Causes and risk factors for skin cancer - the current state of knowledge

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ABSTRACT

The most common cancer among all skin cancers is basal cell carcinoma. It occurs five times more likely than squamous cell carcinoma. In total, the incidence of skin cancer in Poland was in 2005, more than 4,300 new cases in women and nearly 4,000 men. Skin cancer is ranked in terms of the incidence of cancer, respectively, the 3 and 5 position. The incidence of skin cancer is associated with exposure to sunlight. Skin cancer most often locates on the exposed parts of the body (hands, face, neck, scalp - particularly in those balding). Most often affects people in 6 and 7 decade of life.

The aim of the study was to present the carcinogenic factors responsible for the development of skin cancers and to briefly discuss individual skin cancers. We analysed Polish and foreign bibliography on the prevention of skin cancers based on the most recent reports.

Key words: skin cancer, major carcinogenic factors, prevention skin cancer

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INTRODUCTION

Skin cancers are the most common malignancies in the United States and malignant melanoma is believed to become one of the major malignancies of the 21st century. For this reason these conditions are a challenge for doctors not only as a cause of mortality but as a source of suffering and considerable disfigurements. The awareness of the risk and early detection of skin cancer are the fundamental conditions for initiating treatment at the right moment. Skin cancer accounts for about 10% of malignancies in Poland, which means that an average of 10,000 new cases are diagnosed each year. In the United States, the lifetime risk of developing basal cell carcinoma for Caucasian men and women is 33-39% and 23-28%, respectively. The higher incidence in the USA or Australia is mainly associated with the higher insolation compared to Northern Europe or Central and Eastern Europe [1-3].

The aim of the study was to present the carcinogenic factors responsible for the development of skin cancers and to briefly discuss individual skin cancers. We analysed Polish and foreign bibliography on the prevention of skin cancers based on the most recent reports.

MATERIALS AND METHODS

For the purposes of this study Medline database was used, provided by Ovid, Elsevier Ebsco. It was searched for the key words: "skin cancer", "major carcinogenic factors", "prevention skin cancer". The search returned 52 articles, of which 22 were selected for analysis of scientific articles published between 1987 and 2013.

Major carcinogenic factors

Exposure to sunlight

The current data suggest that the leading role in the pathogenesis of skin cancer may be played by excessive tanning in the childhood and early adolescence, especially if leading to burns or bullous reactions [3].

In scientific and public communities, there is an ongoing discussion how to balance between positive and negative effects of solar UV-exposure. On the one hand, solar UV-radiation represents the most important environmental risk factor for the development of non-melanoma skin cancer. Consequently, UV protection is an important measure to prevent these malignancies, especially in risk groups. Otherwise, approximately 90% of all vitamin D needed by the human body has to be formed in the skin through the action of UV-radiation. This dilemma represents a serious problem, for an association of vitamin D-deficiency and multiple independent diseases including various types of cancer, bone diseases, autoimmune diseases, infectious diseases, cardiovascular diseases and hypertension has now been reported in a large number of investigative and epidemiologic studies. As a consequence, it has been assumed that for the general population in the US, Europe and other countries, the net effects of solar UV B-radiation on human health are beneficial at or near current levels [4].

Age and gender

The risk of basal and squamous cell skin cancers goes up as people get older. Older people have been exposed to the sun for a longer time. Still, these cancers are now being seen in younger people too, probably because they are spending more time in the sun without protecting their skin [5]. Men are approximately two times more likely to develop basal cell carcinomas and three times more likely to develop squamous cell carcinomas compared with women, and this may also be related to increased exposure to the sun [1].

Exposure to UV radiation at tanning salons

Tanning salons are very popular, especially among young adults, and allow clients to maintain tan even in cool climates all year long. Ultraviolet radiation accelerates skin ageing. UVA radiation damages collagen and elastin fibres, as a result of which the skin loses its flexibility and becomes flaccid. Examples include areas of irreversible discolouration that develop following prolonged and intensive exposure to sun. This is not to say that we should completely avoid sunlight; we should merely apply common sense and not go overboard when using tanning salons [6].

Ionising radiation

The risk of cancer increases with exposure to such factors as X-rays, tar, white arsenic, radium, uranium, arsenium or wood tar. The tragic effects of ionising radiation continue to be observed in Japan, where people who once found themselves within the range of the atomic bombs dropped on Hiroshima and Nagasaki are now suffering from cancer. This type of radiation most commonly causes malignancies of the bone marrow and lymphatic system [5,7].

Race and heredity

Although basal cell carcinoma of the skin is found in representatives of all races and skin types, it is the most prevalent in individuals with fair complexion; individuals with dark complexion are only rarely affected. Malignant melanoma of the skin mainly develops in individuals with fair complexion, who do not tan easily, have a tendency towards sunburns and in individuals with multiple pigmented nevi. The familial distribution of the cancer suggests the involvement of hereditary factors [8].

Exposure to chemicals

Exposure to large amounts of arsenic increases the risk of developing skin cancer. Arsenic is an element found naturally in well water in some areas. Another rare possible cause for non-melanoma skin cancer is overexposure to certain chemicals at work. These include: asphalt, coal tar, creosotes, cutting oils, paraffin waxes, petroleum derivatives, pitch, soot [4].

Multiple pigmented nevi

The risk of malignant melanoma increases with the number of pigmented nevi. Every adult has an average of 15-20 pigmented nevi. Their locations vary and they may be found on the scalp or in areas exposed to sunlight. The presence of more than 100 pigmented nevi in young adults or more than 50 in elderly individuals is a significant risk factor for malignant melanoma. Non-malignant nevi are symmetrical with sharp round or oval outlines and may grow to 6 mm, remain unchanged for years and even disappear in old age [8,9].

Sex

Historically, men have been affected by basal cell carcinoma twice as often as women. This is most likely associated with the more frequent, compared to women, exposure to sunlight both in the professional and leisure setting. This difference is slowly becoming more and more obsolete due to lifestyle changes [5].

Viral infections

Human papilloma viruses (HPVs) are a group of more than 150 viruses that can cause papillomas, or warts. The warts that people commonly get on their hands and feet are not related to any form of cancer. But some HPV types, especially those that affect the genital and anal areas and the skin around the fingernails, seem to be related to skin cancers in these areas [7].

Immunosuppression

The immune system helps the body fight cancers of the skin and other organs. People with weakened immune systems (from certain diseases or medical treatments) are more likely to develop many types of skin cancer, including squamous cell cancer, melanoma, and less common types such as Kaposi sarcoma and Merkel cell carcinoma. Solid organ transplant recipients have a 3-fold excess risk of cancer relative to the age- and sex-matched general population. Cancer is more prevalent in AIDS patients and renal transplant patients undergoing immunosuppressive treatment. People who take drugs that lower their immunity (immunosuppressants) – for example, after a kidney transplant – are at an increased risk of skin cancer. Squamous cell cancers are the most common, but basal cell cancers and melanomas are also more common in these people than in the general population. However, the reason for taking these drugs outweighs the potential risk of developing skin cancer [3].

Cigarette smoke

Cigarette smoke has been thoroughly tested and more than 40 carcinogens have been identified. They include: nitrosamines, aromatic polycyclic hydrocarbons (such as benzopyrene), phenol derivatives, aromatic amines and many, many more. It should be emphasised that staying in a smoke environment is equally harmful as cigarette smoking itself [5-7]. Smokers are more likely to develop squamous cell skin cancers, particularly on the lips. Smoking boosts your risk of squamous cell carcinoma (SCC) by 52 percent, according to a major study. SCC, the second most common skin cancer, affects an estimated 700,000 people in the US annually. There is also an increased risk of oral leukoplakia (precancer) and oral cancer; 75% of cases of oral cancer occur in smokers [7].

Atypical nevus syndrome

Atypical nevi are variants of melanocytic nevi with clinical and histological manifestations suggestive of atypia. They are characterised by a diameter of more than 1 cm, irregular margins, non-uniform colour and often a central elevation [7-9].

Many types of skin tumours are distinguished. Depending on the clinical stage and type of lesions they are divided into: benign connective tissue tumours (fibromas, keloids), premalignant lesions (xeroderma pigmentosum, chemical hyperkeratosis, leukoplakia), in situ tumours (keratoacanthoma, Bowen's disease) [7].

Malignant skin cancers are divided into: Basal cell carcinoma (or basal cell carcinoma epithelioma); Squamous cell carcinoma; Melanoma.

Basal cell carcinoma

This tumour is the most common skin tumour characterised by a relatively low malignant potential, as it is only locally malignant. Its growth is typically slow and it does not often spread. Basal cell carcinoma may be triggered by sunlight. Event in an early stage of development it shows a characteristic morphology of a pearly infiltrate in the form of a nodule with fine blood vessels within its surface. Although most dermatologic and oncologic publications distinguish between only four forms of basal cell carcinoma (nodular, superficial, sclerosing and pigmented), therapeutic implications justify identification of a larger number of subtypes. The nodular and superficial forms are most common, accounting for 60% and 10-15% of basal cell carcinoma cases, respectively

[10,11]. Both forms are relatively easy to treat and do not require special therapeutic approaches. The infiltrative form is the form characterised by a considerable tendency to recur and its histological picture often involves a severe fibrotic reaction. In these cases the neoplastic foci are usually small, penetrate far and deep towards the periphery, are not clinically discernible and are frequently missed when resected. The malignant potential of basal cell carcinomata assessed by the potential to metastasise is very small (1 in 50,000 cases). However, due to the nature of infiltration and location the tumour may aggressively spread locally, destroy the underlying tissues and in particular cases put the patient's life in direct danger. The histological character of the lesions is an important factor in determining refractoriness to treatment and propensity to recur, which is why a skin biopsy is mandatory in each case of suspected malignancy [3]. Coexistence of several forms in one neoplastic lesion is often observed. The histological structure on the periphery of a resected tumour is very important, as the growth in the infiltrative and sclerosing forms may be well advanced (up to 8 mm), taking the form of subclinical infiltration. In these forms recurrences are frequent, lead to considerable mutilation and even death [7,12].

Squamous cell carcinoma

The development of squamous cell carcinoma is usually associated with excessive exposure to ultraviolet radiation. Similarly, exposure to ionising radiation, arsenium compounds and other chemicals may increase the risk of squamous cell carcinoma. The tumour may also develop in chronic inflammatory changes of the skin (lupus vulgaris, chronic cutaneous lupus), in scars, ulcerations, fistulas or in the course of other dermatoses. Immunocompromised patients are also at a higher risk of developing squamous cell carcinoma. There are data to suggest that in certain cases the tumour is associated with human papilloma virus infection. The conditions preceding the development of squamous cell carcinoma may take various clinical forms. The tumour is characterised by a tendency to infiltrative growth. This results in numerous metastatic foci, principally in the regional lymph nodes [6,11]. The degree of histological differentiation is usually high, as the tumour may originate from the very epidermis (spinous layer) or skin appendages. The tumour may infiltrate the nerves and small blood vessels and the depth of infiltration is an important prognostic factor. Squamous cell carcinoma metastasises in 2-6% of the cases. The potential to metastasise depends on the type of infiltrate, tumour size, duration of development and anatomical location. Tumours located in the ear and lip metastasise in about 10% of the patients, while those originating in scars, ulcerations, injury wounds, fistulae, irradiation sites undergo distant spread in about 20% of the cases. Locally recurrent squamous cell carcinoma metastasises in 25-45% of the patients. Also tumours developing in mucous membranes, such as those originating in the rubor labiorum, glans or vulva, are characterised by a higher malignant potential than those originating in the skin. The possibilities of effective and radical treatment of cutaneous carcinomas are much higher than it is the case with tumours of internal organs. This results from the tumour biology and the nature of the tissue of origin. The skin has a fibrous structure with a high tendency to immune response associated with hypertrophic collagenisation reaction, which interferes with the development of carcinomas, especially basal cell carcinoma. There is a plethora of surgical and conservative treatment options available [10,12,13].

Malignant melanoma

Malignant melanoma originates from melanocytes or melanocytic cells of the nevi present in the epidermis and dermis. The skin is the most location site of the tumour (over 90% of the cases) with other anatomical sites being less commonly affected (mucous membranes, eyeball). An overwhelming majority of melanomas are associated with excessive exposure to sunlight, which is why the tumour is most commonly observed in the head and neck and in the lower extremities (with the latter being more common in females). A rare but well recognised location is the subungual area and the palmar and plantar surfaces. Most melanomas develop after adolescence. It is estimated that melanoma will become one of the major oncologic problems of the 21st century and is currently the main cause of death from cutaneous malignancies. The incidence of malignant melanoma is increasing faster than that of any other cancer. It dramatically rose from mid-1930s, doubled in 1980s and the progressive destruction of the ozone layer may additionally increase the number of new cases. Malignant melanoma is much more common in Caucasians accounting for about 1% of cancers in Poland. It is characterised by a very high cure rate, if detected early and removed immediately, but the prognosis is poor in advanced disease. In women between 25 and 30 years old malignant melanoma is the most common type of cancer. There is a slight male-to-female predominance in the United States, while in Europe women are more commonly affected. The main risk factors include: race, genetic background, excessive sun exposure, exposure to chemicals, viral infection, immunosuppression, multiple pigmented nevi, asymmetry or irregular shape, irregular colour (motley appearance). Additional features include: diameter exceeding 7 mm, inflammation, and

presence of a crust, oozing or bleeding. The presence of one or more main symptoms is suggestive of malignant melanoma and requires immediate surgical treatment. Mortality in malignant melanoma continues to be too high, given the fact that the lesion can be detected in a stage when it can be cured in nearly 100 percent of the cases. There are many prognostic factors, such as the disease stage (Clark and Breslow stages), sex (higher survival in females), location (high risk: scalp, mandibular area, trunk midline, thighs, hands, feet, popliteal fossa, genitals), ulceration [8-13].

Prevention and early diagnosis

The most important prophylactic tasks for the primary care physician are a thorough skin examination at a consultation for skin-unrelated problems and informing the patient, if any of the above risk factors are identified, about the early symptoms of malignant melanoma and preventative treatment options. Friedman and Rigel developed an ABCDE rule to facilitate the remembering of early symptoms of malignant melanoma within a pigmented nevus. Malignant growth may result in asymmetry (A), irregular border (B), change in colour (C), diameter exceeding 6 mm (D), and elevation (E) of the lesion. Prof. Rona Mackie of Glasgow University provided a description of 3 main and 3 additional symptoms of malignant melanoma [3,7,9,14].

The main preventive measures in a high-risk patient include:

- Protecting the skin when exposed to ultraviolet radiation. Application of sun block in the summer months onto nevi located in sun-exposed areas of the skin. Using products protecting the skin from UV radiation characterised by an SPF of 30 or more (several times a day, generally every 2-3 hours), using waterproof products, avoiding the sun at midday, using a sun protective lipstick, reapplying a body lotion containing a sun block after swimming or physical exertion associated with sweating. Because sunlight plays a crucial role in the aetiology and pathogenesis of other skin tumours as well as malignant melanoma, our society should be particularly made aware of the necessity to avoid sunburns, especially in childhood, by preventive application of sun block containing creams.
- Protecting the face by wearing appropriate apparel, hats, caps, and sunglasses with sun blocks.
- Removing any skin changes that may be premalignant.
- Referring patients with suspected skin lesions or following treatment (at least once a year) for prophylactic examination by an oncologic surgeon either before or just after the summer season.
- For people who take immunosuppressants it is important to consult a doctor regularly to check for early signs of skin cancer.
- Periodic self-examination.
- Regular examination of the whole skin surface in patients with suspected malignant melanoma in a pigmented nevus and in high-risk patients. This is achieved by a microscopic examination using a dermoscope (×10 magnification), which considerably improves the clinical diagnostics of pigmented skin lesions. The percentage of correct diagnoses is about 85%, according to the literature. With the use of a dermoscope connected to a photo camera (Dermaphot) photographs may be taken which may facilitate follow-up of the lesions and documentation.
- Follow-up medical examination should take place every 3-6 months.
- Patients receiving antineoplastic agents and oestrogens should be seen more often [1,2,6,8,10,14].

The only protection of our skin against UVR is its endogenous protection (melanin and enzymatic antioxidants) and antioxidants we consumed with the food (vitamin A, C, E, etc.). Dietary antioxidants thus play a major role in maintaining the homeostasis of the oxidative balance. Vitamin C (ascorbic acid), vitamin E (-tocopherol), beta-carotene, and other micronutrients such as carotenoids, polyphenols, and selenium have been evaluated as antioxidant constituents in the human diet. Many other studies confirmed that acute exposure of human skin to UVR in vivo leads to oxidation of cellular biomolecules that could be prevented by prior antioxidant treatment. There have been many studies performed where different antioxidants or combinations of antioxidants and different phytochemicals were tested in order to find evidence against ROS-induced damage [14,15].

- Many other studies have found that vitamin C can increase collagen production, protect against damage from UVA and UVB rays, correct pigmentation problems, and improve inflammatory skin conditions [15].
- Vitamin E provides protection against UV-induced skin photodamage through a combination of antioxidant and UV absorptive properties. Topical application of alpha-tocopherol on mouse skin inhibits the formation of cyclobutane pyrimidine photoproducts. However, topically applied alpha-tocopherol is rapidly depleted by UVB radiation in a dose-dependent manner [16].
- Supplementation with carotenoids contributes to basal protection of the skin but is not sufficient to obtain complete protection against severe UV irradiation. Studies showed that the efficacy of -

carotene in systemic photoprotection depends on the duration of treatment and on the dose. For successful intervention, treatment with carotenoids is needed for a period of at least ten weeks [17].

- This study showed that both retinyl palmitate and 13-cis-retinoic acid inhibited the development of skin papilloma's and also had a marked effect on skin cancers [18].
- It was recently reported that coenzyme Q10 protects against oxidative stress-induced cell death and enhances the synthesis of basement membrane components in dermal and epidermal cells. Coenzyme Q10 (CoQ10) was reported to reduce ROS production and DNA damage triggered by UVA irradiation in human keratinocytes in vitro [19].
- In cell culture models using human skin cells, it has been clearly shown that glutathione depletion leads to a large sensitization to UVA and near-visible wavelengths as well as to radiation in the UVB. There is a direct correlation between the levels of sensitization and cellular glutathione content. Additional evidence that glutathione is a photoprotective agent in skin cells is derived from experiments which have demonstrated that glutathione levels in both dermis and epidermis are depleted by UVA treatment [20].
- In vitro and in vivo animal and human studies suggest that green tea polyphenols are photoprotective in nature and can be used as pharmacological agents for the prevention of solar UVB light-induced skin disorders including photoaging, melanoma, and non-melanoma skin cancers after more clinical trials in humans. Topical treatment or oral consumption of green tea polyphenols (GTP) inhibits chemical carcinogen- or UV radiation-induced skin carcinogenesis in different laboratory animal models [21,22].
- Exogenous antioxidants like vitamins C and E and many others cannot be synthesized by the human body and must be taken up by the diet. Since the effectiveness of endogenous antioxidant system is diminished during aging, the exogenous supplementation of antioxidants might be a protective strategy against age-associated skin oxidative damage. It can be concluded that oxidative stress is a problem of skin cells and endogenous as well as exogenous antioxidants could play an important role in decreasing it [15].

CONCLUSIONS

The incidence of cutaneous malignancies is dramatically increasing, which is why special emphasis should be placed on education of the society and prevention of malignancies. If a lesion suspected of malignant growth is detected, prompt diagnostic and therapeutic measures should be undertaken. The selected approach should be individual and take into account the tumour histology, location, stage and the patient's overall condition. Radical excision of the primary lesion is the treatment of choice in the case of cutaneous carcinomas and malignant melanoma. Patients who have undergone treatment for skin malignancies and melanoma are patients who are at a higher risk of new disease foci and should undergo careful postoperative follow-up. The chances of cure in malignant melanoma and skin carcinomas depend on the stage of the local lesion and efficacy of the primary treatment. Both in melanoma and in other cutaneous malignancies, classified as stage I, excision of the primary lesion with a margin of healthy tissues offers the chance of cure close to 100%. In stage III and IV, the chances fall to below 10%. This emphasises the importance of prevention and early diagnosis of melanoma and the other skin malignancies. Following the above rules will most definitely allow to improve the infamous mortality statistics related to skin cancers, according to which Poland is among the other European countries.

Conflicts of interest

The authors declare no conflict of interest.

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