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Skin phenotypes can offer some insight about the association between telomere length and cancer susceptibility

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ABSTRACT

The role of telomere biology in cancer has been studied for a wide variety of different cancers but the association with telomere length has been controversial. This is because some cancers have been found to be associated with longer telomeres in circulating white cells whilst other cancer types are more common in individuals with shorter telomeres. Hence, there has been some skepticism as to whether telomere length may be helpful in estimating cancer risk. For melanoma, however, results have been fairly consistent showing that longer telomeres are associated with an increased risk. This link was first discovered because of a link between longer telomeres and a high number of naevi. In contrast, for cutaneous squamous cell carcinomas, the relationship is reversed with higher risk in individuals with shorter telomeres. Differences in skin phenotypes with the presence of high number of naevi versus photoageing with solar elastosis and solar keratoses have already been valuable for dermatologists as the former phenotype is associated with melanoma whilst the latter is more common in patients with squamous cell carcinoma of the skin. The hypothesis is that the differences in cutaneous phenotypes already observed by dermatologists for skin cancers may, in fact, be useful as well for cancer prediction in general as it may reflect underlying telomere biology. This manuscript will address the evidence for links between telomere biology, skin phenotypes and cancer risk.

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Telomeres are repeat TTAGGG sequences at the end of linear chromosomes, which guard against loss of genetic material during cellular replication. Due to an inherent end replication problem, chromosomes are exposed to a potential loss of genetic material so telomeres act as a buffer against loss of chromatin [1]. In normal human somatic cells, telomeres range from 9 to 15 kb initially, with a progressive loss in mean telomere length of 15–66 bp per year [2]. It has been estimated that 17.5% of the inter-individual variation in leukocyte telomere length is due to the ageing process [3]. Repeated cell cycles eventually lead to a critically shortened telomere length which then triggers apoptosis. In cell cultures, the replicative potential of human cells is estimated at an average of 52 mitoses per cell known as the Hayflick limit, by which stage, the critical telomere shortening will lead to the activation of genes pushing the cells in cell cycle arrest [4]. This arrest in proliferation is thought to protect against malignant transformation and a failure to do so results in catastrophic genomic instability and carcinogenesis. Telomeres are thus important in managing genomic stability. This central role in genome maintenance makes telomeres key players in carcinogenesis and an attractive candidate for tumour profiling at the molecular level. Although telomere length has a strong inheritable component [5], it is also influenced by a wide variety of environmental factors such as oxidative stress, chronic inflammation, smoking and obesity [2,6–8]. Telomeres have been estimated to be 240 bp shorter in obese women compared to women with a BMI below 25 and also 5 bp shorter for every cigarette pack year smoked [2].

The link between cancer susceptibility and telomere length has not been easy to elucidate perhaps because there was an assumption that all cancers would show associations with telomere length in the same direction whatever the cancer type. However, when grouping all cancers together it appears that conflicting results emerge [9,10]. It is likely that cancer types need to be analysed separately to observe trends with telomere length. Most studies looking at associations between telomere length and cancer have used circulating leukocytes as blood sampling is easily accessible and telomere length in white cells correlates to telomere length in other human healthy tissues (but very different from neoplastic

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tissues where telomerase and other neoplastic processes affect telomerase) [3,11,12].

Melanoma susceptibility via an excess of naevi was one of the first tumour to show a link with longer telomeres in white cells [13]. The reason why telomere length was measured in individuals with a high number of naevi was because dermatologists working in high risk melanoma clinics had observed that these high risk patients with multiple atypical naevi showed reduced signs of skin ageing and photoageing compared to their peers. It was therefore suspected that their ageing process may be delayed. In fact, many melanoma patients show far less photoageing compared to patients with squamous cell carcinoma, the latter usually associated with sun damaged skin with solar lentigines and solar keratoses. The link between melanoma susceptibility and longer telomeres suggests that these individuals may have a reduced senescence which is likely to affect many cell types and not just melanocytes. It is yet, unproven, if longer telomeres are causal in the formation of a large numbers of cutaneous naevi in these high risk melanoma patients. However, considering the role of the telomere unit in cell replication, it is highly likely that an excess of naevi is a reflection of the lack of senescence in melanocytes and is linked to their longer telomeres [14]. This has potential implications for other tissues as individuals with high numbers of naevi have been shown to be taller than those with fewer naevi and also have higher bone mineral density [15]. Bone mass and growth early in life is likely to be affected by telomere biology well before melanoma susceptibility is evident later in life. Melanoma case-control studies, family studies and analyses of genetic changes in melanoma tumours have all replicated the link between melanoma susceptibility and telomere biology from 2011 onwards. These studies assessed telomere length in melanoma cases compared to controls or reported on polymorphisms in genes which affect telomere length [16–19].

In contrast, cutaneous squamous cell carcinoma susceptibility is associated with shorter telomeres [20–22]. The cutaneous phenotype associated with squamous cell carcinoma of the skin is characterised by epidermal and dermal atrophy, solar lentigines and solar keratoses which are far less common in melanoma patients (albeit in lentigo maligna in elderly patients)[23]. This photoaged skin phenotype is likely to reflect the altered telomere biology via shorter telomeres and increased senescence in cutaneous squamous cell carcinoma patients.

More recently, large genome wide association studies led to the identification of 10 loci associated with telomere length variation [24–29]. Following the discovery of these loci, a large melanoma case-control study from the Genomel Consortium developed a genetic score to estimate melanoma risk based on these SNPs associated with telomere length variation [26]. The combined SNPs score does predict melanoma risk again confirming the role of the telomere unit in melanoma susceptibility [30]. It is, however, important to note these SNPs only explain 1% of the variance in telomere length so many other genes, environmental factors as well as epigenetics factors may explain the rest of the variance in telomere length. Genetic variants reported in the Codd et al. study [26] may not have an effect solely on telomere length as they may have pleiotropic effects on cancer risk via immune responses and DNA repair as well [30].

In fact, well before these recent telomere studies, dermatologists were well aware that phenotypic risk factors for squamous cell carcinomas and melanoma were different. This may be surprising when there is a tendency to combine all skin cancers together and always assume that they are all caused by excessive sun exposure. Squamous cell carcinoma of the skin is usually associated with chronic sun damage whilst many melanoma patients, especially in the context of familial susceptibility, show very little signs of photoageing. A high number of naevi (high risk of melanoma) and severe photoageing with solar keratoses (high risk of squamous cell carcinoma) have already been reported to often be mutually exclusive even after adjusting for age which support the fact that melanomas and squamous cell carcinoma do arise from very different "at risk" cutaneous phenotypes. Of the smaller numbers of melanomas associated with a photoageing phenotype these are more likely to be seen in older patients, be a nodular subtype or lentigo maligna and on chronically sun exposed sites [31,32]. This led to the divergent melanoma pathways hypothesis described in the 1990s via the photoageing or alternatively via the naevus phenotype [31,32]. Whilst it is true that squamous cell carcinoma affects older individuals compared to melanoma, telomere studies looking at SCC have adjusted for age and the association remains with shorter telomeres for squamous cell carcinomas [21]. Shorter telomeres in squamous cell carcinomas may also explain the reduced immune surveillance with less robust lymphocytic response in relation to neoplastic keratinocytes. It is common to find a strong lymphocytic response in melanoma tumours whilst for squamous cell carcinomas, this is not commonly reported histologically. While it is not proven that these differences in immune responses in different types of skin cancers are explained by telomere biology, it is quite likely that longer telomeres have a significant impact on lymphocyte functions [33].

Could these differences in the "at risk" skin phenotypes observed for skin cancers shed any light on the association between telomere length and other cancers? In fact, there are already interesting contrasting results regarding telomere length and lung cancer risk where the squamous cell carcinoma type in the lung is more likely to be associated with shorter telomeres whilst adenocarcinoma of the lung (more common in non-smokers) is linked to longer telomeres and this appears to be consistent across studies [34–37]. SNPs in the *TERT* gene have been associated with adenocarcinomas of the lung but not with squamous cell or small cell lung cancers [38]. This again highlights the issue of histological subtypes when looking at associations between cancer and telomere length or telomere SNPs. The association between shorter telomeres and squamous cell carcinoma type tumours is also often reported for squamous cell tumours of other organs such as oro-pharynx [39,40] oesophagus [41–44] or cervix [45]. Adenocarcinomas of the colon, kidney, prostate, uterus and breast are, on the contrary, more likely to be associated with longer telomeres [46–53]. Still, the association with adenocarcinomas of the colon and breast is controversial as other studies have shown inverse relationships with telomere length or no association at all [9]. The association between telomere length and cancer is therefore quite complex as some studies have reported a U shape curve with risk of cancer seen in the extreme groups of telomere length [54–56]. Telomere length can be also be by affected by environmental factors and these are often not adjusted for, such as, obesity, smoking (apart from lung cancer) and alcohol abuse. Furthermore, there has been discrepant results between studies looking at telomere length measured by Southern Blot (which gives a measurement of the telomere unit in bp but is more time consuming) and those using qPCR (faster and cheaper but does not give an actual length but mean TL ratio) [57]. Recently, whole genome sequencing has been used to measure telomere length and may, in the future, replace qPCR and Southern blot [58].

In Dyskeratosis Congenita, considered a short telomere syndrome caused by mutations in telomere genes, SCCs of the head and neck and oral leucoplakia are reported frequently and the skin is showing all the signs of premature photoageing with keratinocyte dysplasia so again the skin in this syndrome is very informative as it is a window into telomere biology. These patients are also more prone to cutaneous and non cutaneous SCC type tumours and not adenocarcinomas in line with their very short telomeres [59].

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