

REVIEWS

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Is Cutaneous Malignant Melanoma Preventable?

Czy można zapobiegać czerniakowi złośliwemu?

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Abstract

It is forecasted that cutaneous malignant melanoma (CMM) will become one of the most dangerous tumors of the 21st century. Results of treatment of CMM in Poland are very poor compared with highly developed countries. Clinical outcome is strongly influenced by the stage of the disease. The aim of this study was to discuss current data concerning CMM primary and secondary prophylaxis. This is a systematic review of published reports on the primary and secondary prophylaxis of cutaneous malignant melanoma. The search for available literature was performed in the PubMed National Library of Medicine database. The most effective method of reducing morbidity and mortality of CMM is prophylaxis. Primary prophylaxis consists of minimizing UV radiation exposure, achieved by reducing exposure to the sun, wearing proper clothing and sunglasses, following sun-protective behaviors, using sunscreen, and avoiding sunlamps and tanning beds. However, it is unclear whether using sunscreen reduces the incidence of melanoma. Secondary prophylaxis against melanoma consists of regular self and clinical examination of the skin in order to diagnose tumors at an early stage and to identify individuals at increased risk of developing melanoma. Health education, including the dissemination of knowledge on protection from harmful solar exposure and awareness of the early symptoms and signs of skin malignancies, may help improve prognosis. Many countries are trying to introduce skin cancer prevention programs. The efficacy of primary and secondary prophylaxis has been proven by decreases in the mortality rates in the USA and Australia, where prophylaxis and educational programs are well developed (*Adv Clin Exp Med* 2006, 15, 6, 1099–1105).

Key words: malignant melanoma, primary prevention, secondary prevention.

Streszczenie

Šzacuje się, że czerniak skóry będzie jednym z groźniejszych nowotworów XXI wieku. Wyniki jego leczenia w Polsce są bardzo złe w porównaniu z krajami wysoko rozwiniętymi. Skuteczność terapii jest ściśle związana ze stadiem choroby w chwili rozpoznania i rozpoczęcia leczenia. Celem pracy było omówienie aktualnych danych dotyczących pierwotnej i wtórnej profilaktyki czerniaka skóry na podstawie bazy danych PubMed National Library of Medicine. Najskuteczniejszą metodą zmniejszenia zachorowalności oraz śmiertelności z powodu czerniaka skóry jest profilaktyka. Profilaktyka pierwotna obejmuje ograniczenie narażenia na promieniowanie UV przez: zmniejszenie ekspozycji na światło słoneczne, noszenie odpowiedniej odzieży oraz okularów ochronnych, unikanie sztucznych źródeł promieniowania ultrafioletowego (np. solarium), stosowanie kremów z filtrem ultrafioletu (dotychczas nie potwierdzono jednoznacznie, czy używanie kremów z filtrem zmniejsza ryzyko wystąpienia czerniaka). Wtórna profilaktyka obejmuje: regularne badanie kliniczne, samobadanie skóry mające na celu wykrycie nowotworu we wczesnym stadium, a także wyodrębnienie grupy pacjentów podwyższonego ryzyka zachorowania. Edukacja zdrowotna pacjentów dotycząca sposobów ochrony przed szkodliwym działaniem promieniowania UV oraz rozpoznawania wczesnych objawów nowotworów złośliwych skóry może przyczynić się do poprawy rokowania. W wielu państwach wprowadza się programy profilaktyki nowotworów skóry. W krajach, które mają dobrze rozwinięte programy profilaktyki nowotworów skóry oraz prowadzą edukację zdrowotną pacjentów (Australia i Stany Zjednoczone Ameryki Północnej) śmiertelność zmniejszyła się dzięki skutecznej pierwotnej i wtórnej profilaktyce (*Adv Clin Exp Med* 2006, 15, 6, 1099–1105).

Słowa kluczowe: czerniak skóry, profilaktyka pierwotna, profilaktyka wtórna.

There are three main types of skin malignancies: squamous cell carcinoma (SCC), basal cell carcinoma (BCC), together referred to as non-melanoma skin cancer (NMSC), and cutaneous malignant melanoma (CMM). Melanoma has the lowest incidence and basal cell carcinoma the highest. NMSC has an excellent prognosis, but individuals diagnosed with NMSC are at higher risk for developing additional skin malignancies. CMM has a much worse prognosis than NMSC and accounts for approximately three fourths of all skin malignancy deaths [1].

Epidemiology

Cutaneous malignant melanoma is one of the most common types of cancer among young adults (aged 20–29 years) and has the highest rate of mortality [2]. In the year 2000, 47700 new cases of CMM were recorded in the USA, of which 7700 of the people died. Since 1973 its incidence and mortality have increased, respectively, by 150% and 44% [1]. This tendency is also visible in European countries, including Poland. In our country, the incidence increased by 300% and mortality by 200% between 1981 and 1996 [3]. According to the National Malignancy Register in Warsaw (Krajowy Rejestr Nowotworów), there were 822 cases of malignant melanoma among men and 1009 among women in the year 2002, with 424 deaths among men and 451 among women caused by this malignancy in that year. In the city of Wrocław there were 54 cases reported (30 men and 24 women) in 2003. However, it is necessary to be aware of the fact that melanoma seems to occur more frequently than registered due to the low percentage of the cases reported to the National Malignancy Register [4].

The five-year survival rate in Poland is very low. Although it increased from 51% for men and 59.6% for women in the period of 1984–1987 to 65.3% for men and 69.8% for women in the period of 1996–1999 [5], it is still about 40% lower than in the EU countries [6]. For European patients, survival with malignant melanoma in the of period 1990–1994 was fairly good: 94% at one year, 85% at three years, and 81% at five years (ages and sexes combined). In men, the highest (> 80%) age-standardized five-year relative survival rates were in Austria (87.8%), Sweden (84.7%), Switzerland (84.7%), and France (81.8%). The lowest (< 65%) survival rates were reported in Slovakia (52.1%), Estonia (54.1%), Portugal (56.3%), Poland (56.5%), the Czech Republic (60.4%), Slovenia (60.5%), and Wales (63.1%). In women, the highest ($\geq 90\%$) survival was in Switzerland (91.0%),

Iceland (90.9%), Sweden (90.6%), and Scotland (90.1%), and the lowest (< 70%) in Poland (57.9%), Malta (65.0%), Slovakia (65.6%), Estonia (68.0%), and Portugal (68.9%) [6].

Etiology

Exposure to ultraviolet radiation is the major etiological factor for both NMSC and CMM. However, cumulative sun exposure is the main problem in NMSC, while CMM seems to be related to intermittent sun exposure, often resulting in sunburns, especially if they occurred in childhood or adolescence [7, 8]. Apart from the natural UV exposure (related to outdoor activities in sun-exposed zones, especially those of the USA, Australia, and Israel), traveling to southern countries and artificial UV sources, such as sunbeds and tanning lamps, are to be regarded as harmful [9, 10]. Predisposing conditions and genetic factors such as skin color and ethnicity, especially sensitive skin types [10], atypical and multiple benign nevi (moles), melanoma family history [10, 11], inability to tan [11], freckles, age [10], and the lesion location are also considered important.

Therapy

Studies show that five-year survival is strongly related to the lesion thickness at the time of therapy [12, 13]. Surgical excision is the procedure of choice. Neither radiotherapy nor chemotherapy increases CMM survival significantly. Early detection is the most important factor for survival in a cutaneous malignant melanoma patient. That is why primary and secondary prophylaxis are thought to be the most efficient among the factors influencing clinical outcomes in these patients [4, 14].

Primary Prophylaxis

Primary prophylaxis of CMM consists of minimizing UV radiation exposure, which is achieved by reducing sun exposure, wearing proper clothing and sunglasses, protective behaviors, sunscreen use, and sunlamp and tanning bed avoidance [10, 15–25].

Reducing Sun Exposure, Wearing Proper Clothing and Sunglasses

The most natural way of reducing UV radiation exposure is avoiding the sun (especially during

peak hours, e.g. 10 a.m. to 4 p.m.), staying indoors, seeking shade, and wearing sun-protective clothing [15]. Such clothing should be tightly woven [16], dark, dry, not stretched [10], and made of natural cotton or Lycra™ instead of bleached cotton. It has been shown that wearing sun-protective clothing may reduce the number of moles [10]. Head, ears, nose, and cheeks are best protected by wide-brimmed bonnets and Legionnaire hats [10]. While at the beach, wearing long-sleeved shirts reduces UV exposure of the arms [17]. Sunglasses protect the eyes and surrounding skin from UV radiation damage and seem to reduce the risk of skin cancer. According to American Academy of Ophthalmology guidelines, sunglasses should block 99% of UV-A and UV-B radiation. Trees and shade structures offer another way of minimizing UV exposure. Their efficacy, however, depends on their type and the surrounding surface (reflecting surfaces such as sand, snow, water, and concrete can increase the radiation exposure though the shade structures) [10].

Sunscreen Use

Using sunscreen is one of the most commonly practiced methods of preventing skin cancer [10]. It is advised to use sunscreens with SPF (sun protection factor) > 15. The SPF, however, is a measure of protection from UV-B radiation only, determined by the manufacturers by applying an adequate amount of sunscreen on humans and testing under artificial light, which is usually not as strong as natural light [10]. The International Agency for Research on Cancer has concluded that the topical use of sunscreen probably reduces the incidence of squamous cell carcinoma (results of one randomized clinical trial [18]), especially when applied during unintentional sun exposure. However, it is not clear whether it reduces the incidence of basal cell carcinoma or melanoma. On the other hand, sunscreens are effective in reducing moles, which are the precursors and the strongest risk factor for developing melanoma among children who are at high risk for developing this malignancy [10].

It is very important to mention the potential risks related to sunscreen use. Unfortunately, many individuals use sunscreens if they intend to stay in the sun longer (intentional sun exposure), thereby reducing the use of other forms of sun protection. With this false sense of security, they thus tend to acquire the same or even a higher dose of UV radiation than they would have obtained with a shorter stay using no sunscreen [10, 19, 20]. Some epidemiological studies have discovered a higher risk for developing melanoma among

users of sunscreens than among non-users. However, these results may be related to the fact that sunscreen use is more common among fair-skinned people, who are in general at higher risk for developing melanoma, than among people with darker skin. A recent meta-analysis of population-based case control studies found no effect of sunscreen use on the risk for melanoma [20].

The available data cannot preclude that sunscreen use could be harmful if it encourages longer, intentional stays in the sun without complete protection from UV radiation. In order to prevent such situations, the International Agency for Research on Cancer report guidelines recommend using various methods which reduce UV radiation exposure, such as avoiding the sun, seeking shade, and wearing protective clothing as the first line of protection against skin cancer. Sunscreen use is recommended as a complementary protective measure [10]. However, to be effective, sunscreen should be applied correctly. To provide proper protection it should dry before going outdoors and being exposed to UV and it should be reapplied after leaving the water, sweating, or drying off with a towel [10, 21]. Use of insufficient quantities of sunscreen is another concern [10]. Finally, being a pharmaceutical agent, sunscreens may provoke adverse reactions. From the few studies available, skin irritation, rather than an actual allergic response, seems to be the most common adverse reaction [22]. Among the ingredients to be avoided are para-aminobenzoic acid (PABA), which is rarely used today, and benzophenone-3 dibenzoyl methanes [10, 23].

Sunbeds and Tanning Lamps

Sunbeds emit mostly UV-A and some UV-B radiation, both of which can damage the DNA in cells of the skin. The sunbed lamps manufactured in recent years produce higher levels of UV-B to mimic the solar spectrum and speed the tanning process. While UV-B has well-known carcinogenic properties and excessive exposure to it is known to lead to the development of skin cancer, recent scientific studies suggest that high exposures to the longer-wave-length UV-A could also have an impact on the occurrence of skin cancer [24].

A certain relation between sunbed use and malignant melanoma has been found [25]. Six of nineteen case-control studies found a positive association between the use of sunlamps or tanning beds and melanoma, but most of them did not adjust for recreational sun exposure or for the dosage and timing of artificial UV radiation expo-

sure [20]. Among nine studies that examined the frequency, duration, or timing of additional artificial radiation exposure, four found a positive association, especially if the dose of exposure was high, if it started before 36 years of age (teenagers and young adults) [25], or if it caused burning [10], which correlate with melanoma risk among persons with sunburns in childhood [7, 8, 11].

According to the World Health Organization (WHO) 2005 guidelines, which are consistent with those of International Commission on Non-Ionizing Radiation Protection (ICNIRP) and the Europe Skin Cancer Prevention (EUROSKIN), it is recommended that the individuals under 18 years of age should not use sunbeds and tanning lamps. In its 2003 publication, ICNIRP recommends against the use of UV-emitting appliances for tanning or other non-medical purposes. ICNIRP states that the following groups are at particularly high risk of incurring adverse health effects from UV and therefore should be particularly counseled against the use of tanning appliances: people who have skin phototypes I or II; children (i.e. less than 18 years of age); people who have large numbers of nevi (moles); persons who tend to freckle; individuals who have a history of frequent childhood sunburn; people who have pre-malignant or malignant skin lesions; people who have sun-damaged skin; those who wear cosmetics. These may enhance their sensitivity to UV exposure; persons taking medications. In this case they should seek advice from their physician to determine if the medication will make them UV sensitive [24].

Secondary Prophylaxis

Secondary prophylaxis of melanoma consists of regular self- and clinical examination of the skin in order to diagnose tumors at an early stage and to identify individuals at increased risk of developing melanoma [26–28]. The efficacy of chemopreventive agents (isotretinoin, beta-carotene) in melanoma prevention has not been proven [29], although a high-dose isotretinoin therapy was proven successful in preventing new cancers in individuals with xeroderma pigmentosum [30].

Although the only evidence for the effectiveness of self-examination of the skin comes from a single case-control study [20], it is useful in identifying individuals at increased risk of developing melanoma (e.g. freckling status, skin type, moles) [26]. By visiting the web-site of the Skin Cancer Foundation (www.skincancer.org), everyone may obtain useful information about self-

examination of the skin. The self-examination should be supported by regular clinical examination [31] and sun protection education. It is very important that these behaviors be learned already in childhood. In Australian schools in Perth was an educational program “Kidskin” in 1995–1999. Its aim was to reduce sun exposure among children. It had successful results, but its benefits did not last beyond the life of the program [17, 32].

Many countries are developing systems of early skin malignancies detection called the “National Skin Cancer Prevention Programs”. Australia and the United States have well-established campaigns and have been investing in this field for over 20 years. According to a randomized trial of population screening for melanoma in Queensland (Australia), the specificity of whole-body skin examination as a screening method for the suspicion of melanoma was shown to be highly effective [33], although some authors suggest that an additional whole-body skin examination in melanoma screening is not indicated except in cases of suspected melanoma and dysplastic naevi [34]. In 2003, nearly 7000 people were included in free skin cancer screenings supported by the 3M company and 41 medical institutions such as the University of Pennsylvania, Northwestern University, University of California in Los Angeles, and Yale University. In Switzerland in 2003, in a campaign called “Solmobile”, a part of the National Skin Cancer Prevention Program coordinated by the Swiss League Against Cancer, a mobile unit visited 29 Swiss towns offering sun protection behavior education and skin examination performed by a dermatologist [35]. Such prophylactic measures were also undertaken in Heidelberg, Germany. Combined with a short questionnaire, free, on-site skin examinations were offered to the employees of five large companies in Germany. Although the rates of suspected melanoma were low in that population (0.2%), about one third of those screened with increased risk for developing skin cancer will benefit from the screening [36]. Surveys among specialists (pediatricians, dermatologists, plastic surgeons) are also very helpful in improving the attitudes of medical personnel towards skin malignancy detection and protective behaviors [37].

Some efforts to improve melanoma secondary prophylaxis are also being undertaken in Poland. In collaboration with the local authorities, a Prophylaxis and Early Detection Program was introduced in the city of Wrocław in 2002. The aim of the program is to inform patients about primary and secondary prophylaxis and the early detection and treatment of skin malignancies. The patients are informed about skin self-examination, risk factors,

and protective measures. Diagnostic procedures are undertaken and detected lesions are treated. Due to this program, 53 new skin malignancies were diagnosed in 2002 and 69 in 2003 [4].

The guidelines for skin examination are not yet unified [4]. The American Cancer Society suggests regular clinical skin examination starting from the age of 20 and UV radiation reduction education. According to National Foundation for Cancer Research information, it is currently recommended that individuals between the ages of 20 and 40 undergo a melanoma-related examination every three years, and those over 40 every year. The checkup should include skin and lymph node examination as well as an interview including detailed information on family history, sun exposure pattern, and other risk factors. It has also been shown that a careful follow-up, including detailed self-examination of the skin after the diagnosis of a primary melanoma, facilitates the detection of second melanomas at an earlier stage [38]. The Warsaw Oncology Institute and The Polish Cancer Committee suggest the following scheme: annual clinical skin examination for persons over the age of 14 and education in self-examination of the skin and UV radiation reduction [7, 39]. The best approach seems to be education about the risks associated with sun exposure and sunburns and sun protection strategies, especially among children, adolescents, and their parents [17, 27, 28, 32]. The American Cancer Society, the American Academy of Dermatology, the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, and the National Institutes of Health consensus panel all recommend patient education concerning sun avoidance and sunscreen use [20].

Cutaneous malignant melanoma is a skin malignancy with a very unfavorable prognosis. Its treatment, even at an early stage, is difficult and the disease has high mortality [1]. It is forecasted that melanoma will become one of the most dangerous tumors of the 21st century due to its rapid metastasis and a rising morbidity of increasingly younger people. The most effective method of reducing the morbidity and mortality of CMM is prophylaxis. The efficacy of primary and secondary prophylaxis has been proven by the decreases in the mortality rates in the USA (-0.4% per year between 1990 and 1995 [1]) and Australia [40], where prophylaxis and educational programs are well developed [10, 40]. Primary prophylaxis consists of minimizing UV radiation exposure, achieved by reducing sun exposure, wearing proper clothing and sunglasses, protective behaviors, sunscreen use, and avoiding sunlamps and tanning beds. However, it is unclear whether using sunscreen reduces the incidence of melanoma. It is very important that these behaviors be learned already in childhood.

Melanoma secondary prophylaxis consists of regular self- and clinical examination of the skin in order to diagnose tumors at an early stage and to identify individuals at increased risk of developing melanoma. Health education, including the dissemination of knowledge on protection from harmful sun exposure and awareness of early symptoms and signs of skin malignancies, may help avoid unfavorable prognoses. Most countries have national skin cancer prevention programs, either in the developmental stage or already implemented [33, 40]. These programs are aimed at developing healthy behavior in the sun from childhood in order to avoid skin cancer in the future.

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