Epidemiology and Aetiology of Non-melanoma Skin Cancer

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Introduction

Skin cancer can be categorized broadly into cutaneous melanoma and nonmelanoma skin cancer (NMSC). Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are the most common types of NMSC. Apart from these, rarer cutaneous malignancies, such as Merkel cell carcinoma (MCC) and malignancies of the adnexal structures, also occur. NMSC is by far the most common malignancy encountered in the human body, and is found frequently in primary care settings, which makes it an important public health consideration. It is managed by a variety of medical practitioners, being of multidisciplinary interest to otolaryngologists, head and neck surgeons, plastic surgeons, dermatologists, radiation oncologists, and primary care physicians.

When detected early, NMSC usually is easily amenable to treatment in low-risk outpatient settings; it is associated with low mortality. As such, most cancer registries the world over do not collect information pertaining to NMSC routinely, and therefore, precise epidemiological data are difficult to ascertain. Nonetheless, because of its overall high incidence, NMSC is associated with significant burden of disease and economic cost, particularly in the setting of advanced disease. Accordingly, the epidemiology of NMSC is important to define, as it establishes the magnitude of the problem and can dictate future planning and research priorities.

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Springer India/Byword Books
F. Riffat et al. (eds.), *Non-melanoma Skin Cancer of the Head and Neck*,
Head and Neck Cancer Clinics, DOI 10.1007/978-81-322-2497-6_1

The head and neck is the region most frequently affected by NMSC. This is not surprising, given that this is an area of maximal sun exposure, and UV radiation has long been known to be the most important aetiological factor in the pathogenesis of NMSC. However, a myriad of other genetic and environmental factors also contribute to the development of NMSC.

Epidemiology

Although a common disease, in particular in fair-skinned populations across Europe, North America and Australia, the epidemiology of NMSC shows marked geographical variations [1]. NMSC is more common than any other malignancy and BCC is more than two times as common as SCC [2]. In Australia, a country with the highest worldwide incidence, the prevalence of both SCC and BCC is on the rise [2–4]. This trend has occurred despite significant public health campaigns in recent decades, such as 'SunSmart', which advocates protective clothing, SPF 30+ sunscreen and avoidance of excessive sunlight, in particular during peak sunlight hours [5]. Generally considered to be easily amenable to treatment, NMSC nevertheless incurs a significant burden upon individuals and the healthcare system on account of its high incidence. With the average age of the Australian population increasing, it is anticipated that this burden will rise in coming years [4].

While cancer registries usually do not record epidemiological data, a series of cross-sectional studies in 1985, 1990, 1995 and, most recently, in 2002 has provided periodic estimates of the incidence of NMSC in Australia [2]. In the most recent survey from 2002, the age-standardized incidence of NMSC was estimated to be 1170 per 100,000 [2]. By comparison, the estimated incidence of cutaneous melanoma in 2012 was 62.7 in males and 39.9 in females per 100,000, respectively [6]. NMSC affects all age groups, although it is uncommon in individuals <40 years of age who otherwise have no other risk factors. Incidence rises markedly with age, with a significant increase in risk in those over the age of 70 years [2].

The 2002 survey also indicated roughly 1.8 % of the population were treated for NMSC in the preceding year, and confirmed rates of both BCC and SCC were higher in the northern latitudes of Australia, which are areas of greater sunlight exposure, in Australia-born residents and in poor skin tanners [2]. The median age in Denmark was found recently to be 68 years for BCC and 78 years for SCC [7]. Males are typically affected more commonly than females, especially in older age groups. Multiple tumours are common, and occur in ~25 % of patients with both BCC and SCC.

In contrast, NMSC is a rare disease in darker skinned populations. In India, for example, the estimated incidence is between 0.5 and 2 per 100,000 [8]. In Asian and black races, SCC occurs more frequently than BCC, is a more aggressive disease, occurring preferentially in sun-protected rather than sun-exposed areas and in areas of chronic scarring and ulceration [8–11].

Mortality associated with NMSC is relatively low compared with other cancers. Between 1998 and 2005 there was an average of 382 deaths per year in Australia, i.e. approximately 1–3 per 100,000, a figure representing <1 % of total cancer

deaths in this period [3]. This is not to say that NMSC does not contribute to significant morbidity and mortality. The overall high incidence of disease translates into significant healthcare costs [12]. Morbidity related to NMSC is in terms of lost productivity and perceived loss of quality of life. As an aesthetically important region of the body, surgery involving the head and neck may impact negatively upon patients' quality of life because of cosmetic disfigurement [13]. Furthermore, a recent systematic review of the literature examining the morbidity and mortality costs of NMSC found substantial costs arose because of premature death and lost productivity, which could have been averted with early detection and preventive strategies [14].

Increasing Incidence

Notwithstanding that NMSC is already the most common cancer in fair-skinned populations globally, data accumulated over the past two to three decades indicate that the incidence of NMSC is further on the rise. In Australia, between the 1985 and 2002 surveys, a statistically significant ($p < 0.0005$) rise in the age-standardized incidence was observed in both SCC and BCC—2.1 and 1.3 times the 1985 rates, respectively [2]. Furthermore, data obtained from Medicare Australia for items billed for treatment of NMSC by excision, curettage, laser, or cyrotherapy also indicate a steady annual rise in the number of NMSC cases treated by these methods between 1997 and 2010, with a more significant rise in the older age groups (>55 years of age) [4]. Suggested explanations for this phenomenon include (1) an ageing population, (2) increased detection, (3) changes in recreational outdoor activities, (4) clothing style, and (5) ozone depletion [12, 15].

Similar trends have been observed in Europe and North America, with a suggested 'epidemic' of NMSC. Nevertheless, the magnitude of NMSC in these continents pales in comparison to the absolute figures in Australia [15]. Exact figures are difficult to ascertain because of similar challenges in obtaining epidemiological data. In the USA, data collected between 1994 and 2006 on the basis of Medicare claims show an almost doubling of the incidence of NMSC [16]. In Northern Ireland, the incidence of SCC and BCC was 23–46 per 100,000 and 72–94 per 100,000 between 1993 and 2004, with a rise of 62 % in the number of skin cancer specimens handled by pathology laboratories during this period [17]. Examination of data in a number of other European nations has also shown increased incidence [12].

The implications of the increase in NMSC incidence will be felt over the coming decades and policy-makers will have to respond to the changing needs in treating a cancer that already incurs significant economic burden upon healthcare systems globally. The expense associated with treating individual NMSC cases is not substantial; Medicare data from the USA indicate that the cost of treating NMSC per case is 5–10 % of the cost for other cancers, but overall, it is the fifth most expensive cancer to treat [18]. In Australia it has been estimated that the costs are ~$700 per case. Given the high incidence of NMSC in Australia, it is not surprising that it is the most expensive cancer to treat overall, costing the healthcare system $264 million, or 9 % of total cancer expenditure [19]. Whereas the bulk of NMSC is treated

in outpatient settings, it is important to note that this cancer also incurs significant inpatient costs, with approximately 95,000 hospital admissions in Australia in 2010–11, a figure that is greater than that for any other type of cancer [6].

Aetiology

Risk Factors

The single most important aetiological factor in the pathogenesis of NMSC is UV-induced DNA damage [1]. NMSC is rare in dark-skinned races because of the protective role of melanin in UV-induced damage of skin cells [20]. The pathogenesis of SCC strongly correlates with cumulative exposure of UV radiation, in particular, UV-B (290–320 nm). In contrast, intermittent exposure is more significant in the development of BCC. Consequently, the distribution of NMSC is predominantly in the head and neck and in other areas of maximal sun exposure, such as the arms and back [21]. In Australia, factors shown consistently to be associated with an increased risk of NMSC are: (1) living in northern latitudes where exposure to the sun is maximal, (2) being fair-skinned with poor skin-tanning, and (3) high cumulative sun exposure. In addition, the male gender is affected more commonly than the female gender, as are fair-skinned races over Blacks or Asians. The risk of developing NMSC increases markedly with age [2].

Other risk factors include infection with human papillomavirus (HPV), chemical carcinogens, as well as acquired or inherited immunosuppression [22]. Tobacco smoking is an established risk factor for SCC but not for BCC [23]. Arsenic is a chemical carcinogen, which with chronic exposure is associated strongly with the development of a variety of dermatological manifestations and malignancies, including SCC and BCC [24]. Areas of chronic irritation and scarring also predispose to SCC, which is known to arise in the setting of chronic ‘Marjolin’ ulcers, sinus tracts and scars [25].

Immunosuppression and NMSC

NMSC is associated with significant morbidity in post-transplantation patients and in patients with autoimmune disorders who are on immunosuppressive agents, with increasing risk associated with an increasing duration of immunosuppression [26, 27]. The risk of cutaneous as well as systemic cancers is increased in this group of patients. The risk of developing SCC is particularly high in this group of patients. Recipients of solid organ transplants have an approximate 100-fold increase in the risk of developing SCC compared with a 10–16-fold increase in risk of developing BCC [28]. In a series of Australian heart transplant recipients, the cumulative incidence of NMSC was 43 % over 10 years [29], while in a series of Italian heart transplant recipients the corresponding figure was 35 % [30]. NMSC in this cohort of patients may be particularly aggressive, manifest as recurrent, multifocal, or

metastatic disease, and is therefore far more difficult to manage when compared to the non-immunosuppressed patient [31]. Risk of mortality is approximately 5 % in patients who develop SCC after a renal transplant [32]. With increasing numbers of transplant recipients and longer survival times of such patients, the burden of disease represented by this cohort of patients is likely to increase over the coming years.

Gene Mutations

As with all malignancies, acquired and inherited mutations in genetic code play a role in the pathogenesis of NMSC. The *p53* gene is a tumour-suppressor gene located on chromosome 17, mutations of which strongly correlate with an array of cancers, including SCC and BCC. The *p53* gene plays an important regulatory role in the cell cycle, in DNA repair, and in apoptosis [21]. Alterations in pyrimidine dimers, induced by UV radiation, may inactivate the gene, subsequently causing dysregulation of the cell cycle, failure of apoptosis and tumour formation [33].

Another relevant gene in the pathogenesis of BCC is patched (*PTCH1*). The *PTCH1* gene located on chromosome 9 is involved in the sonic hedgehog signalling cascade. Its involvement in disease was first identified in individuals with the nevoid BCC syndrome, an autosomal-dominant syndrome [25]. Patients with this syndrome have associated defects in the sonic hedgehog pathway and present with multiple BCCs, odontogenic cysts, skeletal defects, palmar and plantar pits, and calcification of the falx cerebri [25]. Mutations, however, also occur in sporadic cases of BCC. *PTCH1* is a tumour suppressor gene that binds to and inhibits smoothened (SMOH), a transmembrane protein that promotes cellular growth. Mutations in the *PTCH1* gene leads to failure of this inhibition and aberrant cellular growth [34].

Other inherited conditions, such as xerodermapigmentosum, also predispose individuals to NMSC. Xerodermapigmentosum is an autosomal-recessive condition wherein cells have a reduced capacity to repair UV-induced damage, leading to multiple SCC and other skin cancers. The mutation involved in xerodermapigmentosum disrupts the nucleotide excision repair, which enzymatically repairs UV-induced DNA damage [21]. Epidermodysplasiaverruciformis is another autosomal-recessive condition, wherein increased susceptibility to viral oncogenesis secondary to HPV leads to widespread wart formation followed by the emergence of cutaneous SCC [35].

Other Cutaneous Malignancies of the Head and Neck

Merkel Cell Carcinoma

MCC is a rare but highly malignant neuroendocrine tumour. Aetiology is also thought to be sunlight-related, although recently additional links have been made with polyomavirus and immunosuppression [36]. As with other types of NMSC,

the head and neck is the most commonly affected region of the body [37]. Data pertaining to the epidemiology of MCC have not been studied extensively. However, a cancer registry from Western Australia between 1993 and 2007 indicated that this region had the highest reported incidence of MCC in the world [38]. Males were found to be affected more commonly than females—1 per 100,000 in males compared to 0.63 per 100,000 in females, with the median age being 77 years [38]. MCC can also often occur in patients with pre-existing SCC or BCC. Prognosis is generally poor, particularly in metastatic disease, with a 5-year survival of 75 %, 59 %, and 25 % for local, regional, and distant disease, respectively [37].

Appendigeal Malignancies

Malignancies arising from the adnexal structures of the skin with apocrine, eccrine, follicular, or sebaceous differentiation are rare, representing <1 % of cutaneous head and neck malignancies [25, 39]. Although sebaceous carcinoma is rare, it is a highly malignant appendigeal neoplasm, with an incidence of ~1 case per million of the population [40]. Although it may occur outside the eyelid, an ocular distribution is more likely usually from a meibomian gland or from the glands of Zeis. The tumour most commonly occurs in patients aged 60–80 years, and affects Asian people more than other races [41]. Women are generally reported to have a higher incidence than men. However, this distribution is questionable, as in a series of 1349 patients, 54 % were men [42]. The presence of other aetiological factors is unclear, although Muir–Torre syndrome, an autosomal-dominant inherited condition, is characterized by sebaceous tumours and visceral neoplasms, and previous irradiation [41, 42].

Dermatofibrosarcoma protuberans: Dermatofibrosarcoma protuberans (DFSP) is a mesenchymal neoplasm of intermediate malignant potential. Although a rare skin tumour overall, it is the most common cutaneous sarcoma. The tumour demonstrates aggressive local growth with a high propensity for recurrence, despite surgical excision [43]. On the basis of population-based cancer registry data, the incidence of DFSP in the USA was found to be ~4 per million, with a small but statistically significant higher incidence in women than in men (4.4 vs. 4.2) [44].

DFSP occurs most commonly on the trunk. However, 10–15 % of cases occur in the head and neck, where it commonly affects the scalp and supraclavicular fossa [43, 44]. Aetiological factors are unclear, although recent advances in the molecular pathogenesis of DFSP have indicated that >90 % of cases are caused by reciprocal translocations between chromosomes 17 and 22. The resultant gene is a fusion between platelet-derived growth factor band (PDGFB) collagen 1A1, which leads to upregulation of the PDGFB protein. This is thought to underlie the pathogenesis of DFSP [45, 46]. Imatinib, an inhibitor of PDGFB, has recently been used to show demonstrable efficacy against DFSP [47, 48]. An association with antecedent trauma to the affected area has also been reported [43].

Angiosarcoma

Angiosarcoma of the head and neck is an exceedingly rare yet extremely aggressive malignancy of vascular origin. Data relating to head and neck angiosarcoma are sparse. Approximately half of all angiosarcomas occur in the head and neck and the scalp has been found to be affected more commonly than any other part of the body [49]. The male gender is affected more than two times than the female gender [50, 51]. One of the largest series of patients with head and neck angiosarcoma reported in the literature is from the Connecticut Tumour Registry between 1980 and 2001 [52]. Of 54 patients studied over a 21-year period, 29 patients had angiosarcoma of the head and neck, with a mean age at diagnosis of 71 years. The authors found a 1-year mortality of 48 % and a 5-year mortality of 28 %. This series also contained one instance of familial angiosarcoma of the head and neck. Documented risk factors include chemical exposure (vinyl chloride, thorium, arsenic) and radiation [53–55].

Summary

Precise epidemiological data pertaining to NMSC of the head and neck are unavailable. Nevertheless, it is clear that the burden of NMSC is increasing globally and that this burden can be significant in terms of personal and societal costs. While a variety of aetiological factors have been associated with NMSC, UV exposure remains the single most important factor for the development of NMSC, particularly in males of fair skin who live in equatorial longitudes.

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