Epidemiology of nonmelanoma skin cancer: a review

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Summary. - The nonmelanoma skin cancers (NMSC), including basal-cell and squamous-cell carcinoma, are the most common type of cancer in white populations. Its incidence has increased worldwide over the last few decades. Mortality from NMSC is low, but the estimated recurrence rate of about 50% at five years and the local invasiveness involve high medical costs and make NMSC a public health concern. Epidemiologic evidence relevant to the effects of UV radiation on the risk of skin cancer comes from both descriptive and analytic studies. More recently, the collaboration between molecular biology and epidemiology has contributed to assess the potential synergism between environmental and genetic factors, such as the capacity of repairing the UV-induced DNA damage, in the etiology of nonmelanoma skin cancer, as by the xeroderma pigmentosum model.

Key words: nonmelanoma skin cancer, epidemiology.

Riassunto (Epidemiologia dei tumori cutanei non melanocitici: una revisione della letteratura). - I tumori cutanei non melanocitici, rappresentati principalmente dalla carcinomatoso basocellulare e dalla carcinoide squamocellulare, sono il tipo di neoplasia più frequente nelle popolazioni bianche. La loro incidenza è aumentata in tutto il mondo nelle ultime decadi. Sebbene presentino una mortalità molto bassa, la frequenza delle ricadute, stimata intorno al 50% a cinque anni, e l’invasività locale implicano costi sanitari elevati e fanno di queste neoplasie un problema di salute pubblica. L’evidenza epidemiologica relativa al ruolo delle radiazioni UV nella patologia di questi tumori deriva da studi sia descrittivi che analitici. Di recente, la collaborazione tra la biologia molecolare e l’epidemiologia ha reso possibile la valutazione della possibile interazione tra fattori ambientali, come le radiazioni UV, e genetici, come la capacità di riparazione dei danni fotoindotti del DNA, nella patologia dei tumori cutanei, come suggerito dal modello rappresentato dallo xeroderma pigmentosum.

Parole chiave: tumori cutanei non melanocitici, epidemiologia.

Introduction

The nonmelanoma skin cancers (NMSC), including basal-cell carcinoma (BCC) and squamous-cell carcinoma (SCC), are the most common types of cancer in western countries and in Australia. About 600,000 new cases, accounting for one third of all cancers combined, are diagnosed annually in the United States [1-3]. Data from all Italian cancer registries indicate for Italy intermediate incidence rates, when compared to world-wide figures [4, 5]. The incidence of NMSC has been increasing rapidly worldwide over the last few decades [6-9].

Mortality from nonmelanoma skin cancer is low and mostly due to squamous-cell carcinoma, but the high recurrence rate and the potentially serious local damage to the skin are likely to involve high medical care costs and make NMSC a public health concern.

In this paper we will review the current knowledge on the epidemiology of nonmelanoma skin cancer, focusing on risk factors and prevention. We will also emphasize the contribution of an emergent discipline, molecular epidemiology, to the understanding of the molecular basis of skin carcinogenesis.

Descriptive epidemiology

Incidence

The available data on incidence of NMSC should be considered conservative estimates. Data from cancer registries are probably inaccurate, as many primary skin cancers are treated in outpatient clinics and fail to reach the sources of cancer registration. In addition, many lesions are treated without histopathological confirmation and some, especially in elderly people, do not come to medical attention.

Incidence of NMSC in white populations seems to be associated with residence in areas with high levels of solar UV radiation. The highest incidence rates, ranging from 161 per 100,000 in Tasmania to 823 per 100,000, have been reported in Australia [1, 10, 11].

High incidences have been reported also in Canada, where an age-standardized incidence rate of 120 per 100,000 in males was estimated in 1987 in British Columbia [8]; data on incidence of NMSC in the United States of America (US) are sparse. A reported figure for NMSC incidence in white males of 4.6 per 100,000 per year [5] is likely an underestimate; a special survey of
eight areas of US in 1977-78 estimated an incidence of BCC in whites of about 247 per 100,000 in men and 150 per 100,000 in women and an incidence of SCC of 65 per 100,000 in men and 24 per 100,000 in women [3]. Projections of these data for 1994 estimated for BCC an incidence rate of more than 400 per 100,000 in men and more than 200 per 100,000 in women [7].

In Europe, relatively high incidence rates of 71.5 and 86.0 per 100,000, respectively, have been reported in Ireland and Switzerland [5, 12]. In Italy, standardized incidence rates of 50.7 per 100,000 in males and 33.8 in females have been estimated, using data from cancer registries of 9 geographic areas spread all over the Country [4].

In Denmark the NMSC incidence was 44.2 in men and 32.8 in women [5], while in Norway an age-adjusted incidence of 40 per 100,000 for BCC and 5 per 100,000 for SCC were reported in a study [13].

Time trends in incidence

The incidence of NMSC seems to be on the increase worldwide. Using population-based data, Miller & Weinstock estimated that the number of cases diagnosed in the US increased from 480,000 in 1978 to around one million in 1994 [7].

An increase of about 60% in mean age-adjusted incidence of basal cell and squamous cell carcinoma was also observed in British Columbia, Canada, between the periods 1973-75 and 1985-87 [8]. In a population-based Australian study an increase of 11% for BCC and 51% for SCC was reported over the 1985-90 period [14]. An incidence study performed in a region of UK over a 14-year period indicated a similar trend [15]. An increase of BCC incidence between the periods 1976-80 and 1986-90 has been recently reported also in a Japanese population [16].

Mortality

Mortality from nonmelanoma skin cancer is low and mostly due to squamous cell carcinoma. For 1993 in the US 2300 deaths due to NMSC, one third of the reported melanoma deaths, have been reported [17]. In Italy, for 1991, 421 deaths due to NMSC (ICD-9, code 173) have been reported, corresponding to a standardized mortality rate of 4.3 per 1,000,000 people. The mortality rate had been steadily around 7 per 1,000,000 per year in the period 1982-86, while a decrease was subsequently noted, starting from 1986 [18].

Mortality data for NMSC are probably imprecise. A population-based study conducted in US revealed a substantial misclassification of about 50% of the deaths attributed to NMSC [19]. Mortality is due in 80% of cases to SCC, which metastasize in 3-10% of the cases [20]. Metastatic BCC is very rare (less than 1 per 4000 cases), but direct extension into vital structures may be cause of death.

Recurrence rates

The estimated risk of recurrence among patients with prior skin cancer was found to be 35% three years after the first diagnosis of basal cell or squamous cell carcinoma, and 50% after 5 years [21-23]. An even higher recurrence rate of 60% at three years was found in an Australian study of non-melanocytic skin cancers [24].

Anatomic distribution

Nonmelanoma cancer of the skin occur mainly in sun-exposed areas. The percentages of head and neck lesion reported by different studies ranged from 40% to 76% for SCC and from 65% to 81% for BCC [8, 12, 15, 25, 26]. An increased incidence of trunk lesions has been consistently reported in several studies [6, 8, 27-29].

Age, sex and ethnic characteristics

Nonmelanoma skin cancer is rare in young people. Its incidence has been reported to increase with age and to be higher in men than in women [10, 12, 13, 25, 28, 29]. NMSC, in particular basal cell carcinoma, is uncommon in dark-skinned populations, and in Chinese and Japanese populations [5, 30-32].

Etiology: evidence from descriptive studies

Epidemiologic evidence relevant to the effects of UV radiation on the risk of skin cancer has been largely indirect, coming from the analysis of a number of features of the occurrence of nonmelanoma skin cancer revealed by descriptive studies, such as place or latitude of residence, migration from places of low insolation to places of high insolation, anatomical site distribution, etc.

Geographic variation in incidence

Nonmelanoma skin cancer incidence and mortality have long been known to increase with increasing proximity to the equator. An inverse correlation between incidence of NMSC and latitude in various countries has been demonstrated in several studies [10, 14, 32-34].

Migrant studies

Studies of migrants to Australia and other countries with high solar irradiance offer the opportunity to evaluate indirectly the effects of exposure to the sun. Most migrants
to Australia come from higher latitudes which have lower levels of exposure to the sun. The age-adjusted incidence rate of NMSC was more than double in the Australian-born population, as compared to that in immigrants from the British Isles [10].

**Anatomical distribution**

The predominant occurrence of skin cancer on sun-exposed sites has generally been considered a strong evidence that it is caused by sun exposure. Data from incidence studies in different populations [3, 8, 12, 13, 29] show that the majority of cases of both SCC and BCC occurred on the head and neck. The site distribution of SCC differed from that of BCC. The most consistent differences were a greater proportion of SCCs on the upper limbs and a greater proportion of BCCs on the trunk.

**Ethnic origin, pigmentary traits**

The risk of NMSC varies according to race and ethnic group. As stated above, skin cancer is rare in black, Chinese, and Japanese populations. This may be due to the protective effect exerted by melanin or to other genetic differences. However, a greatly increased incidence of NMSC among Japanese residents in Hawaii was reported in a study [32]. Among blacks, squamous-cell carcinoma is more common than basal-cell carcinoma and occurs in sites not exposed to the sun [31].

**Etiology: evidences from analytic studies**

A number of studies (case-control, cross-sectional or cohort studies), largely heterogeneous by design, type of population studied, methods for measuring exposures and pigmentary characteristics and methods of analysis, have been conducted to investigate the role of sunlight exposure and potential confounders or effect modifiers in the genesis of BCC and SCC on the occurrence of nonmelanoma skin cancer.

**Pigmentary characteristics**

Several studies reported light hair, eye and skin color as risk factors for BCC and SCC [28, 34-36], although the risk increase was relatively small when adjustment was made for potential confounders [37].

**Sun sensitivity: tendency to sunburn and ability to tan**

Cutaneous sensitivity or "skin phototype" is considered a major determinant of nonmelanoma skin cancer. A skin that tans poorly and burns easily was identified as a risk factor for BCC in all studies in which it was investigated [2, 14, 34, 37-41]. The estimated relative risks varied from 2 to 4 after adjustment for age, sex, pigmentary characteristics and indicators of sun exposures [37, 40, 41].

**Cumulative sun exposure**

Methods of measurement of cumulative sun exposure are generally poor. Most studies have used surrogate measures, such as "working outdoor", "working as farmer" etc. Only one study attempted a quantitative estimate of the lifetime exposure by combining field-derived and laboratory-derived and published ambient UVB data with personal exposure histories [42]. A study by Gellin et al. [34] reported for BCC a crude odds ratio of 7.7, for average daily outdoor exposure > 6 hours. By contrast, more recent studies [40, 41] did not confirm the association between BCC and measures of cumulative UV exposures, after adjustment for age, gender, pigmentary traits, and ethnic characteristics.

Several population-based studies conducted in Australia and Canada [2, 28, 36, 39] showed a consistent but weak association between BCC and SCC and some measures of outdoors occupations.

**Other causes of nonmelanoma skin cancer**

Other risk factors for nonmelanoma skin cancer include the exposure to chemical carcinogens [42], ionizing radiation [43], PUVA therapy [44], chronic ulceration or inflammation [45], immunosuppressed status [46], viral carcinogens [47], scarring dermatoses [48]. In addition, a few genetic diseases such as xeroderma pigmentosum and nevoid basal-cell carcinoma syndrome [49], have a greatly increased risk of nonmelanoma skin cancer.

**Etiology: the contribution of molecular epidemiology**

_The interface between epidemiology and basic sciences_

Because of its importance in assessing disease etiology and pathogenesis, the collaboration between basic sciences, such as molecular biology, and epidemiology has been increasingly emphasized in recent years. An example of this collaboration is the assessment of the potential synergism between environmental and genetic factors in skin cancer suggested by the xeroderma pigmentosum (XP) model.

Xeroderma pigmentosum is a rare autosomal recessive disorder characterized by clinical and cellular hypersensitivity to solar radiation. XP patients experience a greater than 1000-fold excess frequency of UV-related skin cancers. Coupled with this marked susceptibility is
the consistent laboratory finding that all cells tested from XP patients are defective in the capacity for excision repair of DNA damage induced by UV radiation [50]. XP is a complex disorder comprising at least 10 forms of DNA repair defect (excision defective complementation groups and one excision repair proficient variant group). Evidence of cutaneous sun damage may appear as early as at one or two years of age, in absence of specific protection from the sun. Skin neoplasms, including basal cell carcinoma, squamous cell carcinoma and melanoma, were present in 70% of 132 patients with XP, whose reports were examined [51]. The median age of onset of skin cancer was 8 years, about 50 years younger than the median age of onset of skin cancer in the US general population.

The relevance of the XP model of NMSC etiology for the population at large comes from the observation that the defect in the DNA repair capacity in XP patients is not complete, but is expressed phenotypically as a range of diminished repair efficiencies, leaving residual capacities ranging from less than 2% to 80% of “normal”. If XP is considered to represent the lower range of repair capacity in humans, those individuals expressing a reduced repair response within the upper quintile of the shoulder of a dose-response curve may be at increased risk for skin cancer, given an appropriate exposure. These results have not been confirmed in another study done in Australia, where sunlight exposure is considerable [54]. In addition, the rather broad indices of sunlight exposure in Wei’s study (e.g., “more than 6 severe sunburns”) do not preclude the possibility that DRC could result from cumulative severe sunlight exposure. In fact, in a more detailed analysis of the data, Wei et al. [56] found that among patients who reported frequent sunbathing, poor tanning ability, a history of multiple severe sunburns or multiple medical irradiations, the BCC patients had significantly lower DNA repair capacity than controls (p < 0.05). They concluded that a reduced DRC is one of the underlying molecular mechanisms for sunlight-induced skin carcinogenesis in the general population.

In the light of these observations, it seems of great importance to continue to explore the possibility of an interaction between a genetically determined decreased DRC and sunlight exposure because, if confirmed, it may allow identification of individuals at a specially high risk of developing sunlight-induced BCC. Work in this area clearly underscores the inter-dependence between epidemiology and molecular biology.

Public health issues of skin cancer

Morbidity and costs

Although mortality from nonmelanoma skin cancer is low, the associated morbidity due to the local invasiveness and disfigurement are of great concern. The increasing number of cases per year coming to medical attention and the high recurrence rates are likely to involve high medical care costs. The estimated costs in the US for the different treatments for NMSC, based on Medicare reimbursement, vary from a minimum of $150 of cryo- or electro-surgery to a maximum of about $600 for Mohs’ surgery with repair [57].

Prevention

The predominant role of sun exposure in the etiology of nonmelanoma skin cancer is widely accepted, in the light of the numerous direct or indirect evidences reported in this paper. It is clear that sun exposure is also the major etiologic factor of NMSC for which primary prevention is feasible. Great efforts have been done in countries with high incidence of both melanoma and nonmelanoma skin cancer, such as Australia, to promote education campaigns to limit the dangerous effects of uncontrolled sun exposure. An Australian study on sunburn occurrence in an urban population confirmed the need of behavior change strategies to enhance sun-protection attitudes especially in young people [58]. In the US the degree of awareness of the public on the risks from sunlight has increased only recently [59, 60].
Primary and secondary prevention programs to control skin cancer should rely on multiple strategies, including educational programs through mass media, family physicians and school interventions, screening campaigns, regular screenings for high-risk individuals.

The target of information and prevention campaigns should be primarily children and adolescents, in the light of the numerous evidences linking massive sun exposures at young ages (documented by the history of severe sunburns) with an increased risk of both melanoma and nonmelanoma skin cancer.

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REFERENCES


