“Did you remember to bring the sunscreen?” Public awareness of the need to protect against the risk of melanoma from excessive exposure to UV rays from the sun has risen dramatically over recent decades. ‘Bringing the sunscreen’ is now a normal part of heading off to an outdoor activity or away on holiday, and we’ve seen a cultural shift away from deliberate overexposure – roasting unprotected on beaches or using tanning beds. The development and manufacture of sunscreen lotions is now a major industry.

Despite all this, the incidence of melanoma has increased significantly worldwide over the past several decades. In fair-skinned populations in regions such as North America, Northern Europe, Australia, and New Zealand, annual rates have risen by 4–6%. In the United States alone, the number of new invasive melanoma cases diagnosed annually increased by 27% from 2013 to 2023, with projections indicating over 100,000 new melanoma cases by the end of 2024.

A combination of factors seems to be at play, the primary one being greater UV exposure due to increased outdoor activities and insufficient sun protection. Warmer and dryer summers may have contributed to this trend, with more hours outside and lighter clothing. And while a decrease in the use of tanning beds will have helped the slow rise in incidence, they are still in use, especially among the young, and can increase melanoma risk by as much as 75%. As life expectancy rises, the number of cases among older individuals also rises. Environmental changes play a part too, such as the depletion of the ozone layer, which allows more harmful UVB radiation to reach the Earth’s surface.

The rising incidence is not paralleled by rising death rates. Much of this comes down to improvements in early detection rates, largely due to greater awareness of risk factors and suspicious lesions. For localised, early-stage melanoma, the five-year survival rate exceeds 99%. Progress in treatments for advanced melanomas, with the introduction of BRAF inhibitors, MEK inhibitors, and immunotherapies, has also helped push up survival rates. Yet the five-year survival rate for people with metastatic disease remains below 65% for those diagnosed with stage III disease and only 22.5% for stage IV. That is why heeding prevention messages remains so important.

Physical barriers to UV damage from sunlight have been the mainstay of skin protection from ancient days, well before the connection with melanoma was understood. Different formulations were developed across the globe, mainly in areas with very high sun exposure, some of which remain in use today (see box).

In modern times, as holiday travel, sun lamps, and concepts of beauty changed, populations in less sunny parts of the world learned the hard way about the dangers sun poses, particularly to people with lighter skins. Developing commercial sunscreens soon became a big industry, with modern formulations improving on the early thick, sticky substances to offer more user-friendly textures with broad-spectrum sunscreens that protect against both UVB and UVA rays, and with graded levels of protection (SPF values). Water-resistant formulas now offer enhanced protection during water activities, and multifunctional sunscreens now provide additional skincare benefits. There is also a focus on developing sunscreens suitable for all skin tones and environmentally friendly formulations to address concerns about marine ecosystem impacts. Hawaii’s 2018 legislation banning sunscreens containing oxybenzone and octinoxate, known to negatively impact coral reefs, is a significant step toward more eco-friendly sun protection.

The role of sunscreen in preventing UV-induced damage cannot be overstated. Regular use of broad-spectrum sunscreen with at least SPF 15 is crucial for protecting the skin from harmful UV rays. As is so often the case, however, there are some very human caveats to relying too heavily on this form of protection at a public health level. We don’t all remember to ‘bring the sunscreen’ all the time.

And there is evidence that even when we do, the feeling of invulnerability it confers can result in people spending much more time in the sun, thereby paradoxically increasing their risk. Recent years have seen a growing interest in ways in which we can increase our bodies' own resilience to developing melanoma – especially poor-prognosis disease – as well as improving our chances of a good response to treatment if such a diagnosis is made. Various nutrients and phytochemicals have been shown to play a role in lowering – or in some cases raising – risk levels.

Research has investigated the contributions of macro and micronutrients in preventing and slowing the progression of melanoma. A synergic strategy of nutritional and topical protection promises to offer a more comprehensive and effective approach to melanoma prevention and management.

Diet and nutrients that can protect against melanoma

Getting the right nutrients can help shield the skin from sun damage caused by UV radiation. Consuming antioxidant rich foods like fruits, vegetables, herbs and spices can counteract radicals produced by UV exposure, reducing inflammation and oxidative stress.

The **Mediterranean diet**, characterised by low intake of animal proteins and high consumption of vegetables and fruits, has been linked to a lower risk of various cancers, including melanoma (*J Nutr* 2015, *Int J Epidemiol* 2008). Certain nutrients, such as carotenoids and flavonoids, commonly found in plant-based foods, have antioxidant properties that can potentially reduce the chances of a cancer developing. These compounds act as cellular protectors, shielding cells from harm inflicted by free radicals and UV radiation. By neutralising these damaging agents, antioxidants may contribute to preserving cellular health and integrity, potentially reducing the risk of melanoma development. Some key antioxidants recognised for their effects against melanoma include beta carotene, found in carrots, sweet potatoes and apricots; vitamin C, abundant in citrus fruits (although citrus fruit may be contraindicated for melanoma; see below), strawberries, peppers and broccoli; vitamin E, found in almonds, spinach, avocado, and sunflower seeds; and lycopene present in tomatoes and watermelon. Grapes and berries contain polyphenols that have anti-inflammatory properties and help repair DNA damaged by UV rays.

Vitamin D, particularly in its active form (vitamin D3), has been shown to exert various biological effects that may be beneficial in the context of melanoma. These effects include regulation of cell growth, differentiation, and apoptosis, and modulation of immune responses. Studies have revealed a correlation between higher serum levels of vitamin D and thinner melanoma tumours at diagnosis. This finding is particularly significant because tumour thickness (measured by the Breslow index) is a crucial prognostic factor in melanoma, with thinner tumours generally associated with better patient outcomes. Furthermore, the benefits of vitamin D extend beyond prevention and early-stage disease. Recent studies have explored the potential role of vitamin D in reducing the recurrence rates of melanoma following surgical resection. Vitamin D can be synthesised by the body through sunlight exposure or obtained from certain foods, such as fatty fish, fortified dairy products, and mushrooms. Nutritional vitamin D, through diet and/or supplements is particularly indicated for individuals with, or at risk of, melanoma, whose exposure to sunlight is more actively discouraged.

Zinc is an essential mineral, crucial for maintaining a robust immune system. A deficiency in zinc reduces the levels of biologically active thymulin, a hormone crucial for T cell function, leading to decreased circulating T cells, thus potentially elevating the risk of cancer, including melanoma. Ensuring an adequate intake of zinc is vital for immune health and cancer prevention, included melanoma. Zinc is abundant in red meat, seafood, poultry, and grains.

Caffeine, and specifically caffeinated coffee consumption, has been inversely associated with melanoma risk, suggesting a protective effect potentially through mechanisms such as DNA

methylation and oxidative damage control. A dose-response meta-analysis showed that an increase in coffee consumption of one cup per day was associated with a 3% reduction in melanoma risk (RR=0.97; 95%CI 0.95–0.99). This suggests an inverse relationship between total coffee intake and melanoma incidence. A study conducted by Dorota Wrześniok suggests that caffeine exerts two important effects on melanoma cells: it reduces thiols depletion and promotes apoptosis. Thiols are important antioxidants in cells, and by reducing their depletion, caffeine may be interfering with the cancer cells' ability to manage oxidative stress. Additionally, caffeine appears to promote apoptosis selectively in melanoma cells, which is crucial because cancer cells often evade the body's natural cell death mechanisms.

Tea (especially **green tea**) has been studied for its anti-cancer properties. Research has shown that green tea contains polyphenols, such as epigallocatechin-3-gallate (EGCG), which may inhibit the growth of melanoma cells. A study found that tea polyphenols inhibit the proliferation, migration, and invasion of melanoma cells, suggesting that these compounds may suppress melanoma growth through various mechanisms, including the regulation of the circ_MITF/miR-30e-3p/HDAC2 axis specific molecular pathways.

Curcumin, a natural compound obtained from the turmeric rhizome, shows promising anti-melanoma effects through multiple mechanisms. It inhibits cell proliferation, invasion, and angiogenesis, while promoting apoptosis and autophagy in melanoma cells. Curcumin's anti-cancer properties are mediated by modulating various signalling pathways, including JAK-2/STAT3 and AKT/mTOR, and regulating microRNAs. It also inhibits NFκB activation and nitric oxide production, leading to G2/M cell cycle arrest and apoptosis. Despite its potential, curcumin's low bioavailability limits its efficacy. However, new formulations and delivery systems, such as nanoparticles and liposomes, may enhance its bioavailability and therapeutic effects. While *in vitro* and *in vivo* studies demonstrate curcumin's promise as a melanoma treatment, clinical trials are still needed to confirm its efficacy in humans.

Resveratrol, a natural polyphenol, found on grape peels (and red wine) shows significant anti-melanoma properties. It inhibits melanoma cell viability, migration, and invasion by promoting autophagy through the PI3K/AKT/mTOR signalling pathway. It induces G1/S cell cycle arrest and apoptosis in melanoma cells, potentially via the p53 pathway and caspase activation. It effectively impairs proliferation in both temozolomide-sensitive and resistant melanoma cell lines, primarily by inducing S-phase arrest and apoptosis. Furthermore, resveratrol decreases melanoma cell migration *in vitro* in a dose-dependent manner and affects the expression of genes involved in the epithelial-to-mesenchymal transition. Caution in the consumption of red wine is always advised.

Omega-3 fatty acids, commonly found in fish oil and certain plant sources, have shown promising potential in slowing down the growth and spread of melanoma. Research using specially bred mice that can convert omega-6 fatty acids to omega-3 fatty acids has revealed that these mice experience less melanoma growth and spread compared to normal mice. Omega-3 fatty acids can increase the production of E-cadherin, a protein that helps cells stick together, which can prevent cancer cells from moving and spreading. They also block the signalling pathway β-catenin, which normally promotes cell growth and survival. Additionally, they boost the activity of the PTEN gene, which acts as a tumour suppressor, and modify the structure and function of platelets in ways that may make it harder for cancer cells to spread through the bloodstream. Some of the protective effects may also come from substances produced when the body breaks down omega-3 fatty acids, such as resolvin D2 and E1. These compounds have anti-inflammatory properties that could help prevent cancer growth.

Dietary factors that can raise melanoma risk

Higher intake of **polyunsaturated fatty acids (PUFAs)**, particularly linoleic acid, has been associated with increased risk, especially when coupled with lower soluble carbohydrate intake. A study by Hidetoshi Yamada investigated the effects of different fatty acids on melanoma cells and normal human melanocytes. Saturated fatty acids, such as myristic, palmitic, and stearic acids, increased melanin content in melanoma cells. Conversely, polyunsaturated fatty acids, such as EPA and DHA, decreased melanin content, with DHA notably suppressing glucose transporters and glycolysis-related genes. In normal human melanocytes, fatty acids such as palmitic acid, oleic acid, EPA, and DHA did not affect cell proliferation or melanin levels. Foods rich in PUFAs are fatty fish, nuts and seeds, tofu and plant oils, while saturated fatty acids are found mainly in animal products, dairy products and processed food.

When **alcohol** is consumed, it is rapidly metabolised in the body to acetaldehyde. This metabolite can act as a photosensitiser, meaning it increases sensitivity to light, particularly ultraviolet radiation. In this role, acetaldehyde can trigger the production of reactive oxygen species (ROS) and related compounds. These highly reactive molecules can cause skin damage and carcinogenesis. The risk of melanoma appears to increase with higher levels of alcohol consumption. Some research suggests that white wine may have a stronger association with skin cancer risk compared to other alcoholic beverages, possibly due to lower levels of protective antioxidants.

Dietary/metabolic factors that could impact risk either way

Citrus fruit consumption and its relationship with melanoma risk have been studied extensively, but the results are inconclusive. Some research indicates a potential increased risk, with a meta-analysis showing a 9–12% higher risk per daily serving of citrus fruit, but *not* citrus juice. This heightened risk may be due to psoralens and furocoumarins in citrus, which can make skin more sensitive to UV radiation. Conversely, other studies suggest that high citrus intake may reduce melanoma risk. Given the potential health benefits of citrus fruit, more research is necessary to understand this relationship fully. If the increased risk is confirmed, it may be wise to avoid sun exposure after consuming citrus.

Research in the relationship between **obesity** and melanoma has produced conflicting findings. While some studies suggest that a high body mass index may increase the risk of developing melanoma and lead to more aggressive disease, especially in men, others have even identified unexpected benefits in treatment outcomes for obese patients with metastatic melanoma – a phenomenon known as the ‘obesity paradox’. A recent cohort study found a negative correlation between obesity and incidence of melanoma, reiterating that the most important risk factor remains UV exposure.

Obesity is, however, correlated with greater Breslow thickness at diagnosis, indicating more advanced melanoma. Behavioural factors such as decreased skin self-examination in obese individuals may play a role here, by delaying detection.

Dietary factors in melanoma treatment

In addition to protecting or raising the risk of contracting melanoma, evidence shows that dietary factors can play a role in treatment.

Dietary interventions, especially those involving **high fibre intake**, have shown promise in boosting the effectiveness of immunotherapy for melanoma patients. The gut microbiome significantly influences immune responses, and diet can impact the composition and function of gut microbes. A

study published in *Science* found that melanoma patients who consumed more fibre-rich foods (such as fruits, vegetables, legumes, and whole grains) at the start of immunotherapy had better progression-free survival than those with lower fibre intake. Each additional 5 grams of daily fibre was linked to a 30% lower risk of cancer progression or death. This benefit was most evident in patients who did not use commercial probiotic supplements, suggesting natural dietary fibre is more effective in enhancing the gut microbiome's role in immunotherapy response. A randomised clinical trial is currently enrolling patients with stage III to IV melanoma to study how whole-food-based diets with different fibre contents affect the microbiome and immune response. This trial aims to provide more evidence on the role of diet in improving cancer outcomes through microbiome modulation.

Recent research is exploring innovative approaches to melanoma treatment by targeting the cancer cells' unique nutritional needs. One promising approach is t**argeted nutrient deprivation**. This method has been shown to reduce tumour growth in mice and improve the effectiveness of chemotherapy and immunotherapy. For melanoma, certain amino acids like arginine (abundant in pumpkin and sesame seeds, walnuts, and tofu) and leucine (found in animal protein, dairy products and eggs) are key targets. Many melanoma cells can't produce arginine, making them vulnerable when it is deprived. Leucine deprivation has been found to trigger cell apoptosis due to issues with autophagy, particularly in melanoma cells with genetic mutations in the RAS-MEK pathway. Additionally, general nutritional shortage has been observed to enhance the effects of cisplatin, a common chemotherapy drug, on melanoma cells, especially in metastatic melanoma subtypes. This combination induces cell death through mitochondrial damage and increased production of reactive oxygen species.

Though much remains to be revealed, the evidence already available indicates that, when it comes to melanoma, what we put *in* our bodies can add significantly to the protective effect of what we smear *on* our bodies. This means that, while always asking the question "Did you remember the sunscreen?" remains our first line of defence, taking care of what we eat is how we equip our bodies to mount their own defence against melanoma, should too much of that UV radiation make it through.

With the contribution of Francesca Albini

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