



A prospective study of leukocyte telomere length and risk of phobic anxiety among women

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ABSTRACT

We prospectively examined the relation of relative telomere lengths (RTLs), a marker of biological aging, to phobic anxiety in later-life. RTLs in peripheral blood leukocytes were measured among 3194 women in the Nurses' Health Study who provided blood samples in 1989/90. The Crown-Crisp Phobic Index (CCI, range=0–16) was assessed in 1988 and 2004. Only participants with CCI ≤ 3 (consistent with no meaningful anxiety symptoms) in 1988 were included. We related baseline RTLs to odds ratios (ORs) of incident high phobic anxiety symptoms (CCI ≥ 6). To enhance clinical relevance, we used finite mixture modeling (FMM) to relate baseline RTLs to latent classes of CCI in 2004. RTLs were not significantly associated with high phobic anxiety symptoms after 16 years of follow-up. However, FMM identified 3 groups of phobic symptoms in later-life: severe, minimal/intermediate, and non-anxious. The severe group had non-significantly shorter multivariable-adjusted mean RTLs than the minimal/intermediate and non-anxious groups. Women with shorter telomeres vs. longest telomeres had non-significantly higher likelihood of being in the severe vs. non-anxious group. Overall, there was no significant association between RTLs and incident phobic anxiety symptoms. Further work is required to explore potential connections of telomere length and emergence of severe phobic anxiety symptoms during later-life.

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1. Introduction

Anxiety disorders, the most common of psychiatric disorders in the U.S. population (Kessler et al., 2005), are associated with significant functional impairment and increased risk of morbidity (de Beurse et al., 1999; Lenze et al., 2001; Albert et al., 2005; Sareen et al., 2006; Roy-Byrne et al., 2008). According to the National Comorbidity Survey Replication, the U.S. lifetime prevalence of anxiety disorders is 28.8%, and the 12-month prevalence is 18.1% (Kessler and Wang, 2008). New onset of anxiety disorders primarily occurs among younger persons, and the median onset of anxiety disorders is in childhood/adolescence. Yet, anxiety

disorders can still emerge in later-life (Le Roux et al., 2005; Chou, 2009) and late-life onset of anxiety may be under-recognized (Jeste et al., 2005). Given that the etiology of incident late-life anxiety remains largely unknown, further work is needed to elucidate potential biological mechanisms and to determine whether processes intrinsic to biological aging may increase the risk of newly emergent anxiety in later-life. In recent years, a limited number of cross-sectional epidemiologic studies (Kananen et al., 2010; Okereke et al., 2012) observed that anxiety disorders and high anxiety symptoms, both likely indicators of chronic psychological distress, are associated with accelerated biological aging, as evidenced by shorter telomeres; however, not all studies have found an association between anxiety and telomere length (Surtees et al., 2011; Needham et al., 2015).

Existing epidemiologic studies (Kananen et al., 2010; Surtees et al., 2011; Okereke et al., 2012; Hoen et al., 2013; Shalev et al., 2014; Needham et al., 2015) have typically framed research

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questions from the standpoint of the potential impact of psychiatric disorders and symptoms, including anxiety, on telomere length. However, emerging basic science evidence demonstrates that mechanisms relevant to accelerated biological aging, such as higher oxidative stress, may increase the risk of anxiety disorders (Hovatta et al., 2005; Masood et al., 2008; Lee et al., 2010; Salim, 2014). Telomeres, repetitive TTAGGG sequences at the distal ends of linear chromosomes (Blasco, 2005), progressively shorten with each cell division in somatic cells, and eventually enter replicative senescence or undergo apoptosis (Harley et al., 1992; Blackburn, 2005). Oxidative stress and inflammation may accelerate telomere attrition (Harley et al., 1992; von Zglinicki, 2002; Epel et al., 2004; Blackburn, 2005; Cattani et al., 2008); thus, progressive telomere shortening represents a “molecular clock” that may serve as an indicator of biological aging. Recently, rodent models have demonstrated that increased oxidative stress may be involved in the pathogenesis of psychiatric symptoms, including anxiety (Hovatta et al., 2005; Masood et al., 2008; Ng et al., 2008; Rammal et al., 2008; Lee et al., 2010;); however, whether there may be similar effects in humans is unknown. Despite the compelling basic evidence relating oxidative stress to development of anxiety, the established connection of oxidative stress with abnormal telomere length and function, and preliminary cross-sectional associations of shorter telomeres and higher anxiety in humans (Kananen et al., 2010; Okereke et al., 2012), no epidemiological studies have yet addressed prospectively whether telomere length, an index of the process of accelerated biological aging, is independently associated with later-life emergence of anxiety.

Thus, in this study we examined the relation of relative telomere length (RTLs), measured among mid-life and older ages, to risk of incident phobic anxiety at later-life among 3194 participants of the Nurses' Health Study.

2. Methods

2.1. The Nurses' health study (NHS)

The NHS began in 1976 when 121,700 female nurses, aged 30 to 55 years and living in the U.S., completed an initial questionnaire. Subsequent questionnaires have been mailed every two years to collect information on a wide variety of lifestyle and health factors. Total follow-up in the NHS is $\geq 90\%$. Further details on the NHS cohort and validation of various risk factor and outcome measures have been described previously (Colditz et al., 1986). Blood samples, along with information from a supplementary questionnaire, were collected from 32,826 women in 1989–1990. Methods for blood collection have been described elsewhere (Hankinson et al., 1995). For the current analysis, we used RTLs measured among controls from prior nested case-control studies of: endometrial, ovarian, breast, pancreatic, and colon cancer; colon polyps; basal and squamous cell carcinoma; melanoma; stroke; myocardial infarction; and rheumatoid arthritis (Han et al., 2008; De Vivo et al., 2009; Prescott et al., 2010; Nan et al., 2011). RTLs that were assayed from a random sample of healthy participants aged ≥ 70 years and with no history of stroke as part of the NHS cognitive function sub-study were also included (Devore et al., 2011). The current study was approved by the Human Research Committee at Brigham and Women's Hospital, Boston, MA, USA.

2.2. Assessment of relative telomere length

Using the blood samples collected in 1989–1990, genomic DNA was extracted from peripheral blood leukocytes with the QiAmp (Qiagen Inc., Valencia, CA) 96-spin protocol. RTL was measured using quantitative polymerase chain reaction (qPCR) (Cawthon,

2002; Wang et al., 2008). Each sample was assayed in triplicate by laboratory technicians who were masked to participant characteristics; variability was assessed with inclusion of quality control samples on each plate. RTL was calculated as the exponentiated ratio of telomere repeat copy number to single gene (36B4) copy number (T/S) (Livak and Schmittgen, 2001; Cawthon, 2002; Du et al., 2013). In our hands, coefficients of variation (CVs) for the telomere and single gene assay were $< 4\%$, and CVs for the exponentiated T/S ratio were $\leq 18\%$. Although this assay measures relative telomere length, in work by Cawthon (Cawthon, 2002), the T/S ratio correlates well with absolute telomere length provided by Southern blot ($r=0.82$, $p < 0.0001$).

2.3. Assessment of phobic anxiety

Symptoms of phobic anxiety were assessed with the Crown-Crisp Index (CCI) in 1988 and 2004. The CCI contains 8 questions that assess fear and desire for avoidance (Crown and Crisp, 1966). Each item has 2–3 levels of possible responses, yielding a sum score of responses on all items that ranges from 0 to 16 points; higher scores indicate greater phobic anxiety. If women were missing 1–2 items on the CCI, we computed the sum score based on non-missing responses (i.e., we did not generate scores by imputing missing responses to the mean), as this is a more conservative approach used in our prior work (Okereke et al., 2012). We did not calculate the sum score for women who were missing > 2 items from CCI assessed in 1988 or 2004 (Kroenke et al., 2010; Okereke et al., 2012). The CCI has been validated in psychiatric outpatient clinics and has been shown to have good discrimination (Crown and Crisp, 1966; Burgess et al., 1987). Previous analyses (Okereke et al., 2012) in the NHS have found that the CCI is reliable within this cohort and has moderate internal consistency (Cronbach coefficient alpha for CCI in 1988=0.62) comparable to that originally reported by Crown and Crisp (Crown and Crisp, 1966) among a clinical sample (Cronbach coefficient alpha=0.69).

2.4. Assessment of covariates

Information on covariates was obtained using the supplementary questionnaire completed at the time of blood collection or the most proximal cohort questionnaire (i.e., the 1988–1990 questionnaire cycle). We ascertained information on a variety of *a priori* potential confounding factors that have been related to anxiety and/or telomeres in previous literature: age (in years) (Kananen et al., 2010), educational attainment (Regier et al., 1990; Steptoe et al., 2011), race (Breslau et al., 2006; Needham et al., 2013), physical activity (in MET-hours/week) (Goodwin, 2003; Du et al., 2012), cigarette smoking (pack-years) (Cuijpers et al., 2007; Du et al., 2012), body mass index (BMI) (kg/m^2) (Petty et al., 2008; Du et al., 2012), and paternal age-at-participant's birth (Prescott et al., 2012). Antidepressant use at blood draw was collected as a proxy for history of clinical depression. Furthermore, we considered demographic factors, including spouse/partner's education, and employment status; lifestyle factors, such as alcohol intake (grams/day); medical comorbidities (diabetes, hypertension, high cholesterol, cancer, and chronic respiratory disease); and medication use (e.g., regular use of hormones and multivitamins) to help further address potential sources of confounding by socioeconomic/socio-demographic, lifestyle, and/or other health factors.

2.5. Determination of sample for analysis

There were 5808 women who provided blood samples as controls in the previous nested case-control studies or healthy participants in the cognitive function sub-study. We performed a

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