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Cigarette smoking and telomere length: A systematic review of 84 studies and meta-analysis

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ABSTRACT

Background: Cigarette smoking is a risk factor for ageing-related disease, but its association with biological ageing, indicated by telomere length, is unclear.

Methods: We systematically reviewed evidence evaluating association between smoking status and telomere length. Searches were performed in MEDLINE (Ovid) and EMBASE (Ovid) databases, combining variation of keywords "smoking" and "telomere". Data was extracted for study characteristics and estimates for association between smoking and telomere length. Quality of studies was assessed with a risk of bias score, and publication bias was assessed with a funnel plot. I^2 test was used to observe heterogeneity. Meta-analysis was carried out to compare mean difference in telomere length by smoking status, and a dose-response approach was carried out for pack-years of smoking and telomere length. A sensitivity analysis was carried out to examine sources of heterogeneity.

Results: A total of 84 studies were included in the review, and 30 among them were included in our meta-analysis. Potential bias was addressed in half of included studies, and there was little evidence of small study bias. Telomere length was shorter among ever smokers compared to never smokers (summary standard mean difference [SMD]: −0.11 (95% CI −0.16 to −0.07)). Similarly, shorter telomere length was found among smokers compared to non-smokers, and among current smokers compared to never or former smokers. Dose-response meta-analysis suggested an inverse trend between pack-years of smoking and telomere length. However, heterogeneity among some analyses was observed.

Conclusion: Shorter telomeres among ever smokers compared to those who never smoked may imply mechanisms linking tobacco smoke exposure to ageing-related disease.

1. Introduction

Telomeres are ribonucleoprotein structures at the end of linear chromosomes essential for maintaining genome stability (Blackburn, 2001; Cech, 2008; O'Sullivan and Karlseder, 2010). Consisting of tandem arrays of TTAGGG sequence, telomeres serve as dispensable DNA sequences that shield genomic DNA from inevitable shortening during replication (Lingner et al., 1995). In addition, the special cap structure at the end of telomeric repeats, formed by 3' G-strand overhang and telomere associated binding proteins, prevent recognition of the linear chromosome ends as DNA double strand break by the DNA repair machinery that may result in chromosome fusions (Griffith et al., 1999; Longhese, 2008; Van Steensel et al., 1998; Verdun and Karlseder, 2007).

Human telomeres shorten with each cell division and as telomeres become critically short, cells will cease proliferating and become senescent. As such, telomere length has long been considered as a marker of cellular aging (Bernadotte et al., 2016; Fyhrquist et al., 2011; Kuilman et al., 2010). In addition to genetic factor (Broer et al., 2013), environmental influences play an important role in determining telomere length (Huda et al., 2007; Starkweather et al., 2014). Tobacco smoking is a well-known health risk factor and exposure to harmful

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chemicals in cigarettes may induce oxidative stress and irreparable damage to the telomeric DNA (Alexandrov et al., 2006, 2016; Asami et al., 1996; d'Adda di Fagagna et al., 2003; Opresko et al., 2005; Von Zglinicki, 2002). Despite this biological link, there have been inconsistencies in the literature regarding association between telomere length and smoking, with some studies showing shorter telomeres with smoking (Mirabello et al., 2009; Revesz et al., 2015) whereas a lack of association was reported in other studies (Brouilette et al., 2003; Harris et al., 2012). We therefore performed this systematic review and meta-analysis to determine whether combined evidence supports association between telomere length and smoking.

2. Methods

2.1. Search strategy

The meta-analysis was conducted according to the MOOSE (Stroup et al., 2000) And PRISMA guidelines (Moher et al., 2009). MEDLINE (Ovid) and EMBASE (Ovid) databases were searched from their inception to 29 April 2016, with the final search performed on 02/05/2016. We applied a search strategy as follows: (smoking OR cigarette*) AND (telomere OR telomeres) as free text. Searches were limited to studies conducted in humans. No language restriction was applied. References from eligible studies were hand-searched for additional studies. Two investigators independently identified eligible studies, and any discrepancies were resolved by consensus with a third investigator. There was no prior review protocol published for this study.

2.2. Inclusion criteria

We included studies that investigated an association between cigarette smoking status (including smoking status e.g. smokers, former smokers and never smokers and smoking intensity) and telomere length in humans, in which smoking status and telomere length were measured in the same subjects. Studies were either cross-sectional, cohort, or case-control studies in humans. We included studies in which smoking or telomere length was used as an adjustment variable if individual estimates of association between smoking and telomere length were available.

2.3. Exclusion criteria

Duplicated publications or additional studies of already included studies were excluded. We also excluded studies which did not fulfil any inclusion criteria, for instance, those which did not provide estimates for association between smoking and telomere length.

2.4. Data extraction

Data from eligible studies were independently extracted using a standard form. The following information was collected: first author, year of publication, type of study, description of study population (age, sex, race, country of study), method of telomere length measurement, source of sample used, description of smoking exposure assessment, sample size, comparison method, main results including maximally adjusted effect size and standard error or confidence intervals, any adjustment variables, and any other relevant information.

When information was available in the included studies, estimates for the following comparisons were collected: 1) current smokers and non-smokers, the latter of which consisted of former and never smokers, 2) ever smokers, which included both current and former smokers, and never smokers, 3) current smokers and former smokers, 3) current smokers and never smokers, 4) former smokers and never smokers, 5) smoking intensity, expressed as pack-years of cigarette, defined a product of packs of cigarettes smoked per day and smoking duration in years (Müezzinler et al., 2015), 6) levels of cotinine, a metabolite of nicotine (Block et al., 2006). When multiple measurements were available, we collected smoking status and telomere length measured at the same time, or closest to each other.

For studies which only reported estimates for categories e.g. quartiles of pack-year of cigarettes, we assigned interval scores of categories from the original studies based on medians or means when available. Category midranges were applied for the remaining closed-ended categories. For upper open-ended categories with b_i as the lower bound of the ith interval and the intervals indexed by $i = 1,\ldots,n$, interval scores were assigned as $b_n + 0.5\ (b_n - b_{n-1})$ (Greenland and Longnecker, 1992; Il'yasova et al., 2005). Correspondingly, interval scores for the lower open-ended categories were assigned as $b_2 - 0.5\ (b_2 - b_1)$.

2.5. Assessment of quality of included studies

Although quantitative scores have been used for meta-analysis of observational studies (Mundstock et al., 2015), interpretation could be challenging. We adapted assessment criteria from items in Critical Appraisal Skills Programme (CASP) questionnaires (Critical Appraisal Skills Programme, 2017) to assess cohort and case-control studies and use these criteria to assess included studies: (i) Did the study address a clearly focused issue? (ii) Did the authors use an appropriate method to answer their question? (iii) Was the exposure accurately measured to minimise bias? (iv) Was the outcome accurately measured to minimise bias? (v) Have they taken account of important confounding factors in the design and/or analysis? (vi) Do the results fit with other available evidence? Each item was answered with 'Yes', 'No' or 'Don't know', according to information presented in the publications.

2.6. Assessment of publication bias

Assessment for publication bias was carried out by assessing funnel plot asymmetry for comparisons including at least 10 studies (Sterne et al., 2011). Data points were derived from estimates and standard errors from individual studies in relation to the pooled estimate effect. Asymmetrical distribution of data points for smaller studies (those with wider standard errors) indicates small study effects, which may be caused by publication bias. In addition to visual inspection of the funnel plot, we also conducted Egger's test, which applies weighted linear regression analysis to test for funnel plot asymmetry. A p-value of < 0.1 was considered to represent significant asymmetry (Egger et al., 1997). Where asymmetry was indicated, sensitivity analysis was performed to seek potential sources of asymmetry.

2.7. Assessment of heterogeneity

The studies were evaluated clinically and methodologically to assess if it was reasonable to consider combining data. Statistical heterogeneity was measured by the visual inspection of the forest plots and statistically through an assessment of homogeneity based on the Chi^2 test (Higgins and Greenland, 2011). The I^2 measurement was calculated as an indicator of the amount of statistical variation not attributable to sampling error. A value of more than 75% was considered to represent high heterogeneity (Higgins et al., 2003).

2.8. Meta-analysis

A random effects meta-analysis was performed to obtain pooled results for each aforementioned comparison. Because different methods were used to assess telomere length, a standardised mean difference (SMD) approach was applied in the analysis. Summary results were obtained from final values and their variance in individual studies. A sensitivity analysis was performed by excluding studies one at a time. Where difference in means were presented for categories of exposure, e.g. for pack-year of smoking, we performed a two-stage meta-analysis approach (Crippa and Orsini, 2016). First, a dose-response model was