

## Shorter Telomeres Associate with a Reduced Risk of Melanoma Development

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### Abstract

Epidemiologic studies have linked shortened telomeres with the development of many cancers. However, recent studies have suggested that longer telomeres may lead to prolonged senescence in melanocytes, providing increased opportunity for malignant transformation. We therefore examined whether shorter prediagnostically measured relative telomere length in peripheral blood leukocytes (PBL) was associated with a decreased risk of cutaneous melanoma. Telomere length in prospectively collected PBLs was measured in incident melanoma cases and age-matched controls selected from participants in three large prospective cohorts: the Women's Health Initiative Observational Study (WHI-OS), the Health Professionals Follow-up Study (HPFS), and the Nurses' Health Study (NHS). Shorter telomere lengths were associated with decreased risk of melanoma in each cohort. The  $P_{\text{trend}}$  across quartiles was 0.03 in the WHI-OS and 0.008 in the HPFS. When combining these two datasets with published data in the NHS ( $P_{\text{trend}}$ , 0.09), compared with individuals in the fourth quartile (the longest telomere lengths), those in the first quartile had an OR of 0.43 (95% CI: 0.28–0.68;  $P_{\text{trend}}$ , 0.0003). Unlike findings for other tumors, shorter telomeres were significantly associated with a decreased risk of melanoma in this study, suggesting a unique role of telomeres in melanoma development. *Cancer Res*; 71(21); 6758–6763. ©2011 AACR.

### Introduction

Telomeres are long hexameric (TTAGGG)<sub>n</sub> repeats capping both ends of linear eukaryotic chromosomes. They play a critical role in maintaining genomic stability by preventing fusion of chromosomal ends, nucleolytic decay, end-to-end fusion, and atypical recombination (1). Human telomeres shorten by 30 to 200 base pairs after each cycle of mitotic division and have been likened to a "molecular clock" reflecting the number of divisions a cell has undergone (2). Epidemiologic

studies have observed links between shortened telomere length in peripheral blood leukocytes (PBL) and the development of many cancers, such as bladder, gastric, and renal cancers (3–6). However, telomere shortening has been implicated in several aspects of tumorigenesis, including senescence, apoptosis, and genomic instability (7–9). Hence, depending on the distinct proliferative features of different cell types, telomere shortening may play roles in both suppressing and facilitating carcinogenesis (10).

Cutaneous melanoma is the most serious form of skin cancer and accounts for 74% of all deaths from skin cancer (11). Melanoma arises from the malignant transformation of melanocytes, which reside in the basal layer of the epidermis (12). Melanocytes are characterized by low levels of proliferation and have a limited capacity to undergo apoptosis (13). Instead, melanocytes are more likely to undergo senescence in response to oncogenic stress, which allows them to remain functional while preventing propagation of the oncogenic mutation (13). Longer telomeres in melanocytes that already have oncogenic mutations (activating BRAF and silenced/deleted p16) may delay senescence, allowing these cells to acquire additional mutations and increasing the probability of malignant transformation. Prolonged senescence leads to the increased formation of nevi (14–15), which are strongly associated with increased risk of melanoma (16–17).

To evaluate whether shorter telomeres are associated with a decreased risk of melanoma, we conducted a prospective study nested within 3 large cohorts: the Women's Health Initiative Observational Study (WHI-OS), the Health Professionals Follow-up Study (HPFS), and the Nurses' Health Study (NHS),

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to examine the relation between prediagnostically measured telomere lengths in PBLs and risk of incident melanoma.

## Materials and Methods

### Study population

The study population consisted of 557 melanoma cases and 579 controls selected from individuals who had previously provided a blood sample in 3 large prospective cohorts: the WHI-OS (233 female cases and 237 female controls), the HPFS (120 male cases and 120 male controls), and the NHS (204 female cases and 222 female controls, published previously; ref. 18). Detailed descriptions of these 3 cohorts, blood collection protocols, and selection of cases and controls are presented in Supplementary Information. Briefly, we used blood collection time as the baseline for follow-up. Incident melanoma cases and matched controls (on age,  $\pm 1$  year) were selected from each cohort for up to 15 years of follow-up in WHI-OS, 13 years in HPFS, and 11 years in NHS. Only pathologically confirmed melanoma cases diagnosed after blood collection were included in this study. All cases and controls were free of previously diagnosed cancer and were of self-reported European ancestry. The study protocol was approved by the Committee on Use of Human Subjects of Brigham and Women's Hospital, Boston, MA in accordance with an assurance filed and approved by the Department of Health and Human Services, and written informed consent was obtained from all participants.

### Telomere length measurement

Details of the measurement method for relative telomere length are described in Supplementary Information. Briefly, we assessed relative telomere length of PBL DNA using a modified quantitative PCR assay, which determines the Telomere repeat copy number to Single-copy gene (*36B4*) copy number (T/S) ratio, a value proportional to the average telomere length (19). All samples for both the telomere and single-copy gene (*36B4*) reactions were done in triplicate on different plates. In addition to the samples, each 384-well plate contained a 6-point standard curve from 1.25 ng to 20 ng using pooled buffy coat-derived genomic DNA. The purpose of the standard curve was to assess and compensate for inter-plate variations in PCR efficiency. The slope of the standard curve for both the telomere and *36B4* reactions was  $-3.65 \pm 0.11$ , and acceptable linear correlation coefficient ( $r^2$ ) values for both reactions was 0.99. The T/S ratio ( $-dC_t$ ) for each sample was calculated by subtracting the average *36B4*  $C_t$  value from the average telomere threshold cycle ( $C_t$ ) value. The relative T/S ratio ( $-ddC_t$ ) was determined by subtracting the T/S ratio of the 5 ng standard curve point from the T/S ratio of each unknown sample. Relative telomere lengths were reported as the exponentiated relative T/S ratio.

Blinded quality control (QC) samples were interspersed throughout the dataset to assess variability of  $C_t$  values. These quality controls were duplicated samples. From 11 pairs of duplicate samples, the intraclass correlation coefficient (ICC) for the telomere assay was 0.83 [95% confidence interval (CI): 0.65–0.93], and that for the *36B4* single-gene assay was 0.79 (95% CI: 0.59–0.91).

### Statistical analyses

We examined separately the association between telomere length and melanoma risk in the WHI-OS and the HPFS, followed by combined analyses of the WHI-OS, HPFS, and NHS to increase statistical power. We categorized the participants into quartiles based on the relative telomere length distribution in each cohort-specific control population; the fourth quartile (i.e., those with the longest telomere lengths), served as the reference group. We used conditional logistic regression to calculate odds ratios (OR) and 95% CIs. Tests for trend were conducted by assigning the cohort-specific median value of each quartile of telomere length among controls to both cases and controls in each category and modeling it as a continuous variable. Before combining the data, we assessed for heterogeneity between the results across the 3 cohorts by conducting a likelihood ratio test comparing nested models with and without interaction terms between cohort (modeled categorically) and telomere length (modeled continuously). For the combined analysis, data were pooled and individuals (cases and controls) in the same quartile of telomere length in each cohort were grouped together. To conduct tests for trend in the combined analysis, the weighted median value for each quartile was calculated by weighting cohort-specific medians by the proportion of observations in each cohort, among controls only.

To determine whether the association between telomere length and melanoma risk differed by tanning ability, hair color, and mole count, we conducted likelihood ratio tests comparing nested models with and without interaction terms between telomere length and these variables. We modeled tanning ability, hair color, and mole count as ordinal variables and telomere length continuously. The  $P$  values were 2-sided;  $P < 0.05$  were considered statistically significant. We used SAS Version 9.1 software (SAS Institute Inc.).

## Results

### Descriptive characteristics of the study population

Basic characteristics of cases and controls in the 3 cohorts are presented in Table 1. The mean ages at diagnosis of incident melanoma cases in the WHI-OS, HPFS, and NHS were 68.2, 65.3, and 63.6 years, respectively. This was later than the age of diagnosis in the general U.S. population (60 years; ref. 20), and was likely because participants included in this study were near 60 years and free of diagnosed melanoma at the start of follow-up. The childhood tanning ability of cases was less than that of controls across the 3 cohorts. In the HPFS and NHS, melanoma cases were more likely to have red or blonde hair compared with controls. In addition, melanoma cases tended to have a higher mole count on the arms than controls.

### Telomere length and risk of incident melanoma

The results for the association between telomere length and the risk of melanoma are presented in Table 2. In the separate analyses, shorter telomere lengths were associated with a decreased risk of melanoma in both the WHI-OS ( $P_{\text{trend}}$ , 0.03) and the HPFS ( $P_{\text{trend}}$ , 0.008). These results were consistent with the nonsignificant association previously reported among

**Table 1.** Characteristics of melanoma cases and controls in each cohort

Characteristic	WHI-OS (females)		HPFS (males)		NHS (females)	
	Cases (n = 233)	Controls (n = 237)	Cases (n = 120)	Controls (n = 120)	Cases (n = 204)	Controls (n = 222)
Age at diagnosis, mean (SD)	68.2 (7.3)	NA	65.3 (9.5)	NA	63.6 (7.5)	NA
Age at blood draw, mean (SD)	63.8 (6.8)	63.9 (7.0)	59.9 (9.1)	59.9 (9.0)	57.5 (7.1)	57.8 (7.0)
Red or blonde hair color (%) <sup>a</sup>	NA	NA	21.3	12.2	23	11.2
Tanning ability, tan without burn (%)	17.8	26.4	14.9	30.2	17.4	24.8
Mole count on the arms, 3+ (%) <sup>a</sup>	NA	NA	27.7	9.4	23.9	8.8

<sup>a</sup>The information on hair color and mole count was not available in the WHI-OS.  
NA: not applicable (age at diagnosis) or not available (hair color and mole count).

204 melanoma cases and 222 controls in the NHS conducted by our group, as shown in Table 2 for the purpose of comparison ( $P_{\text{trend}}$ , 0.09; ref. 18). The association between telomere length and melanoma risk did not statistically differ across the three cohorts ( $P_{\text{interaction}}$ , 0.75). In the combined analysis of all three cohorts, compared with individuals in the fourth quartile, those in the first quartile had an OR of 0.43 (95% CI, 0.28–0.68;  $P_{\text{trend}}$ , 0.0003). This result remained essentially the same after adjusting for melanoma risk factors (OR = 0.43; 95% CI: 0.27–0.70 for first vs. fourth quartile;  $P_{\text{trend}}$ , 0.0009). To rule out the influence of preclinical disease from cases diagnosed soon after blood collection, we conducted a sensitivity analysis excluding cases diagnosed within the first 2 years of blood collection, and the results remained similar in 486 cases and

467 controls [OR (95% CI), 0.44 (0.27–0.72) for first vs. fourth quartile]. We did not observe effect modification of the association between telomere length and melanoma risk by tanning ability ( $P_{\text{interaction}}$ , 0.10), mole count ( $P_{\text{interaction}}$ , 0.07), or hair color ( $P_{\text{interaction}}$ , 0.46). In addition, there was no appreciable difference in the results by age at diagnosis (first vs. fourth quartile; OR = 0.51 (95% CI: 0.26–0.99) for 65 years or older; OR = 0.38 (95% CI: 0.20–0.72) for more than 65 years).

## Discussion

The observed positive association between relative telomere lengths and melanoma risk contrasts with the inverse associations previously reported for basal cell carcinoma of the skin

**Table 2.** OR and 95% CI of incident melanoma by relative telomere length

	4 <sup>th</sup> quartile <sup>a</sup>	3 <sup>rd</sup> quartile	2 <sup>nd</sup> quartile	1 <sup>st</sup> quartile	$P_{\text{trend}}$
<b>WHI-OS (females)</b>					
Cases (%)	58 (24.9)	76 (32.6)	60 (25.8)	39 (16.7)	
Controls (%)	59 (25.0)	59 (25.0)	60 (25.0)	59 (25.0)	
OR (95% CI)	1.00	1.14 (0.62–2.11)	0.77 (0.39–1.53)	0.40 (0.18–0.88)	0.03
<b>HPFS (males)</b>					
Cases (%)	41 (34.2)	31 (25.8)	28 (23.3)	20 (16.7)	
Controls (%)	28 (23.3)	33 (27.5)	27 (22.5)	32 (26.7)	
OR (95% CI)	1.00	0.49 (0.21–1.12)	0.47 (0.20–1.12)	0.18 (0.06–0.56)	0.008
<b>NHS<sup>c</sup> (females)</b>					
Cases (%)	63 (30.9)	49 (24.0)	44 (21.6)	48 (23.5)	
Controls (%)	55 (24.8)	54 (24.3)	58 (26.1)	55 (24.8)	
OR (95% CI)	1.00	0.76 (0.43–1.34)	0.54 (0.29–1.01)	0.59 (0.31–1.13)	0.09
<b>Combined study of WHI-OS, HPFS, and NHS</b>					
Cases (%)	162 (29.1)	156 (28.0)	132 (23.7)	107 (19.2)	
Controls (%)	142 (24.5)	146 (25.2)	145 (25.0)	146 (25.2)	
OR (95% CI)	1.00	0.84 (0.58–1.21)	0.62 (0.41–0.93)	0.43 (0.28–0.68)	0.0003
Multivariate OR (95% CI) <sup>b</sup>	1.00	0.84 (0.57–1.24)	0.60 (0.39–0.94)	0.43 (0.27–0.70)	0.0009

<sup>a</sup>Longest relative telomere length group.

<sup>b</sup>Conditional logistic regression adjusting for hair color, tanning ability, and the number of moles on arms.

<sup>c</sup>NHS results were published previously (18).

and other tumors (3–6, 18). Recently, a germline genetic variant rs401681[C] near telomere reverse transcriptase (*TERT*), a gene responsible for telomere maintenance, was associated with decreased risk of melanoma, but with increased risk of basal cell carcinoma of the skin and other tumors at various sites (lung, bladder, prostate, and cervical cancer; refs. 21, 22). Consistent with this finding, our data suggest that the role of telomere biology in melanoma pathogenesis differ from that in other tumors.

One potential mechanism underlying this difference is that shorter telomere lengths protect against the malignant transformation of cells within melanocytic nevi by limiting proliferative capacity and triggering the entry to senescence stage. Recent studies have shown that senescence provides a unique barrier to the progression of melanoma (23). Senescence is tightly controlled, induced by telomere shortening, and seems to be regulated in melanocytes in a manner that differs at least partially from other studied cell types (15, 24).

Melanocytic nevi (moles) are considered a potential precursor of melanoma, and a relatively high number of nevi on the body is a well-known risk factor (17, 25). Supporting the above mechanism and our melanoma association results, a previous study reported a positive correlation between PBL telomere lengths and total body nevus counts in 1,897 Caucasian women aged 18 to 79 years (age-adjusted *P* value, 0.0001; ref. 26). Consistent with those findings, in our previous study, shorter telomeres in PBLs were associated with fewer moles on the arms in 870 controls (age-adjusted *P* value, 0.003; ref. 18). Our results on telomere length and melanoma risk remained essentially unchanged after adjusting for mole count, and other risk factors, suggesting that telomere shortening may help prevent melanoma development by reducing the malignant transformation of cells within melanocytic nevi, rather than by decreasing nevus count.

Similar to our findings for melanoma, unlike other chronic diseases (3, 27–30), shorter telomeres have been associated with decreased risk of Parkinson's disease. A nested case-control study of 96 cases and 172 age-matched controls within the HPFS suggested that men with shorter telomeres had a lower risk of Parkinson's disease (multivariate adjusted RR for the lowest vs. the highest quartile 0.33; 95% CI: 0.12–0.90; ref. 31). Emerging evidence suggests a potential link between Parkinson's disease and melanoma. Studies have observed a decreased risk of cancer among Parkinson's disease patients, with the important exception of melanoma (32–33). Melanoma and Parkinson's disease share similar host susceptibility risk factors, such as red hair color and family history of melanoma (34–35). Unlike other chronic diseases, cigarette smoking and rotating nightshift work are both associated with a lower risk of both diseases (36–39). Melanocytes are derived from a single group of neural crest cells, and we speculate that dopamine-containing nerve cells and melanocytes may share unique molecular mechanisms that defend against cellular damage and stress.

A potential limitation of this study is that relative telomere lengths were not directly measured in DNA extracted from skin tissue. However, telomere length in PBLs has been significantly correlated with that in skin tissues ( $r^2$ , 0.71; *P*, 0.018), indicating

that telomere length in PBLs could serve as a surrogate marker (40). As telomere length may uniquely influence progression toward malignancy in different cell types, a similar distribution of telomere lengths may not necessarily reflect similar telomere biology in melanocytes compared with other tissues.

In this study, PBL relative telomere length was measured using quantitative PCR, a widely used method in epidemiologic telomere research. Although this technique does not measure the absolute telomere length, as shown in previous studies, the T/S ratio obtained using quantitative PCR assay is highly reproducible and shows strong correlation with mean telomere restriction fragments as measured by traditional Southern blot, suggesting the reliability and validity of the quantitative PCR-based approach (19, 30, 41).

We identified a significant association between shorter relative telomere length and decreased risk of incident melanoma. Both men and women were included in this study, and this relationship should be generalizable to Caucasian populations. This finding provides novel insights supporting the notion that telomere-induced senescence may uniquely influence melanoma development.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

#### Authors' Contributions

H. Nan: data analysis, literature search, data interpretation, and manuscript writing. M. Du: data collection, literature search, data interpretation, and manuscript writing. I. De Vivo: data collection and manuscript revision. J.E. Manson: study design and manuscript writing. S. Liu: study design and manuscript revision. A. McTiernan: study design and manuscript revision. J.D. Curb: study design and manuscript revision. L. Lessin: study design and manuscript revision. M.R. Bonner: study design and manuscript revision. Q. Guo: data analysis and manuscript revision. A.A. Qureshi: data interpretation and manuscript revision. D.J. Hunter: data interpretation and manuscript revision. J. Han: literature search, tables, study design, data collection, data analysis, data interpretation, and manuscript writing.

#### WHI study Appendix

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