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Review article

Telomere length and the risk of cutaneous melanoma and non-melanoma skin cancer: a review of the literature and meta-analysis

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ABSTRACT

There is much evidence supporting the role of telomeres in cancer pathogenesis, however the studies that investigated the association between telomere length and skin cancer risk provided inconsistent results. To help clarify this issue, we performed a systematic review and meta-analysis of published papers on the association between peripheral leukocytes telomere length (PLTL) and the risk of cutaneous melanoma and non-melanoma skin cancer (NMSC).

We calculated summary relative risks (SRR) and 95% confidence intervals (95%CI) using random effect models with maximum likelihood estimates, and explored causes of between-studies heterogeneity of risk estimates.

We included 1629 cutaneous melanoma and 1439 NMSC from eight independent studies published until March 2015. The SRR of cutaneous melanoma for those in the lowest (vs. highest) category of PLTL distribution was 0.25 (95% CI 0.09–0.67). The results were less clear for NMSC, with two studies reporting no association and one study showing an increase in risk for those in the lowest (vs. highest) category of PLTL distribution. For both cutaneous melanoma and NMSC, the between-studies heterogeneity was large, mainly due to inclusion of hospital-based case-control studies.

Our meta-analysis shows evidence of an association between short PLTL and reduced risk for cutaneous melanoma.

Contents

Abbreviations: NMSC, non-melanoma skin cancer; BCC, basal cell cancer; SCC, squamous cell cancer; UV, ultraviolet; PLTL, peripheral leukocyte telomere length; RR, relative risk; OR, odds ratio; CI, confidence intervals; SRR, summary relative risk.

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1. Introduction

The incidence of cutaneous melanoma has been increasing for several decades in Europe and among populations of European descent in Northern America and Australia, and it ranks ninth among the most incident malignancies in Europe, with an estimated incidence rate of 11.1/100,000 person-years [1]. Non melanoma skin cancers (NMSC) (including basal cell carcinoma [BCC] and squamous cell carcinoma [SCC]) are the most common malignancies in fair-skinned populations and, despite their case-fatality is low, they represent an increasing challenge for health-care systems worldwide [2].

The transition from normal skin cells (melanocytes and keratinocytes) to cancer is caused by somatic mutations (mostly caused by exposure to ultraviolet [UV] radiation) of several genes implicated in cell replication, apoptosis and DNA repair [3–4]. Recently, much attention has been paid to the role of telomeres and telomere-maintaining genes in the pathogenesis of skin tumours. Telomeres are tandemly repeated DNA sequences (TTAGGG)n located at the end of chromosomes that help maintain genome integrity by protecting the chromosomes from degradation and end-to-end fusion with neighbouring chromosomes. In somatic cells, human telomeres shorten by 30–200 base pairs with each cell replication, therefore telomere length reflects the number of divisions a cell has undergone. When reaching a critically short length, telomeres induce cellular senescence and eventually apoptosis [5]. In germline cells instead, telomeres are replenished after each cellular division by an enzyme complex known as telomerase [6].

Previous studies have shown that shortened telomere length as measured in peripheral blood leukocytes correlates with the incidence of major chronic diseases, like cancer at several sites [7], cardiovascular disease [8] and diabetes [9], and with overall mortality as well [10–11]. Although the mechanisms underlying these associations are yet to be fully elucidated, a shortened peripheral leukocytes telomere length (PLTL) is commonly seen as a marker of biological ageing and risk of age-related diseases. However, this tells only a part of the story, because the risk of some cancerous [12–14] and non-cancerous [15–16] diseases is associated with longer, instead of shorter, PLTL. Clearly, there are multiple pathways linking telomere dynamics and human health.

There is much evidence supporting the role of telomere length in the pathogenesis of skin cancer. The incidence of skin cancer is increased following mutations in genes implicated in the maintenance of telomeres integrity [17–19] and among patients suffering from telomere-related genetic syndromes [20]. Moreover, telomere length is positively associated with nevus count [21], which is a major indicator of skin cancer risk [22–23]. Finally, telomerase activation is frequent in both cutaneous melanoma and NMSC, while it is a rare event in sun-protected skin and benign proliferative skin lesions [24–25].

Over the last few years, several papers investigated the association between PLTL and skin cancer risk, but the results are not consistent. Here, we present the results of a systematic review and meta-analysis of published papers on the association between PLTL and the risk of cutaneous melanoma and NMSC.

2. Materials and methods

2.1. Literature search and data extraction

We planned and conducted the literature search and analysis of data according to MOOSE guidelines for meta-analysis of observational studies [26]. We searched the following database: PUBMED, Ovid Medline, EMBASE, Google Scholar and ISI Web of Knowledge, to identify papers published until March 31st, 2015, that reported on the association between PLTL and the risk of cutaneous melanoma or NMSC. The literature search was conducted by using any combination between the term "telomere" and one of the following MESH terms denoting a malignancy of the skin: melanoma, basal cell (or basocellular) cancer (or carcinoma), squamous cell (or squamocellular) cancer (or carcinoma), non-melanoma skin cancer, skin cancer. Extracutaneous melanoma (like mucosal and ocular melanoma) and malignancies of the skin other than melanoma and NMSC (like lymphoma of the skin) were not considered as outcomes of interest in this meta-analysis.

We read the abstract of all retrieved papers and obtained the full copy of those that were considered as potentially eligible for this meta-analysis. The reference list of all papers obtained in full copy (including those that were eventually not used in the analysis) was checked to find additional eligible papers. Two authors (SC and SG) independently evaluated the eligibility of all papers; conflicts were solved by consensus.

To be eligible for inclusion, a paper must present a measure of relative risk (RR) (this includes risk ratio, incidence rate ratio, odds ratio [OR], hazard ratio and standardized incidence ratio) for the association between PLTL and a malignancy of the skin, along with its 95% confidence intervals (95% CI) or another measure of statistical uncertainty (like the standard error, variance or exact *p*-values). Studies with cohort, case-control, nested case-control or case-cohort design were eligible for inclusion; instead, we excluded ecological studies, case reports, reviews, meta-analysis and editorials. We applied no time or language restrictions.

We extracted from each paper the RR and 95% CI for the comparison of skin cancer risk among those in the lowest vs. highest (or vice versa) category of PLTL distribution, or (if not available) the RR and 95% CI for the change in skin cancer risk associated with a fixed increase (or decrease) in PLTL. When a measure of RR for a given association was available from two or more non-independent papers (i.e., reporting results of studies with partially or totally overlapping study samples), we only considered that based on the highest number of cases or, in case of equal sample size, the most adjusted one, and discarded the others. The following information was also extracted from all eligible papers: country of the study, year of publication, study design, source and sex and age distribution of cases and controls (non-cases for cohort studies), sample size, distribution of melanoma cases in terms of histotype (superficial spreading, nodular, other) and body site (trunk, limbs, head and neck, other), matched design and variables used for matching, methods to assess PLTL, statistical methods and variables used to adjust the risk estimate.

2.1.1. Statistical analysis

The measures of RR for the comparison of skin cancer risk among those in the lowest vs. highest category of PLTL distribution