Etiology of melanoma (C43) in Central and South America

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Relationship with exposure to ultraviolet radiation

Most melanomas are thought to be caused by intense exposure to ultraviolet radiation (UVR), but this relationship is complex and depends on the sensitivity of individuals to the sun, which is reflected in phenotypic characteristics such as fair and red hair, fair skin, and light-coloured eyes [1–3]. The presence of melanocytic naevi (moles) is also an important risk factor, and is strongly influenced by exposure to UVR [4–6]. A few studies on melanoma across the South American continent have shown that European ancestry was strongly related to the risk of melanoma [7–10]. The incidence of and mortality from melanoma was very high in populations with a high proportion of white=skinned people in Brazil [11, 12].

High exposure to UVR at a young age increases the risk of developing melanoma later in life. Important evidence for this correlation has been found in 'migration studies' in countries with high exposure to UVR. Some studies in Australia, Israel, and New Zealand revealed that the overall incidence of and mortality from melanoma were lower in migrants from northern Europe than in the locally born population [13–15]. People who migrated from a country with low exposure to UVR to a country with high exposure within the first 10 years of life had the same risk (relative risk [RR], 1) of developing melanoma as those who were born locally, whereas those who migrated later in life had a lower risk (RR, ~0.2) [14].

The increased risk of developing melanomas after exposure to UVR during pre-pubertal childhood may be explained biologically. The bulge region of hair follicles that hosts melanocytic stem cells is located deeper in the skin – and therefore has greater protection from UVR – in adults (terminal hair) than in pre-pubertal children (vellus hair) [16, 17].

Results from a meta-analysis revealed that predominantly white populations who used sunbeds (an artificial source of UVR) have 20% higher risk of developing melanoma than those who never used sunbeds (RR, 1.20; 95% confidence interval [CI], 1.08–1.34 for ever use versus never use) and the risk was even higher if first sunbed use occurred before the age of 35 years (RR, 1.59; 95% CI, 1.36–1.85). When the analysis was limited to studies that provided data on the risk associated with the number of sunbed sessions per year (n = 4), the risk of melanoma increased

by 1.8% (RR, 1.018; 95% CI, 0.998–1.038) for each additional sunbed session per year [18].

Data from case–control studies have mostly been interpreted according to a hypothesis of 'intermittent sun exposure' [19] whereby partaking in certain sun-intensive activities, such as sunbathing, outdoor recreation, and holidays in sunny climates, by people who spent most of their time indoors was related to increased risks of melanoma, whereas, more continuous patterns of and total exposure to the sun generally showed weak, null, or inverse associations [19, 20]. However, recent studies showed that melanomas of the head and neck were strongly associated with indicators of chronic exposure to UVR and melanomas on the trunk were strongly associated with acquired naevi (intermittent exposure) [20–26].

Geographical factors related to exposure to UVR and melanoma

Both altitude and latitude are important in determining exposure to UVR. In general, the amount of UVR that reaches the Earth's surface decreases with distance from the equator. In the southern hemisphere, however, the "hole" in the ozone layer has modified this general rule and has caused an increase in UVR that has been estimated at 5% per decade at 30º South to 40% per decade at 85º South and very high levels of UVR have been observed in southern South America [27, 28]. Although the ozone layer is gradually recuperating, the higher exposures in the recent past will probably result in a higher incidence of melanoma in current and future years. In Punto Arenas, the southernmost city of Chile, the number and incidence of skin cancers have been found to be increasing [29].

The average skin colour may also vary with latitude, with greater pigmentation close to the equator, although complex migration patterns have distorted the original skin pigmentation gradient of the continent [30, 31]. A plot of the age-standardized incidence rates from cancer registries by their latitude shows a clear correlation with latitude for both men and women (Figure 1). A study on mortality from melanoma in Brazil showed that mortality rates in the southern Brazil, where more than 83% of the population is white, were 7 times higher than those in the northern region, where more than 70% of the population is non-white [11].

Another geographical factor that determines exposure to UVR is altitude: higher areas receive more UVR than lower areas at the same latitude. In general, each 300-m increase in altitude increases the sun-burning effectiveness of sunlight by about 4% [32]. Correa et al. [28] reported that South American cities in areas of high altitude are at risk of dangerous levels of UVR [28].

Other risk factors

An association with exposure to UVR is probably not true for plantar melanomas (occurring on the soles of the foot and palms of the hands), which are the most common types of melanoma in populations of non-European descent and are usually of the acrolentiginous (ALM) subtype. Numerous case reports and several case–control studies have suggested that trauma (defined as deep penetrative injuries, burns, cuts, or thorn pricks) is a risk factor for melanomas occurring at acral sites or specifically for ALM [33]. Benign naevi on the soles or toes and have also been

associated with an increased risk of melanomas on the hands and feet and/or ALM [33]. Trauma (frequency and severity) has been identified as a risk factor for melanoma in two case–control studies [33–35], although the interpretation of these data is problematic because differences in the definitions and frequencies of trauma (i.e., severe, single, and chronic injury) and the time since the trauma occurred and recall bias are liable to prejudice study results.

The incidence of ALM in Koreans was shown to be higher on the sites of the feet that are more physically stressed by walking, such as the centre of the heels and the inner forefoot, and the spreading pattern of the melanomas was also in accordance with the effects of long-term pressure [35].

These data provide indications that pressure or trauma may be risk factors for ALM and/or melanomas occurring on the hands and feet. However, the evidence to date is inconclusive and how trauma interplays with naevi, UVR, genetic, and other risk factors in potentially causing melanomas is unclear.

Molecular biology

Many gene mutations are related to melanoma, some in familial melanoma: *cyclin-dependent kinase inhibitor 2A* (*CDKN2A*) and *retinoblastoma 1* (tumour suppressor genes), melanocortin 1 receptor (a key protein involved in regulating mammalian skin and hair colour), cyclin-dependent kinase 4, and microphthalmia-associated transcription factor (a factor involved in melanocyte development). The major gene associated with melanoma is *CDKN2A/p16* (also known as *MTS1*, *INK4*, and *MLM*), a tumour suppressor gene coding two proteins, $p16^{INK4a}$ and $p14^{ARF}$ – both inhibitors of cellular senescence – which mediates cell cycle arrest at the G1 and G2/M checkpoints and thereby facilitates the cellular repair of DNA damage. Mutations in *CDKN2A* account for 35–40% of familial melanomas, are also involved in increased risks for pancreatic and familial melanoma syndromes related to these genes, and may also be related to increased risks of cancers of the breast and the neural system [36–39]. The melanocortin 1 receptor mutation is strongly associated with the typical ‘melanoma-prone’ phenotype (pale skin, red or blond hair, and blue eyes) and is probably less prevalent in Central and South America than in predominantly Caucasian populations [40]. The mitogen-activated protein kinase (MAPK) pathway, a cellular pathway involved in growth factor signalling, appears to be very important in the risk of melanoma: one of the most important mutations for melanoma, *BRAF*, is in this pathway, as well as several other melanoma mutations [40]. About 50% of all melanomas carry *BRAF* mutations, leading to kinase activation in the MAPK pathway which induces the proliferation of melanocytes and the impairment of apoptotic response to metabolic stress [40–43]. These *BRAF* mutations occur more frequently in superficial spreading melanomas, in younger individuals, and on areas of human skin that are intermittently exposed to UVR compared with melanomas that develop on more chronically exposed parts of human skin [40, 44], indicating that patterns of exposure to UVR are determinants in the induction of mutation. Several selective *BRAF* inhibitors are under development or already available to treat melanomas with *BRAF* mutations, the best known of which are vemurafenib and dabrafenib [45]. A few relatively small case series studies on mutations in melanomas in Latin American populations have shown that the prevalence of *BRAF* mutations ranges from 32.7% in Colombia (cutaneous melanomas) to 39% in Brazil and 78% in Uruguay.

Mutations in the *KIT* gene (a proto-oncogene) are much less frequent in melanomas, occurring in less than 1% of melanomas overall, but are relatively common in acral and mucosal melanomas, with estimates of prevalence varying from 17% to 39% for mucosal and from 14% to 36% for acral sites [46, 47]. A case series of 81 melanomas in Colombia showed a prevalence of *cKIT* mutations of 4.9% in melanomas overall and 33% in ALM [48], whereas a series in Brazil did not find any *cKIT* mutation [49].

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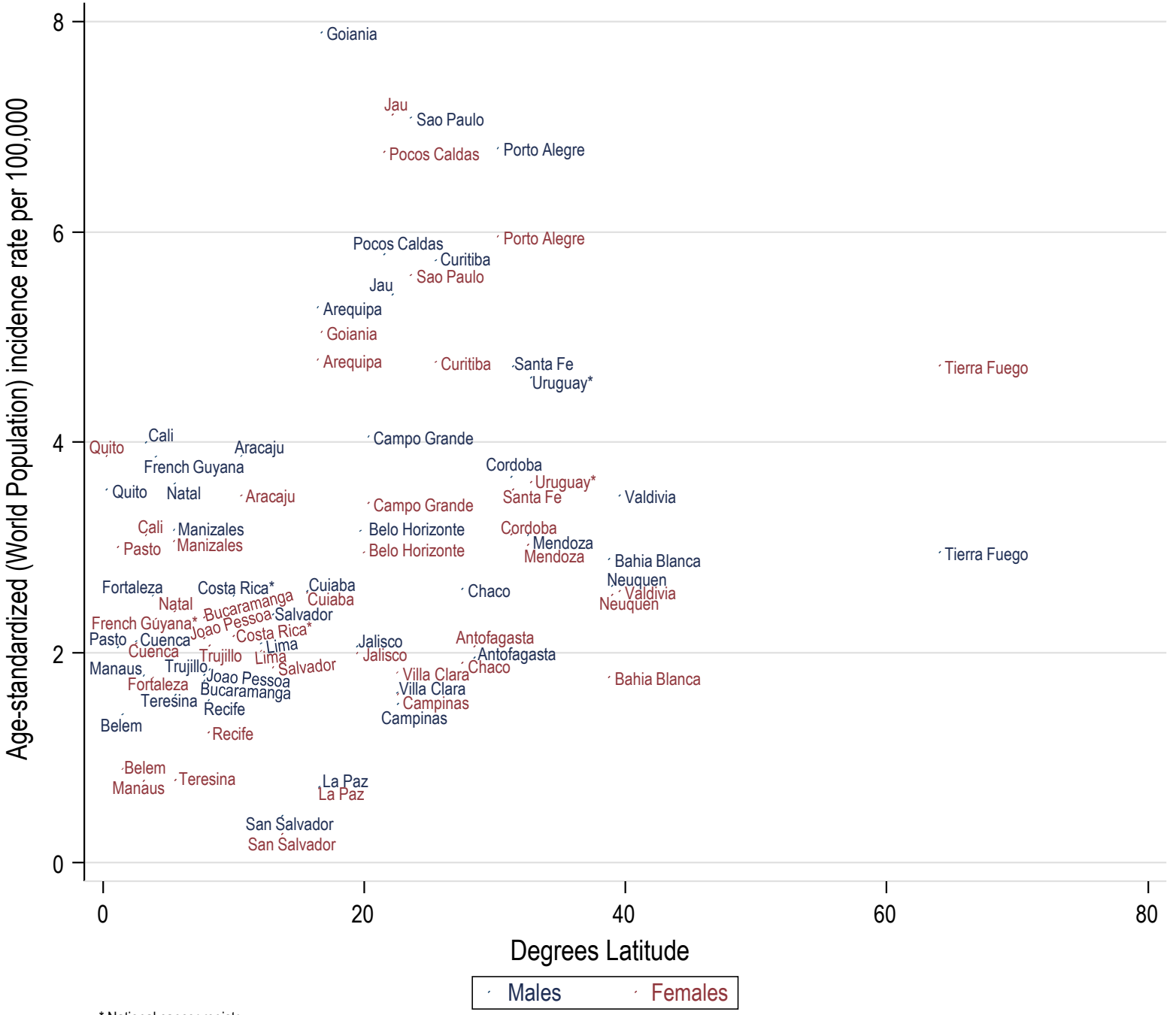
Melanoma of skin (C43)

Age-standardized incidence rates (per 100,000) in Central and South America versus latitude†
Most recent period



* National cancer registry

† Latitude based on cancer registry's geographical location

Pearson correlation coefficient=0.623 for males, p-value<0.01; and 0.615 for females, p-value<0.01 (two-tailed test, weighted for population size of the registries)