No Association between Telomere Length in Peripheral Blood Leukocytes and the Risk of Non-melanoma Skin Cancer

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Abstract

Background—Recent reports have shown that telomere length was associated with the risk of various cancers, but the results have been inconsistent.

Methods—We prospectively evaluated the association of telomere length in peripheral blood leukocytes with the risk of skin squamous cell carcinoma (SCC) in 241 cases and 241 controls within the Health Professionals Follow-up Study (HPFS), and the risk of skin basal cell carcinoma (BCC) in 623 cases and 1943 controls within the Nurses' Health Study (NHS).

Results—No significant association was observed between telomere length and risk of SCC (longest quartile vs. shortest quartile, odds ratio (OR) =1.09, 95% confidence interval (CI), 0.62–1.93, *P* trend=0.81). Null findings were also observed between telomere length and risk of BCC in two independent sets (OR=0.96, 95%CI, 0.49–1.87, *P* trend=0.83; and OR=0.91, 95%CI, 0.66–1.25, *P* trend=0.39).

Conclusion—We found no evidence that telomere length in peripheral blood leukocytes was associated with risk of non-melanoma skin cancer.

Impact—Our prospective study suggests that telomere length in peripheral blood leukocytes is less likely to play a substantial role in non-melanoma skin cancer development.

Keywords

skin cancer; telomere length

Introduction

Telomeres are long hexameric (TTAGGG)n repetitive structures capping the ends of eukaryotic chromosomes that protect against fusion and degradation of chromosomal ends

and help maintain structural integrity. Recent reports have suggested that telomere length plays an important role in cancer development (1–3). In our previous study, we found that telomere length in peripheral blood leukocytes may be associated with risk of skin cancer (4), the most common malignancy in the United States. To confirm and extend our observations, we prospectively evaluated the association between telomere length and risk of skin squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) within the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS).

Materials and Methods

Study population

HPFS nested case-control study of SCC—We conducted a nested case-control study within the HPFS, which was initiated in 1986 among 51,529 U.S. male professionals, aged 40–75 years at study entry. Between 1993 and 1994, 18,159 study participants provided blood samples. Eligible cases consisted of men with pathologically confirmed incident SCC from the subcohort who gave a blood sample, with a diagnosis after blood collection up to 2006. Participants who had cancer previously were excluded. For each case, one control was matched by age (±1 year) and was free of cancer up to and including the questionnaire cycle in which the case was diagnosed. In total, there are 241 Caucasian SCC cases and 241 matched Caucasian controls.

NHS nested case-control study of BCC 1—The NHS was established in 1976 among 121,700 female registered nurses between the ages of 30 and 55. Between 1989 and 1990, blood samples were collected from 32,826 of the cohort members. We have accrued 2,857 incident cases of BCC from the subcohort who had given a blood specimen, with a diagnosis between 1998 and 2008. We randomly selected a subset of BCC cases. Participants who had previously diagnosed cancer were excluded. One control was matched to each case by age (±1 year) and was free of cancer up to and including the questionnaire cycle in which the case was diagnosed. The nested case-control study consisted of 260 Caucasian BCC cases and 260 matched Caucasian controls.

NHS nested case-control study of BCC 2—In addition, we had telomere length measurements in several nested case-control studies within the NHS, including stroke, myocardial infarction, and endometrial cancer. We used all the controls from these studies. All cases were women diagnosed with BCC after blood collection and up to 2008 without personal history of other cancer. Controls were restricted to participants without a personal history of any cancer. We identified 363 Caucasian cases and 1683 Caucasian controls.

Information regarding skin cancer risk factors was obtained from the prospective biennial questionnaires. The study was approved by the Brigham and Women's Hospital Institutional Review Board for Human Subjects Research.

Telomere length detection—Genomic DNA was extracted from peripheral leukocytes using the QIAmp 96-spin blood protocol. The relative average telomere length was determined by a high-throughput 384-well Real-Time PCR assay with an Applied Biosystems 7900HT PCR System. The T/S ratio (−dCt) for each sample was calculated by subtracting the average 36B4 Ct value from the average telomere Ct value. The relative T/S ratio (−ddCt) was determined by subtracting the T/S ratio value of the 5ng standard curve point from the T/S ratio of each unknown sample. The blind quality-control samples were interspersed throughout the sets for assessing inter-plate and intra-plate variability. The coefficients of variation (CV) of the telomere Ct and 36B4 Ct were 2.97% and 1.76%, respectively.

Statistical analysis—In the HPFS nested case-control study of SCC and the first NHS nested case-control study of BCC, relative telomere length was categorized into quartiles according to the distribution in each study-specific control population. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to examine the relationship between relative telomere length and skin cancer by conditional logistic regression. In the second NHS nested case-control study of BCC, we calculated a z score in each set and pooled the z scores for further analysis. The z scores were categorized into quartiles according to the distribution among BCC controls. Unconditional logistic regression was employed to calculate OR and 95% CI. All statistical tests were two-sided.

Results

The characteristics of cases and controls in the SCC and BCC case-control study are presented in Table 1. Cases were more likely to have light pigmentary phenotypes, including lighter hair color and less tendency to tan. The association between relative telomere length and each type of skin cancer were examined separately (Table 2). No significant association was observed between telomere length and risk of SCC (*P* trend=0.81). Similar null findings were observed between telomere length and risk of BCC in both studies (*P* trend=0.83 and 0.39).

Discussion

Recent studies have shown that telomere length is a potential biomarker of risk of various cancers, including bladder, breast, lung, stomach, head and neck cancers (1–3,5,6). However, other epidemiologic investigations suggest that the associations between telomere length and cancer risk are inconclusive (7,8). The heterogeneity across different tumors could likely be explained by the different telomere dynamics in different types of tissue. Telomere shortening and malignant transformation in different types of cells varies in response to environmental DNA damage exposure.

We previously observed that shorter telomere length was associated with a decreased risk of skin melanoma (4), and this finding was replicated in additional studies [manuscript in submission]. Our previous data revealed no association between telomere length and skin SCC risk (*P* trend =0.30) (4). Consistently, we found no associations between telomere length and risk of SCC in the present study. We previously observed that shorter telomere length was non-significantly associated with an increased risk of BCC (*P* trend =0.09) (4). In the present study of two prospective datasets, our results suggest that telomere length is not associated with BCC risk. The combined evidence indicates that the role of telomere length in BCC development is minimal.

In conclusion, the present prospective study found no association between relative telomere length in peripheral blood leukocytes and risk of non-melanoma skin cancer. It suggests that telomere length may not be a useful biomarker for non-melanoma skin cancer risk assessment.

Acknowledgments

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Table 1

Characteristics of cases and controls

Characteristic	SCC study		BCC study 1		BCC study 2	
	Cases (n=241)	Controls (n=241)	Cases (n=260)	Controls (n=260)	Cases (n=363)	Controls (n=1683)
Age at diagnosis, mean (SD)	69.0 (8.4)	--	66.1 (8.0)	--	69.3 (7.0)	--
Age at blood draw, mean (SD)	63.1 (8.2)	63.1 (8.2)	56.3 (6.4)	56.4 (6.4)	61.0 (5.8)	59.5 (6.6)
Red or blonde hair color (%)	16.2	10.1	18.1	12.4	18.9	16.2
Tanning ability, tan without burn (%)	19.7	28.3	21.1	27.6	19.9	22.9
Gender	men	men	women	women	women	women

SD, Standard deviation

Table 2

Association between telomere length and non-melanoma skin cancer risk

	4th quartile	3rd quartile	2nd quartile	1st quartile	P for trend
			SCC (HPFS)[*]		
Case, n(%)	63(26)	55(23)	57(24)	66(27)	
Control, n(%)	60(25)	59(25)	63(26)	59(24)	
OR(95%CI)	1.00	0.90(0.56–1.45)	0.88(0.51–1.50)	1.09(0.62–1.93)	0.81
			BCC (NHS 1)[*]		
Case, n(%)	66(25)	67(26)	62(24)	65(25)	
Control, n(%)	66(25)	64(25)	64(25)	66(25)	
OR(95%CI)	1.00	1.03(0.60–1.78)	0.96(0.53–1.74)	0.96(0.49–1.87)	0.83
			BCC (NHS 2)[†]		
Case, n(%)	96(26)	94(26)	82(23)	91(25)	
Control, n(%)	421(25)	420(25)	426(25)	416(25)	
OR(95%CI)	1.00	0.95(0.69–1.31)	0.82(0.59–1.13)	0.91(0.66–1.25)	0.39

SCC, squamous cell carcinoma; BCC, basal cell carcinoma; OR, odd ratio; CI, confidence interval

[*] Conditional logistic regression.

[†] Unconditional logistic regression adjusted for age.