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REVIEW ARTICLE

Epidemiology of Skin Cancer

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Abstract

The skin is the most common site of malignancy. Due to several mostly unknown factors, the frequency of skin tumors is increasing. Except for malignant melanoma, reliable statistical data on the frequency of skin tumors are scarce.

Discussion on the epidemiology of skin tumors may take different aspects and factors into consideration: (1) histogenetic type; (2) race, (3) sex; (4) age, (5) localization; (6) environment. Moreover, precancerous conditions also may play an important role in this context.

Epithelial tumors, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most frequent tumors of the skin. Figures show a wide range between 40 and over 700 or 5 and 250 respectively per 100 000 inhabitants per year depending on the country or area of report.

Malignant melanoma is more frequently seen in Caucasians living in sunny regions (40) than in northern countries or in dark skinned races (4–12 per 100 000 per year), representing 4% of all skin tumors, but being responsible for 79% of skin cancer deaths.

Other types of skin tumors like cutaneous lymphoma, Kaposi sarcoma, lipomas, adnexal tumors etc. are either not reported regularly and reliable epidemiologic data is not available, or are rare cutaneous tumors (taken all together < 1%).

Introduction

Cancer of the skin is the most common of all cancers. It accounts for more than 40% of all cancers. Cancers of the skin can be divided into melanoma and non-melanoma skin cancers (NMSC). Melanoma is the most aggressive cutaneous tumor accounting for 4% of all cutaneous tumors, with an estimated incidence rate of 14 and a mortality rate of 2.3 per 100 000 people each year. About 7400 people will die of melanoma in 2002. NMSC consists of basal cell carcinoma (BCC; 75%), squamous cell carcinoma (SCC; 20%) and other tumors (less than 1%). Population-based cancer registries, which are the main sources of cancer incidence statistics, generally do not include NMSC patients. Hospital cancer registries are unfortunately of little use in estimating the number of NMSC since these tumors are usually treated in out-patient practices. The American Cancer Society estimates that about 1.3 million cases of NMSC are found in the United States each year and that about 2,200 people will die of NMSC in 2002.

Despite a clear understanding of tumor initiation by sunlight, there is enough epidemiological

and laboratory evidence to suggest a broad approach to the problem. A primary prevention approach, that is, reduction in sunlight exposure, is therefore being considered by an increasing number of organizations. It also suggests the need to recommend avoidance of suntanning and particularly the excessive exposures that lead to sunburn.

Actinic Keratoses

Actinic keratoses (AKs), also known as solar keratoses, are dysplastic epidermal lesions and believed to be precursors of SCC [1]. AKs are extremely common lesions, especially in fair-skinned Caucasians. The 'prone phenotpye' refers to those who are fair skinned, have light-colored eyes (blue, green, haze), and red or blond hair. Individuals are unable to tan, have the tendency to sunburn readily , and the ability to form freckles. One of the most important factors is age. All epidemiologic studies indicate that AKs increase in prevalence with advancing age [reviewed in 2]. The prevalence rate was found to be less than 10% in the third decade of life, but more than 80% in the seventh decade of life [3].

AKs represent the third most frequent reason for consulting a dermatologist [2]. In a survey of outpatient visits, it was estimated that 11.5% office visits to the dermatologist were for evaluation and treatment of AKs [2]. It is obvious, that not all AK do progress to invasive SCC, since there are many more AKs than SCC. It is unclear, however, which individual AKs will progress into SCC and estimates are ranging in the literature between 0.1% to 10% [2], mainly due to studies of different age populations.

It is widely accepted that, as for BCC, Bowen's disease and SCC, chronic exposure to the ultraviolet component of solar radiation is the major environmental cause of AKs. Persons with occupational or recreational outdoors exposure, such as commercial fisherman, construction workers and retiree golfers, have higher incidence rates of AKs than their indoor worker counterparts [2]. Similarly, those living at latitudes closer to the equator are exposed to more lifetime solar radiation and display relatively more AKs [3]. Skin cancer, however, due to sun exposure may additionally greatly be influenced by intrinsic factors such as DNA repair capacity and the degree of melanin pigmentation. Immunosuppressed patients and patients receiving long-term photochemotherapy (PUVA) are especially predisposed to the development of NMSC [4]. The anatomic distribution of the lesions correlates with the exposed areas that receive the most long-term and intense solar radiation, namely the upper limbs/head and neck (80%) [5]. There are relatively more AKs on the dorsum of the hand and forearms than there are SCCs in these locations when compared with AK/SCC ratio on the face, indicating that local factors contribute to the development of more SCCs on the head and neck [2]. Due to the fact that AKs occur common, have a very low risk of malignant transformation towards SCC, and are easily treated, biopsy and histological confirmation of the diagnosis would be both logistically and ethically unacceptable. In practice, very few AKs are histologically confirmed [6], and therefore little data exist on the accuracy of the clinical diagnosis. In a clinical referral setting, however, a high degree of accuracy is possible and a diagnostic accuracy of 94%, based on histological confirmation, was reported (Ponsford). It is interesting to note that the occurrence of AK's can be prevented by the use of sunscreen [7].

Squamous Cell Carcinoma

Squamous cell carcinomas are malignant epithelial tumors which often begin within the epidermis as carcinoma in situ and progress after a variable time to real invasive malignant tumors. SCC accounts for about 20% of all cutaneous tumors and is the most frequent form of malignant tumor in the transition from the skin to the mucosa and in the mucosa itself. They grow in a destructive way and metastasize mainly via the lymphatic system. The same risk factors apply to SCC as were noted for AKs. There are approximately 200 000 new SCCs in the United States each year. It has been estimated that a Caucasian male born in 1994 has a 9% to 14% chance of developing an SCC within his lifetime. The estimates for white women range from 4% to 9% [8]. In Europe, the incidence of SCC is estimated to occur at a yearly rate of 5–27 per 100 000 [9], while the number of SCC in Australia is estimated to occur at a yearly rate of 250 per 100 000 inhabitants [10]. In the latter survey, a yearly increase could be found of up to 10% [10]. Newer data, however, indicate that the numbers are levelling out or are even dropping [11,12]. High-risk SCCs for metastases and death are those that grow rapidly, become larger than 2 cm, invade deeply and reach a thickness of at least 6 mm, have been treated previously, or are located in high-risk areas such as the vermillion lip, the ear, and the columella of the nose [2].

Basal Cell Carcinoma

Basal cell carcinomas (BCC) originate from the basal cells in the epidermis and the hair follicles and grow with local infiltration and destruction of tissue. Since they do not metastasize, they have been termed 'semimalignant' or locally aggressive tumors. Since many cancer registries do not collect information on BCC, its incidence is often determined on the basis of clinical surveys. Incidence rates therefore vary tremendously between 40–726/100 000/year [13], with the highest numbers in Australia (726) and the lowest in a survey performed in Norway [14]. In this study, age-adjusted incidence rate rose by 2.4 times between 1991 and 1995 (49 and 45 per 100 000 persons-years in men and women, respectively) [14]. The incidence of BCC was highest in old urban communities and lowest in rural areas. Mortality rate of BCCs are generally low, since BCC do usually not metastasize. A mortality rate of 0.08 in men and 0.05 per 100 000 in women is documented [14]. Interestingly, the incidence of BCC increased more rapidly between 1956 and 1976 (about 6% annually) than in the last 10 years [14]. This might not only be attributable to an underdiagnosis and underreporting of BCC's, but also to the effect of a variety of sun prevention programmes and public sun awareness.

Melanoma

Melanoma accounts for about 4% of skin cancer cases, but causes about 79% of skin cancer deaths. The American Cancer Society estimates that about 53,600 new melanomas will be diagnosed in the United States during 2002. Since 1973, the incidence rate for melanoma (the number of new melanomas diagnosed per 100 000 people each year) has more than doubled from 5.7 to 14.3. The highest melanoma incidence rates – occurring in whites – are reported in Australia, where rates among men exceed 30 per 100 000 [15]. High rates are also reported in New Zealand (15.6 per 100 000 for men, and 21.4 per 100 000 for women), while the lowest rate of melanoma was reported in Eastern Europe with rates as low as 2.3 for men and 3.8 for women [16]. The lifetime risk of developing melanoma for a white US child born in 1990 was estimated at 1.4% for white men, and 1.1% for white women [17]. About 7,400 people in the U.S. are expected to die of melanomas during 2002. Since 1973, the mortality rate for melanoma (the number deaths from melanoma per 100 000 people each year) has increased by about 44%, from 1.6 to 2.3. Melanoma mortality rates have remained stable during the past 10 years. This might partly be attributed to the diagnosis of thin lesions or 'pseudodisease' in the last years. Clinically, one may delineate different types of melanoma: superficial spreading melanoma (50%), nodular melanoma (30%), lentigo maligna melanoma (10%), acrolentiginous melanoma (5%) and other types (5%; amelanotic, desmoplastic, polypoid). Lentigo maligna melanoma occurs in older people and tends to appear on the face, neck, head, and backs of the hand, areas with chronic exposure to sunlight. Primary cutaneous melanoma are measured according to depth (i.e. Breslow) in millimeter. The depth of invasion is directly related to the likelihood of metastases and is still considered the most important prognostic factor. Additional prognostic factors include gender, with better survival among women, and tumor site, with a better prognosis for tumors of the extremities than for those of the trunk. Men are more likely to have tumors of the trunk, and women are more likely to have extremity tumors [16]. Several lines of evidence indicate that UV radiation is involved in the etiology of melanoma. Melanoma occurs most frequently in white subjects, and occurrence is rare among African Americans who are better protected. It is hypothesized, that areas of the skin that receive occasional sun are prone to melanoma development. The ozone layer is least protective near the equator – variations in melanoma incidence with respect to latitude therefore offer inconsistencies concerning the sunlight hypothesis. Phenotypic traits, including freckling, complexion, hair color and eye color have been reported in relation to melanoma and support the hypothesis, that the ethnic background (Nordic, Celtic) is also associated with melanoma risk and is probably a marker for sun sensitivity [18]. Migration studies have shown that rates among migrants to high-risk areas exceed those of the place of origin [19].

Epidemiological data seem to underline an association of melanoma development with intermittend (recreational or vacational) sun exposure [20]. Pooled analysis, however, found no evidence that childhood sunburns are more strongly associated with melanoma risk, and, therefore, the notion that childhood sun exposure is more influential than adult exposure seems questionable [21]. The influence of fluorescent light on melanoma development is probably overestimated. Data are not conclusive (reviewed in 16). However, PUVA treatment and possibly tanning devices, who also emit UVA light, are associated with increased melanoma risk [22].

A large number of studies have noted an association between the number of nevi and melanoma development. Large nondysplastic nevi (>20 cm) have also been associated with increased melanoma risk [23].

Other tumors

There is a variety of other cutaneous tumors (all together accounting for less than 1% of all cutaneous neoplasias), including Bowen's disease, cutaneous lymphoma, Karposi-sarcoma, lipomas, tumors of adnexal origin etc. The frequencies of these tumors, however, is too low to gain reasonable epidemiological data.

The role of melatonin

Melatonin is a hormone (N-acetyl-5 methoxytryptamine) produced especially at night in the pineal gland. Its secretion is stimulated by the dark and inhibited by light. Melatonin is believed to act directly on suprachiasmatic nuclei to influence circadian rhythms. Melatonin has been widely used to reduce Jet-lag and sleep disturbances, and to prevent aging and cancer [24].

The role of reactive oxygen species and oxygen-derived free radicals in ultraviolet radiation induced skin damage is being increasingly recognized [25]. These reactive oxygen species and free radicals, especially the highly damaging hydroxyl radical, cause injury by reacting with biomolecules such as lipids, proteins and nucleic acids as well as by depleting the skin of endogeous enzymic and/or non-enzymic antioxidants [26]. It was demonstrated, that topical preirradiation treatment of the skin with melatonin at a dose of 0.6mg/cm^2 before UV irradiation significantly inhibited the development of erythema. Since melatonin, which is not metabolized in human skin, does not absorb UVA or UVB, a direct sunscreen effect of this substance could be excluded. Identical effects could also be shown with other antioxidant substances or a combination of vitamins E and C [27]. However, when these antioxidant substances were applied after irradiation, no protective effect was found [27]. The authors concluded, that the antioxidants did most likely not reach the site of action in relevant amounts during occurrence of oxidative stress, which is a very rapid process. The systemic use of melatonin or any antioxidant to decrease the number of melanoma and NMSC seems questionable, although a variety of studies have been performed, with inconclusive results.

Conclusion

Widespread primary prevention public health programmes have been running in many countries for almost 20 years. The data measuring the effect of these programmes indicate a very large shift in knowledge atti-

tudes and beliefs about sunlight exposure and suntans, and major shifts in behaviour [11]. Cohort analysis of the incidence rates for melanoma and NMSC show that the incidence of these tumors is levelling out and is dropping in some instances [12]. Following initial dramatic changes in all the behavioural variables related to the programme, a period of consolidation with continuing effort and more specific targeting will be required in the coming decades to maintain the improvement.

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