short review

memo (2019) 12:235–238
https://doi.org/10.1007/s12254-019-0512-7

memo
magazine of european medical oncology

Cutaneous melanoma—The benefit of screening and preventive measures

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Received: 18 April 2019 / Accepted: 8 July 2019 / Published online: 25 July 2019

Summary The incidence rates of cutaneous melanoma are continually rising in the Caucasian population with the highest rates in Australia and New Zealand. The genesis of melanoma is a complex interplay between genetic predisposition and exogenous factors. The major known exogenous risk factor of this potentially lethal malignancy is ultraviolet (UV) radiation. In the last decades diverse prevention strategies have been developed which in case of primary prevention are aimed to protect the skin from high-dose UV radiation. Although its effect is only visible after a long period of time and despite the growing awareness in the general population, it seems that primary prevention interventions are often not carried out as recommended. It was proposed that particularly in Europe where incidence rates are still increasing, the development and implementation of primary prevention campaigns should be pursued further. Secondary prevention implies early detection of melanoma by using skin cancer screenings. However, according to recent reviews there is only limited evidence on impact and benefit of routine skin cancer screenings in the adult general population. Thus, it was suggested that future research should focus on effects of targeted screening in population subgroups with increased risk for melanoma.

Keywords Cutaneous melanoma · Risk factors · Primary prevention · Secondary prevention

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Epidemiology and risk factors of cutaneous melanoma

Cutaneous melanoma is a very aggressive cancer with potential lethality as soon as it has become invasive. In the past 50 years, the incidence of melanoma has risen considerably in predominantly white populations [1]. Incidence rates vary worldwide with highest rates in Australia and New Zealand [2]. In 2018 the estimated age standardized incidence rates per 100,000 persons were 33.6 in Australia, 12.7 in the USA and 11.2 in Europe [2]. In recent years, a stabilization of incidence was observed in high incidence countries among younger age groups, which may be a benefit of preventive measures [3].

The genesis of melanoma is a complex interplay between environmental factors and genetic predisposition [4]. Ultraviolet (UV) light is the major known exogenous risk factor [4–6]. Absorption of UV light causes DNA damage, which can result in mutations if not repaired [4]. UV signature mutations can be found in large quantities in cutaneous melanoma [7]. In contrast to cutaneous squamous cell carcinoma, which is induced by chronic UV light exposure [8], development of cutaneous melanoma is primarily associated with intermittent but intense episodes of UV light exposure and sunburns [4, 6, 8], especially in childhood [9]. The rising incidence among light colored people may be in conjunction with changing UV light exposure patterns in the last decades with increased sun seeking behavior, beach holidays in winter [1, 4, 6, 8] or the use of indoor tanning beds [10]. Host factors for developing melanoma include multiple nevi [11], a personal history of melanoma [12], a positive family history [13] and phenotypic characteristics like light hair, eye and skin color [5]. Approximately 10% of all melanoma cases are associated with autosomal dominant inherited germline mutations that increase the

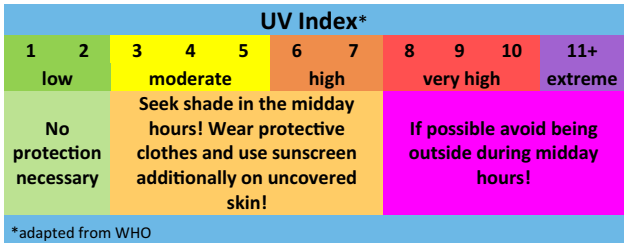

Fig. 1 UV index

risk of developing melanoma [14]. The most common is a mutation in *CDKN2A*, which encodes a tumor suppressor [14].

Because of the rising incidence of cutaneous melanoma a variety of prevention campaigns were developed in the past decades in many countries, most prominently in Australia [15]. Primary prevention takes the long-term approach and intends to protect the skin from high doses of UV radiation [15], with the aim of achieving stable or even decreasing incidence rates [15]. As prognosis of cutaneous melanoma is strongly associated with tumor thickness and stage of invasion at time of diagnosis [16], secondary prevention implies early detection of melanoma, when it still can be cured. This approach focuses on the goal of reducing mortality rates [5].

Primary prevention

Avoidance of sunburns and utilization of protective measures during peaks of UV radiation can theoretically contribute to a reduced melanoma risk; thus information and education of the population are essential [17]. The UV index, ranging from 0 to 11+ may be helpful to recognize the risk of high dose UV radiation [18], albeit at the moment it does not have a crucial influence on behavior-oriented prevention [19]. The World Health Organization recommends people to seek for shade and use protective clothes, sunglasses and sunscreen on uncovered skin when the UV index reaches 3. When the UV index reaches 8, sun should be completely avoided in the midday hours ([18]; Fig. 1). Since there is no definite evidence that the use of sunscreen reduces melanoma risk [20] and the use of sunscreen itself may encourage people to extend the time of sun exposure [19], seeking shade and protective clothes should be utilized in the first place. Moreover, skin should be slowly habituated to the sun and children in particular require special protection as they are at higher risk of suffering damage from exposure to UV radiation than adults ([19]; Table 1).

Table 1 Sun protection rules

Sun protection rules [a]
Avoid sunburns in any case
Limit sun exposure time in the midday hours
Pay attention to the UV index and adopt sun safety practices accordingly
Seeking shade and protective clothes should be used as primary preventive measures
Sunscreen should be used as an additional protection on uncovered skin
Sunscreen should never be used to extent the duration of sun exposure
Sunscreen should be reapplied every two hours
Slowly habituate the skin to sunlight
Children especially need to be protected from the sunburn rays

[a] Adapted from World Health Organization recommendations and S3 Leitlinie Prävention von Hautkrebs (S3 prevention of skin cancer guideline)

Primary preventive measures started in Australia in the 1960s and developed to large public nationwide educational programs, including mass media campaigns on television and radio with the goal of changing the community attitude towards sun bathing in the 1980s [5, 21]. One to two decades later incidence rates slowly started to stabilize or even slightly decrease, particularly in the younger age group [3], which is likely a result of the changing UV exposure behavior [15]. A similar trend of declining incidence rates was observed in other high incidence countries with comparable campaigns like New Zealand, USA and some northern European countries [3]. In many European countries small prevention campaigns like "Euromelanoma" are annually organized, providing public information about skin cancer and offering skin cancer screenings free of charge [22]. Sometimes special educational programs are also offered in schools and kindergarten [23]. However, it has been shown that successful primary prevention of skin cancer is difficult to achieve despite the growing awareness [24]. In most European countries incidence rates are still increasing. This phenomenon might be an effect of the overexposure to high dose UV radiation as well as attributed to the increased detection of thin melanomas [3]. A recently conducted, international cross-sectional survey on public awareness of UV light exposure risks and preventive behavior revealed wide variations in the results [25]. Overall, the surveyed populations were aware of the risks of sun exposure, but the prevention behavior was superior in most at-risk geographical areas, women, people aged over 45, people with high socioeconomic status and education level and in persons with skin type I [25]. In general, the practice of primary prevention was not performed correctly. For example, sunscreen was often used instead of and not added to primary sun protective methods or applied at suboptimal levels by using insufficient quantities and without frequent sunscreen reapplication. Furthermore, most of the participants did not know their individual risk factors like skin type, number and size of moles [25]. Other studies have shown that primary prevention behavior can be improved by a personal medical consultation and sun protective advice [26].

Secondary prevention

Definition of secondary prevention is early detection of melanoma in a presumed healthy person with the aim of decreasing mortality rates [19] as survival of cutaneous melanoma highly depends on tumor thickness and stage of invasion at time of diagnosis [16]. Hence, skin cancer screening has the potential to reduce melanoma mortality by detecting tumors at an earlier stage with better prognosis. However, benefits of skin cancer screening remain controversial.

Although benefit of regularly skin self-examination has been identified [27], multiple studies have shown that melanomas detected by a physician are thinner tumors compared to melanomas self-detected by the patient [28]. A large systematic population-based skin cancer screening (SCREEN) project including 360,288 participants (19% of all eligible citizens) was conducted between 2003 and 2004 in Schleswig Holstein, Germany. Interestingly, a reduction of thick melanoma incidence and a considerably decreased melanoma mortality were observed after 5 years, whereas the melanoma mortality rate remained stable in the rest of the country and neighboring Denmark, where screening did not take place [29]. This data suggest that skin cancer screening possibly leads to the detection of more in situ and thin invasive melanoma as indicated by an incidence increase. As a result of this outcome a national statutory skin cancer early detection program was established in Germany in 2008 [29]. This program is unique in its kind in the world [30] allowing health insured German residents aged 35 years and older to receive a skin cancer screening every two years [29]. Contrariwise, recent reviews arrive at the conclusion that the impact and benefit of routine skin cancer screening, especially on melanoma mortality, has only limited evidence [31, 32] mainly because well-designed population-based randomized controlled trials are lacking [30]. Indeed, such kinds of studies are time consuming and expensive. Due to the low yearly mortality rate of melanoma it may take years before any effect is seen. Furthermore, it cannot be ruled out that the increased incidence of skin cancers may be attributable to increased public or physician awareness and increasing skin biopsy rates rather than the specific screening interventions. In addition, the observed decline in melanoma mortality could be associated with factors other than skin cancer screening such as an improved melanoma treatment or bias in ascertainment of death causes. A follow-up research of the SCREEN publications revealed that the decline in melanoma mortality was only transient, and melanoma mortality has returned to prescreening levels [33]. Additionally, a recent report revealed that German nationwide skin cancer screening appears to be associated with increased incidence, but mortality was not reduced yet [33]. All that explains why routine melanoma screening is not generally recommended by many professional organizations worldwide [30]. To date, the US Preventive Task Force concludes that current evidence is insufficient to assess the balance of benefits and potential harms of screening the adult general population [32]. In fact, skin cancer screening can be accompanied by psychosocial harms, cosmetic harms or overdiagnosis [32].

Conclusion

Evidence on the association between skin cancer screening and mortality is still very low.

Referring to primary prevention, it was proposed that particularly in Europe where incidence rates of melanoma are still increasing in many countries, further development and implementation of primary prevention campaigns are needed [3]. Regarding secondary prevention, it was suggested that future research should focus on the effects of targeted screening in those populations with higher risk for melanoma [32]. The benefits of skin cancer screening may be greatest among subgroups most likely to develop melanoma such as older people with light skin color, persons with atypical moles and/or a positive family history [17]. Those high-risk populations could be selected within the scope of routine medical checkups or in the future by using artificial intelligence, and then referred to dermatologists.

There is no question that educational efforts are crucial, ranging from population-wide education about skin cancer prevention particularly focused on children and young adults to education of high-risk population and all physicians in performance of skin examination and recognition and early diagnosis of melanoma.

Conflict of interest M. Seidl-Philipp and V.A. Nguyen declare that they have no competing interests.

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