically [1]. Immunosuppression by solar-simulated UVR in men has been observed at doses three times lower than those required for immunosuppression in women [1,26].

1.3.3. Tanning of the skin

UVR-induced melanogenesis, or tanning, is widely recognised as the major defence of exposed skin against further UV damage [27]. Two types of tanning can be distinguished according to their UV-wavelength dependence: UVA-induced early pigmentation (immediate pigment darkening, IPD) and UVB-induced delayed pigmentation (delayed tanning, DT). Tanning provides a limited degree of protection against subsequent UVR (though not against the primary mutagenic effects of UV exposure). Tanning induced by solar-simulated UVR in human skin (skin types II and III) induces only moderate protection against erythema [28], and pigmentation delivers a sun protection factor of only about 2 for CPD induction in persons of skin types III/IV (i.e. it doubles the amount of UVR exposure necessary to produce a similar effect) and gives no protection at all for skin types I/II [29,30].

The tanning process appears to involve cross-talk between keratinocytes and melanocytes, and results in the transfer of melanin-containing melanosomes into the more superficially located keratinocytes, where the pigment forms a "cap" over the sun-exposed surface of the nucleus [31].

However, the stimulus that triggers the tanning pathway [27] is DNA damage. Therefore, it is very unlikely that tanning can occur without an increase in carcinogenic risk. The proposed concept of "safe tanning" thus warrants scientific scepticism [32], and tan should be considered a sign of damaged skin, not a sign of good health.

1.3.4. Vitamin D production

UVB triggers cutaneous synthesis of pre-vitamin D from 7-dehydrocholesterol [33,34]. This is the body's principal source

of vitamin D, because usually only small amounts are obtained from the diet [35]. It has long been known that vitamin D deficiency leads to severe bone disorders such as rickets and osteomalacia. There is also strong evidence that vitamin D deficiency is associated with secondary hyperparathyroidism, bone loss, fractures, muscle weakness and reduced calcium absorption [36,37].

In addition to these well-known positive effects of vitamin D, there is some debate as to whether increased levels of vitamin D (and thereby UVR) potentially have a protective effect on the development of certain types of cancer. The evidence base of such an effect is still poor, and current evidence from randomised trials does not support it.

Other beneficial effects of vitamin D on many other conditions (in addition to cancer) have been suggested: for instance, cardiovascular disease, metabolic syndrome, diabetes, asthma, multiple sclerosis, neuropsychological functioning, pregnancy outcomes, and overall mortality. The evidence for such effects is weak, and alternative explanations for findings in observational studies are plausible (e.g. confounding, reverse causation, etc.); further randomised trials seem warranted [38–41].

The World Health Organization (WHO) and other institutions request more "balanced" communications when dealing with UVR protection [42], but more scientific evidence backing up this request appears to be needed, especially in the context of UV causing skin cancer. In 2008, a literature review by the IARC suggested a possible protective role for high vitamin D levels in colon cancer and adenomas of the colon [43–46]. However, a protective role for vitamin D supplementation in the development of colon cancer was not observed in one of the largest interventional trials on vitamin D supplementation [47].

2. Cancer association with ultraviolet radiation (UVR)

2.1. Carcinogenicity of UVR

UVA and UVB from the sun and from UV-emitting devices (e.g. sunbeds) are classified as known carcinogens in humans (IARC Group 1) [1]. This classification is based on experimental and epidemiological data and their meta-analyses. It was concluded that there is sufficient evidence in humans for the carcinogenicity of solar radiation in CM, BCC and SCC. With regards to artificial sources of UVR, there is sufficient evidence for an increased risk of CM and of ocular melanoma, and a positive association was observed between sunbed use and SCC [1].

Skin cancer is the most common type of cancer in fair-skinned populations around the world [48]. CM accounts for about 5–10% of all skin cancers, whereas of non-melanoma skin cancer (NMSC) BCC accounts for approximately 80–85% and SCC for 15–20%. CM derives from pigment- (melanin-)producing melanocytes, whereas NMSC develops from epidermal keratinocytes.

Overwhelming evidence from epidemiological studies and basic science shows that the main risk factor for the three main types of skin cancer is UVR; most other important risk factors are related to sensitivity to UVR (sensitive skin type, characterised by low MED) [1].

Most of the evidence for a causal relationship between solar radiation and CM comes from descriptive epidemiological and case-control studies. The main measures of exposure were participant-recalled sun exposure. "Intermittent" sun exposure – which loosely equates with certain sun-intensive activities such as sunbathing, outdoor recreations, and holidays in sunny climates – has shown moderate to strong positive associations with melanoma, particularly if exposure occurred during childhood or adolescence (see below). However, "chronic" or "more continuous" exposure, which generally equates with "occupational" exposure, and total sun exposure (sum of "intermittent" and "chronic" exposure) generally showed weak, null or negative associations [1,49].

Recent large meta-analyses indeed show that most risk factors for CM are associated with UVR, such as the number of acquired nevi (which are UV-induced), number of atypical nevi, sunburn, intermittent sun exposure, presence of actinic tumours and total sun exposure (all statistically significantly related with CM). Chronic sun exposure seemed not to be associated with overall CM risk. However, studies which focus more on the anatomical site of the melanoma show that CM of the head and neck is strongly associated with actinic keratoses (caused by "chronic" UVR exposure), whereas CM on the trunk is strongly associated with acquired nevi ("intermittent" UVR exposure) [1,50,51].

About 50–60% of all CMs carry BRAF mutations, leading to kinase activation in the MAPK pathway inducing proliferation of melanocytes and impairment of apoptotic response to metabolic stress. BRAF mutations occur more frequently in CM on intermittent UVR-exposed human skin areas than in CM in more chronically exposed areas of human skin [52], indicating that UVR exposure pattern is a determinant of mutation induction. Although BRAF mutations make up only about 2–3% "UV signature mutations" [53], they seem to play an important role in the aetiology of CM. This has been shown in a recent sequencing study of a melanoma metastasis genome, which demonstrated that about 70% of single- and di-nucleotide substitutions in the genome represent C–T, CC–TT "UV signature mutations" [54].

Important risk factors for NMSC are closely related to the individual sensitivity of the skin to UVR, such as skin type [55,56]), presence of actinic keratosis [57], a personal history of NMSC [58], and immunosuppression [59–61].

There is increasing evidence that certain risk factors for CM (e.g. intermittent UVR exposure and sunburn) are also relevant for BCC [62,63]; UV signature mutations have been found in the p53, PTCH and smoothened genes [64,65], all involved in BCC development. This has been taken as a further indication that UVR plays an important role in the aetiology of BCC.

SCC appears frequently on sun-exposed areas of the human body (nose, forehead, ears) and depends to a high degree on total cumulative sun exposure [49]. Therefore, SCCs are common in occupationally UVR-exposed populations such as farmers, street workers, or seamen.p53 mutations are found in more than 90% of in situ SCC cases [66]. These mutations are predominantly of a "UV signature" type and occur non-randomly in the p53 gene in so-called "mutational hot spots", which are located in the gene in certain positions where nucleotide excision repair of pre-mutagenic lesions (CPDs) is hindered [67]. According to a well-described model for SCC development, specific p53 mutations lead to a pre-cancerous skin lesion (actinic keratosis, AK) where one allele of the p53 gene is already mutated. This mutation disturbs the p53-dependent apoptosis of UVR-damaged cells ("sunburn cells") and favours clonal expansion of AK cells [68]. If AK cells are further exposed to UVR, this can induce mutation of the second p53 allele, leading to a total loss of the "p53 checkpoint" responsible for cell-cycle control in skin keratinocytes. This leads to uncontrolled cell division and eventually to the development of invasive SCC alongside additional gene mutations (e.g., RAS) [69,70]. There is good evidence that SCC in mouse models as well as in human skin originates from inter-follicular epidermal stem cells [71] which might not be able to fully repair UVR-induced damage and therefore accumulate persistent DNA lesions (CPD retaining basal cells) [72,73].

2.2. Burden of skin cancer

The incidence of both CM and NMSC has increased steeply in fair-skinned populations over the past 50 years [74,75]. Worldwide,

the highest incidence rates are by far those observed in Australia and New Zealand, where fair-skinned populations are exposed to intensive UVR [74,75].

According to estimates for 2012, more than 230,000 new cases of CM occurred globally, of which 100,000 occurred within Europe [76]. The lifetime risk of CM is highest in New Zealand and Australia (3.6%) compared to 0.3–1.6% in European countries [74]. In Europe, incidence rates are particularly high in the Nordic countries, Switzerland, the Netherlands, the Czech Republic and Slovenia, while Mediterranean countries, as well as the Baltic and Eastern European countries, tend to have lower rates [74,76] (Fig. 2). In most parts of Europe, the incidence rates are higher among women than among men. Recent findings indicate a uniformly increasing trend in European countries over the last decades, with the strongest increases seen among older ages and with strong North-to-South and East-to-West variation (higher incidences in the North and East) [74,77]. However, for Norway and perhaps also France and Iceland indications of a levelling off in CM incidence rates are observed, most notably in young people aged 25–44 years. Nonetheless, incidence rates continue to rise irrespective of age in most European populations, and predictions suggest a continuation of this trend [74,77].

Incidence rates and time trends are difficult to estimate for NMSC, as they are often either not registered at all or incompletely covered by population-based cancer registries [75]. Of the specific NMSC types, SCC is included in relatively few cancer registries. Actinic keratosis is considered by some to be in situ SCC, and to our knowledge is not registered by any population-based cancer registry; registration of BCC is either absent or rather sporadically registered in population-based cancer registries.

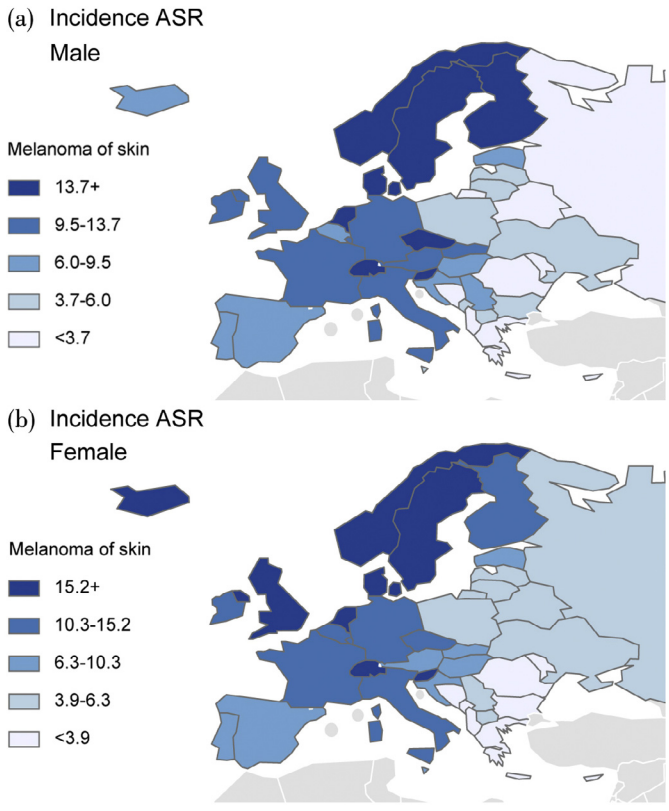


Fig. 2. Estimates of age-standardised incidence rates (ASR) of malignant melanoma in 2012: European variation in estimates of national age-standardised cutaneous malignant melanoma incidence rates (per 100,000) in 2012 (a) among men, and (b) among women, all ages.
Adapted from Ferlay J, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr.

Among European countries, Denmark, Finland, Scotland, Malta and the Netherlands have extensive population-based registration of NMSC over long time periods. Age-standardised incidence rates (ASRs) of primary BCC are estimated to be 77–158 cases per 100,000 person-years in those regions [78]. In Denmark, the BCC ASR increased from 27.1 to 96.6 cases per 100,000 among women and from 34.2 to 91.2 cases among men between 1978 and 2007 (world standard population). For the Netherlands, an increase from 34.4 to 157.3 among women and from 40.2 to 164.7 among men was observed between 1973 and 2009 (per 100,000, European standard) [79]. The largest relative increases in BCC in both Denmark and the Netherlands occurred in young women [79,80]. A recent systematic review of geographical variations and trends worldwide indicated that the BCC incidence rates have increased at a similar rate (about 5.5% per year on average) over the past four decades in mainland Europe [75].

In comparison to BCC, the SCC incidence rates are much lower [75,80,81]: for instance, 12 cases per 100,000 person-years among women and 19.1 among men in Denmark (world standard) [80], 13.8 among women and 36.9 among men in Scotland [81], and 20.5 among women and 35.4 among men in the Netherlands (per 100,000, European standard) [82]. However, SCC incidence rates are increasing rapidly, although the rate of increase varies between populations [75].

In general, the steep increase in incidence rates of all skin cancers has been attributed to population changes in lifestyle from sun avoidance towards sun-seeking behaviour, as well as improved diagnosis and registration. A more positive attitude towards sunbathing, more revealing fashion trends (e.g. the bikini in the 1960s), more outdoor leisure activities, and an increasing trend of holidays spent at sunny destinations has resulted in increasing both intermittent and cumulative sun exposure, and probably to increasing skin cancer rates [83,84]. In the 1960s, artificial UV sources (e.g. tanning devices such as sunbeds) were introduced and became increasingly popular during the following decades [85,86].

According to recent estimates 55,500 deaths from melanoma occurred worldwide in 2012, including 22,200 in Europe [76]. Whilst NMSC represents the most frequent type of cutaneous cancer, and contributes to the rising morbidity as well as to a significant economic burden to health services, mortality has remained consistently low (only $<$0.1% of diagnosed cases die because of NMSC) [87,88]. CM is the most serious skin cancer due its high potential for metastasis [89]. CM mortality rates in Europe range between 3.6/100,000 in Norway and 0.7/100,000 in Malta (Fig. 3) [76]. Overall, mortality rates continue to rise in several European countries as a result of increasing incidence, particularly in older age groups. However, in some countries – for instance Scandinavia – mortality rates appear to be already levelling off [90]. Survival of CM depends on the gender of the patient (better in women irrespective of stage), histological type, tumour thickness, body site, and – most importantly – stage at diagnosis [86]. A steady improvement in survival among CM patients has been reported over the last decades, with 5-year survival exceeding 80% in Europe [91]. Improvements in survival are most likely due to diagnosis at earlier stages of the disease for which effective treatment is available. Recently important breakthroughs have been made in the treatment of late-stage cases, which may be reflected in improved survival in the coming years [92].

2.3. UVR risk in children

Epidemiological findings from several migrant studies into countries with a high UVI indicate childhood as a susceptible

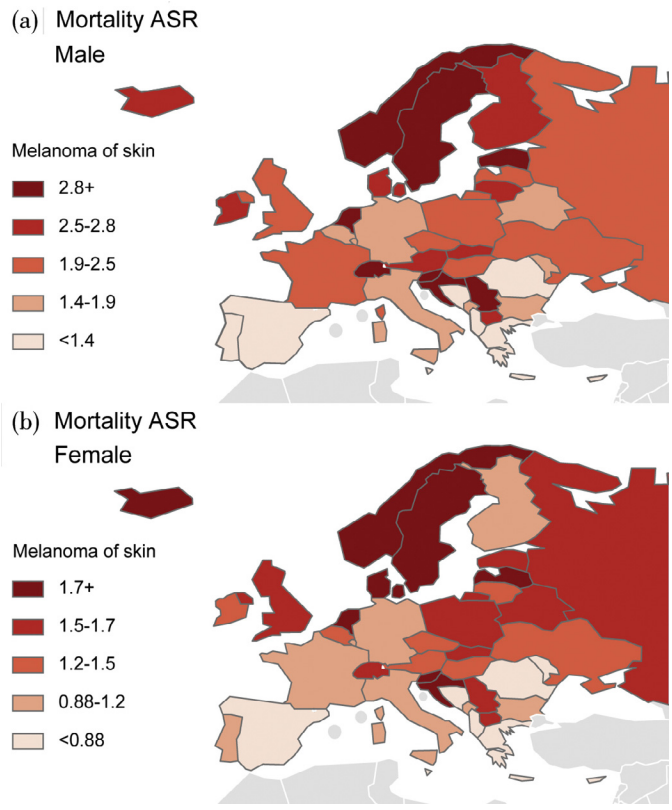


Fig. 3. Estimates of age-standardised mortality rates (ASR) of malignant melanoma in 2012; European variation in estimates of national age-standardised cutaneous malignant melanoma mortality rates (per 100,000) in 2012 (a) among men, and (b) among women, all ages.
Adapted from Ferlay J, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr.

period for UV carcinogenesis. In some studies conducted in Australia the incidence of and mortality from NMSC was generally lower in migrants from Northern Europe than in those born in Australia [93,94]. However, immigrants who arrived during the first 10 years of life had the same risk of BCC as people born in Australia. Migration into Australia later in life resulted in a lower relative risk (of the order of 0.2) compared to that in people born in Australia. Similar results were obtained in migration studies in Israel, Australia and New Zealand, showing that persons who migrated during childhood had the same relative risk of developing CM as if they were born in the country to which they moved, while the relative risk decreased if they migrated later in life [95–98]. The underlying cellular and molecular biological mechanisms for an increased risk of CM induction at young ages may lie in the fact that the bulge region of hair follicles hosting melanocytic stem cells are located deeper (more UV-protected) in the skin in adults (terminal hair) than in pre-pubertal children (vellus hair) [99,100].

3. Scientific justification for the recommendation

The carcinogenicity of UVR is well documented [1]. UVR is the predominant cause of all types of skin cancer, which is the commonest cancer in fair-skinned (i.e. the European) populations. CM, when diagnosed at a late stage, is a lethal disease, while early-stage CM and (normally) NMSC have very good prognoses. However, NMSC sometimes occurs at visible body sites (e.g. the face), resulting in disfigurement, and carries a substantial economic burden. In the UK, UVR has been estimated to cause 3.4% of all cancers in men (90% of all CMs), 3.5% of all cancers in women (82% of all CMs), and altogether 3.5% of cancers in both sexes combined (86% of all CMs), NMSC being excluded from this analysis; the population-attributable fractions are likely to be comparable for other European countries [101].

UVR is received mainly from natural but also from artificial sources, and individual exposure to either source can be relatively easily modified. UVR from the sunlight can be reduced, but cannot be completely avoided. Moreover, complete avoidance of UVR exposure should not be the aim, because of the health benefits of UVR exposure (largely related to vitamin D, see below), and also the health benefits related to physical outdoor activities [102]. Effective sun protection methods allow being outdoors without excessive direct sun exposure. There is scientific evidence that too much UVR exposure should particularly be avoided during childhood and adolescence.

Specifically with regard to artificial UVR, a 2012 meta-analysis including 27 epidemiological studies reported a meta-relative risk of ever versus never use of sunbeds for CM of 1.20 (95% confidence interval (95%CI) 1.08–1.34), increasing to 1.59 (95%CI 1.36–1.85) if the first sunbed use was before the age of 35 years (13 studies) [103]. A dose–response relationship was seen with a 1.8% (95%CI 0–3.8%) increase in CM risk for each additional session of sunbed use per year. From this, an estimated 5% of all CM cases in Europe could be attributable to sunbed use, most of them occurring in women. In the meta-analysis, relative risk estimates of ever versus never sunbed use for SCC was 2.23 (95%CI 1.39–3.57) and for BCC 1.09 (95%CI: 1.01–1.18) [103].

UVR from artificial sources (i.e. tanning devices) can be completely avoided by the individual.

Overall, this leads to the evidence-based recommendation: "Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds."

4. Individual action for protection

The best protection against natural UVR is to avoid exposure by staying inside when the UVI is highest or, second best, by seeking shade. However, even in the shade one receives UVR, depending on the source of the shade [104,105] and the amount of reflection from the ground surface. A parasol used on a beach might block around 40–50% of the UVR [105]; the rest reaches the skin by passing through the parasol or being reflected by the sand (up to 15%).

Alternatively, the skin can be covered with textiles, clothing and a (preferably wide-brimmed) hat; loose clothing with long sleeves made of tightly woven fabrics provides good protection (UV protection factor >15) [106,107]. Sunglasses with UV protection shield the eyes against the harmful effects of sunlight [107].

Application of sunscreens is another possibility for reducing the harmful effects of UVR exposure. Sunscreens have been developed to prevent sunburn. If sunscreens are properly used, they have been shown to reduce the risk of developing actinic keratosis (AK) and NMSCs [108–110]. There was concern that sunscreen use could increase the risk of CM as it motivates people to stay longer in the sun, but recent studies show that proper application of sunscreens, under controlled conditions, reduces the CM risk as well [111,112]. According to the standards of the Food and Drug Administration of the United States (US FDA) for sun protection factor (SPF) testing, proper application requires 2 mg/cm^2 of sunscreen on the body surface to protect the skin [113]. However, application thickness in "real life" is estimated to be 0.5–1.0 mg/cm^2, which lowers the effective SPF. Sunscreen failures can therefore stem from insufficient amounts being applied, but also from infrequent reapplication [114,115]. The American Academy of Dermatology (AAD) recommends regular sunscreen use to prevent skin cancer. Selecting a sunscreen with broad band (UVB/UVA) coverage is vital, and daily use of an SPF30 product is

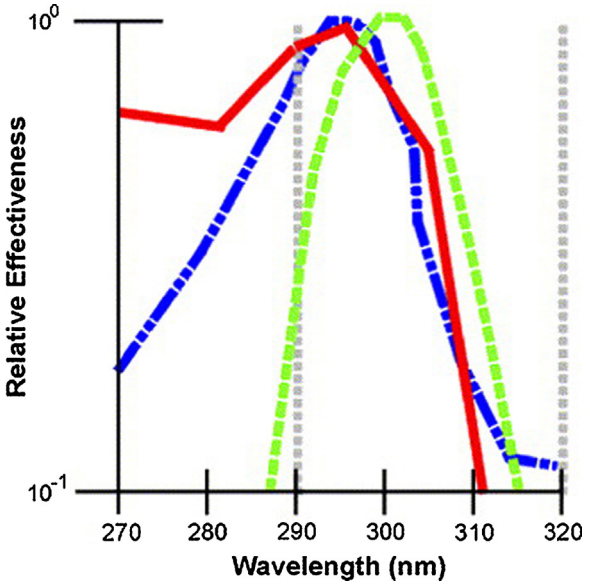


Fig. 4. Action spectra for pre-vitamin D3 formation (blue), induction of squamous-cell carcinomas (SCCs) and cyclobutane-pyrimidine dimers (CPDs) (nearly identical, green), and erythema induction (red) (taken from [118]).

recommended. Sunscreens must be applied uniformly, 15–30 min before exposure. To remain effective, they must be re-applied often (at least every 2 h), especially when perspiring or swimming [113]. The vehicle type of the sunscreen determines its durability and water resistance. The FDA designates sunscreens with intact photo-protective properties after 20 min exposure to water as "water-resistant" [113].

Exposure to artificial UVR should be completely avoided, unless under medical guidance. In contrast to what is often advertised by the tanning industry, the use of sunbeds to increase (or stabilise) vitamin D serum levels in order to "stay healthy" is not necessary. The action spectrum for the induction of UV-induced DNA damage, skin cancer induction and cutaneous vitamin D production are broadly alike (Fig. 4), with their most effective wavelengths in the UVB range 290–310 nm. Therefore, no such advertised vitamin D production is possible without increasing DNA damage and hence an increased skin cancer risk [116].

Recent findings have shown that the amount of UVR needed to produce a sufficient level of vitamin D under "realistic" conditions (e.g. summer sun at noontime, informal clothing such as T-shirt and short trousers) is limited to 27–38 min, depending on latitude (30–60° N). However, one should keep in mind that these times are already long enough to induce erythema for sensitive skin types (skin type I/II). Times longer than 27–38 min are needed to produce sufficient vitamin D, if UV exposure does not occur around noontime or in other seasons of the year. To reach the levels of UVR exposure sufficient to regulate vitamin D levels one does not have to spend much time in the sun, or use sunbeds. Short periods outdoors, perhaps repetitively, are sufficient in most circumstances [117,118]. People with vitamin D deficiency should consult their physician.

Worldwide, several countries have legislative limits or bans on sunbed use for minors [119]. Regulatory action is also required to support the individual to take action. For outdoor workers, sun protection has to be provided, complemented with education on how and when to apply it, and with instructions to comply with the safety guidelines. For the general public shady places need to be provided where people tend to stay in the sun for longer time periods, in particular in kindergartens and schools.

Overall, scientific knowledge on the excess cancer risk from UVR and on effective protection measures leads to the evidence-based recommendation: "Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds."

Conflict of interest

The authors declare no conflict of interest.

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