Published OnlineFirst August 21, 2012; DOI: 10.1158/1055-9965.EPI-12-0657

Cancer Epidemiology, Biomarkers & Prevention

Association of Leukocyte Telomere Length with Colorectal Cancer Risk: Nested Case –Control Findings from the Shanghai Women's Health Study

Yong Cui, Qiuyin Cai, Shimian Qu, et al.

Cancer Epidemiol Biomarkers Prev 2012;21:1807-1813. Published OnlineFirst August 21, 2012.

Published OnlineFirst August 21, 2012; DOI: 10.1158/1055-9965.EPI-12-0657

Cancer Epidemiology, Biomarkers & Prevention

Research Article

Association of Leukocyte Telomere Length with Colorectal Cancer Risk: Nested Case–Control Findings from the Shanghai Women's Health Study

Yong Cui[1], Qiuyin Cai[1], Shimian Qu[1], Wong-Ho Chow[2], Wanqing Wen[1], Yong-Bing Xiang[3], Jie Wu[1], Nathaniel Rothman[2], Gong Yang[1], Xiao-Ou Shu[1], Yu-Tang Gao[3], and Wei Zheng[1]

Abstract

Background: Telomeres are specialized chromatin structures essential for maintenance of chromosomal integrity and stability. Abnormal alteration of telomere length has been linked to several cancers; however, epidemiologic evidence about the association of telomere length with colorectal cancer risk has been conflicting.

Methods: We conducted a nested case–control study to evaluate the association between telomere length and colorectal cancer risk using peripheral blood samples collected before cancer diagnosis. The study included 441 women with incident colorectal cancer and 549 matched controls. Monochrome multiplex quantitative PCR was applied to measure relative telomere length. Multiple logistic regressions were used to derive adjusted OR with 95% confidence intervals (CI) as the measure of association between telomere length and subsequent colorectal cancer risk.

Results: A U-shaped association was observed between telomere length and colorectal cancer risk (test for nonlinearity $P = 0.0112$). Women with telomere length in the third quintile (40th–60th percentiles) had the lowest risk of colorectal cancer, and the risks were elevated with a shorter or longer telomere length. This U-shaped association did not statistically differ for colon cancer and rectum cancer.

Conclusions and Impact: Our prospective study revealed a U-shaped association between telomere length in peripheral blood cells and colorectal cancer risk. Our findings provide strong evidence that both very short and very long telomeres are associated with increased risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev; 21(10); 1807–13. ©2012 AACR.*

Introduction

Telomeres are specialized dynamic chromatin structures at the termini of eukaryotic chromosomes, composed of highly conserved tandem hexameric nucleotide repeats (*TTAGGG*)*n* (1). Telomeres cap the ends of chromosomes and are essential for preserving chromosomal integrity and stability by preventing fatal incidents such as chromosome ends fusion, nucleolytic degradation, and aberrant recombination (2). Telomere length is maintained by the expression of telomerase, a ribonucleoprotein complex consisting of a reverse transcriptase catalytic subunit and an RNA component (TERC), which adds (*TTAGGG*) repeats onto the telomeric ends of the chromosome (3, 4). In normal somatic cells, telomerase is not expressed or presents at very low levels of activity. Thus, telomeres undergo progressive shortening with each mitotic cell division because of the inability of DNA polymerase to completely synthesize the daughter strand at chromosomal ends (2, 5). The rate of telomere shortening is also modified by factors other than the mitotic replication rate, such as oxidative stress and chronic inflammation (6). When telomeres shorten to a critical length, they become dysfunctional, and Rb and p53 signal pathways are triggered to initiate either cell senescence or apoptosis (5, 7). On rare occasions, cells that aberrantly bypass replicative senescence with critically short telomeres may develop genomic instability and potentially become tumorigenic (5). In cancer cells, however, telomerase is highly expressed, and reactivation of telomerase helps compensate telomere erosion, allowing cancer cells to escape the normal limits of cellular proliferation, or preventing them from undergoing senescence/apoptosis (4, 8–10). Thus, telomere length reflects the result of the balance between processes that shorten telomeres or lengthen telomeres (11).

Authors' Affiliations: [1]Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center and Vanderbilt-Ingram Cancer Center, Nashville, Tennessee; [2]Occupational Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; and [3]Department of Epidemiology, Shanghai Cancer Institute, Shanghai, PR China

Corresponding Author: Wei Zheng, Vanderbilt Epidemiology Center and Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, 2525 West End Avenue, 8th Floor, Nashville, TN 37203-1738. Phone: (615) 936-0682; Fax: (615) 936-8241; E-mail: wei.zheng@vanderbilt.edu

doi: 10.1158/1055-9965.EPI-12-0657

Published OnlineFirst August 21, 2012; DOI: 10.1158/1055-9965.EPI-12-0657

In humans, the best example of short telomere phenotype is dyskeratosis congenita. Patients with this disease carry mutations in the components of telomerase complex, which results in short telomeres leading to bone-marrow failure and elevated risk of cancer (12). Mouse models also support the notion that telomerase deficiency and short telomere length increase the risk of tumor (4, 13). Studies using histopathological samples obtained from patients with solid tumors have well documented that telomere length in neoplastic tissues and/or noninvasive precursor lesions alters frequently, showing telomere attrition or elongation, as compared with matched adjacent normal tissues (6, 14). Recently, several epidemiologic studies have evaluated telomere length as a potential predictor for cancer risk and prognosis, measured using DNA from peripheral blood cells or buccal cells (6, 15, 16). About colorectal cancer, results from previous studies have been mixed, reporting shorter telomeres associated with increased colorectal cancer risk in one retrospective study (17), null associations between telomere length and colorectal cancer risk in 3 prospective, nested case–control studies (17–19), and longer telomeres associated with increased colorectal cancer risk among carriers of the common allele at a single-nucleotide polymorphism (SNP) near TERC in the most recent study (20). Reasons for the apparently contradictory results remain unknown. Differences in study populations, study designs, sample sizes, analytic approaches, and background exposures could contribute to inconsistent findings. To investigate the association between telomere length and colorectal cancer risk, we conducted a large case–control study nested within the Shanghai Women's Health Study (SWHS) using blood samples collected before cancer diagnosis.

Material and Methods

Study population

Subjects of this study were participants of the SWHS, an ongoing prospective cohort study of environmental and genetic risk factors for cancer. A detailed description of the rationale and methods for the SWHS has been reported elsewhere (21). Briefly, from December 1996 through May 2000, 74,942 Chinese women ages 40 to 70 years who were permanent residents in 7 urban communities were enrolled in the cohort study with a participation rate of 92.7%. The baseline survey included an in-person interview and self-administered questionnaire for collecting information about socio-demographic characteristics, lifestyle-related factors, and medical history. Anthropometric measurements were taken by trained interviewers using standardized protocols at enrollment. Of the study participants, 56,831 (75.8%) provided a blood sample. All participants provided written informed consent at enrollment. Study protocols were approved by the relevant Institutional Review Boards for human research.

The cohort has been followed using a combination of biennial home visits and record linkage to cancer incidence and mortality data collected by the Shanghai Cancer Registry and death certificate data collected by the Shanghai Vital Statistics Unit. For cohort members who were diagnosed with cancer, medical charts were reviewed to verify the diagnosis, and detailed information was obtained about pathologic characteristics of the cancer.

The current nested case–control study included 441 incident colorectal cancer cases identified during follow-up of the cohort through December 2009, as well as their 549 matched controls. Incidence-density sampling method was used to select controls. Cases and controls were individually matched on age ($\leq$730 days), date ($\leq$30 days), and time (morning or afternoon) of sample collection, time interval since last meal ($\leq$2 hours), antibiotic use in the past week (yes/no), and menopausal status at time of sample collection.

Measurement of telomere length and quality control

Genomic DNA was extracted from buffy coats using QIAamp DNA kit (Qiagen) following the manufacturer's protocol. Relative telomere length was measured using a monochrome multiplex quantitative PCR method described recently by Cawthon (22) with minor modifications (23). Briefly, telomere length assay was carried out in a 15 μL PCR reaction consisting of 1 × QuantiFast SYBR Green PCR Master Mix (Qiagen), 700 nmol/L telomere primers telg and telc, 200 nmol/L albumin primers albugcr1 and albdgcr1, and 5 ng DNA. A multistep thermal cycling procedure was conducted on a Bio-Rad CFX384 Real-Time System. Following amplification, a dissociation curve was conducted to confirm the specificity of the reaction. For each standard curve, 2-fold serial dilutions of a reference DNA sample were used to produce a standard curve. In addition, a calibrator DNA (same as the reference DNA), 2 negative controls, and 2 quality-control (QC) DNA samples–one with a long and one with a short telomere length (Roche, Telo *TAGGG* Telomere Length Assay kit) were included in each of the 384-well assay plates. Bio-Rad CFX manager software (version 1.6) was used to determine the relative telomere length through a 2-step relative quantification. In the first step, the ratio of telomere repeat copy number to single-copy gene copy number (T/S), as a measure of relative telomere length, was determined for each sample based on the standard curve. In the second step, the T/S ratio for each sample was normalized to the calibrator DNA to standardize sample values across all reaction plates. Laboratory personnel were blinded to each subject's case–control status. Inter-plate T/S CVs were 15.6%, and 16.2%, respectively, for the long and short telomere QC samples. Inter- and intraplate CVs of calibrator DNA samples were 12.2%, and 5.3%, respectively. Mean ratio of long to short telomere QC samples in our assays was 2.9, very close to the mean ratio of 2.7 determined by Southern Blot method (Roche, Telo *TAGGG* Telomere Length Assay kit).

Statistical methods

Means and percentages of selected baseline characteristics for cases and controls were calculated and compared

Published OnlineFirst August 21, 2012; DOI: 10.1158/1055-9965.EPI-12-0657

using t test (for continuous variables) and χ^2 test (for categorical variables). Data about relative telomere length were log-transformed so that these data were approximately normally distributed.

We compared the case–control difference of the geometric means of the log-transformed telomere length using a 2-way (case–control status and matched sets) ANOVA. As DNA samples for cases and controls in the same matched sets were assayed on the same plates, interplate differences for the matched sets were accounted for automatically. To evaluate the association between colorectal cancer risk and telomere length, ratio for telomere length was categorized into quintiles based on distribution among controls. ORs and 95% confidence intervals (CI) were estimated using conditional logistic regression models to account for the matched sets. Tests for linear trend were estimated using the median value for each telomere-length quintile. Restricted cubic spline function with 3 knots (24), which resulted in the best fit of the model, was used in the conditional logistic regression model to evaluate the shape of the association. Likelihood ratio tests were used to evaluate linear effect, nonlinear effect, and overall effect of telomere length with colorectal cancer risk. Stratified analyses were conducted to evaluate potential interactions. All statistical tests were based on 2-sided probability.

Results

Table 1 presents baseline characteristics of 441 cases and 549 matched controls, including age at blood collection, educational levels, menopausal status, obesity status [measured by body mass index (BMI)], cigarette-smoking status, alcohol use, physical activity, fruit and vegetable intake, meat intake, history of inflammatory bowel disease, and family history of colorectal cancer. Overall, distributions were comparable between cases and controls. Telomere length was inversely correlated with age at blood collection ($r = -0.22$, $P < 0.0001$; data not shown in table). Geometric means of telomere length were approximately 7.4% (cases) and 5.6% (controls) shorter in women aged 50 to 59 years, and 8.7% (cases) and 7.3% (controls) shorter in those aged 60 and older, compared with those younger than 50 years (data not shown in table).

Overall, no significant difference was found in geometric mean of telomere length between cases and controls ($P = 0.1620$; Table 2), and no linear association between telomere length and colorectal cancer risk was detected ($P_{trend} = 0.1633$; Table 3). However, a U-shaped association was observed: the lowest risk was observed in women with telomere length in the third quintile (40th–60th percentiles), and risks were elevated with a shorter or longer telomere length as compared with the lowest risk group (Table 3). A similar pattern of the association was also seen after excluding cases diagnosed within the first year after blood collection, or grouping study subjects based on the interval between blood collection and cancer diagnosis (<5 years or ≥5 years), or being examined by colon cancer or rectum cancer separately (Tables 2 and 3).

To further evaluate the shape of the association, restricted cubic spline function was used in a conditional logistic regression model (Fig. 1). Similar to the categorical analysis presented in Table 3, a clear U-shaped, statistically significant association between telomere length and colorectal cancer risk (test for linearity: $P = 0.1633$; test for nonlinearity: $P = 0.0112$; and overall: $P = 0.0152$). Again, excluding cases diagnosed within the first year after blood collection, or stratifying women based on the time interval between blood collection and cancer diagnosis, or based on colon cancer or rectum cancer did not apparently affect the overall association observed (figures not shown).

We also investigated potential interactions of telomere length with age, BMI, or physical activity in relation to colorectal cancer risk. However, we did not detect a

Table 1. Comparison of demographic characteristics and known colorectal cancer risk factors between cases and their matched controls

Baseline characteristics	Cases ($N = 441$)	Controls ($N = 549$)	P for difference
Age, mean ± SD	58.5 ± 8.7	58.6 ± 8.6	0.9732
Postmenopause, %	76.6	76.9	0.9342
Body mass index, BMI, mean ± SD	24.6 ± 3.3	24.8 ± 3.5	0.3608
Education ≥ high school, %	31.8	31.7	0.9860
Family history of colorectal cancer, %	3.2	2.4	0.4386
History of inflammatory bowel disease, %	0.9	0.5	0.5010
Ever smoked cigarettes regularly, %	2.5	3.8	0.2393
Ever consumed alcohol regularly, %	3.2	2.9	0.8124
Ever exercised regularly, %	46.9	44.1	0.3692
Ever used aspirin regularly, %	2.5	4.4	0.1119
Fruit and vegetable intake, g/d; mean ± SD	556.9 ± 292.4	549.8 ± 282.0	0.6983
Meat intake, g/d; mean ± SD	48.9 ± 41.6	49.6 ± 37.2	0.7818

P values were derived from t tests for continuous variables or χ^2 tests for categorical variables.

Published OnlineFirst August 21, 2012; DOI: 10.1158/1055-9965.EPI-12-0657

Table 2. Comparison of adjusted geometric means of telomere length between cases and controls

	Relative telomere length		
Subjects, N	**Mean (95% CI)[a]**	**Ratio (95% CI)[b]**	***P***
All subjects			
Cases (441)	0.976 (0.959, 0.993)		
Controls (549)	0.960 (0.945, 0.975)	1.017 (0.993, 1.040)	0.162
Excluding cases diagnosed within 1 year since blood collection			
Cases (413)	0.975 (0.958, 0.992)		
Controls (511)	0.963 (0.947, 0.979)	1.012 (0.988, 1.037)	0.325
Interval between blood collection and cancer diagnosis less than 5 years			
Cases (178)	1.008 (0.979, 1.039)		
Controls (236)	0.982 (0.956, 1.009)	1.027 (0.987, 1.068)	0.190
Interval between blood collection and cancer diagnosis 5 years or more			
Cases (263)	0.954 (0.935, 0.974)		
Controls (313)	0.946 (0.928, 0.964)	1.009 (0.981, 1.038)	0.513
Colon cancer			
Cases (276)	0.948 (0.929, 0.967)		
Controls (345)	0.944 (0.926, 0.961)	1.004 (0.977, 1.032)	0.760
Rectum cancer			
Cases (165)	1.024 (0.993, 1.056)		
Controls (204)	0.987 (0.959, 1.016)	1.037 (0.995, 1.082)	0.085

[a]Adjusted for matched sets.
[b]The ratio (95% CI) of the geometric means in cases over geometric means in controls.

significant interaction in our study population (data not shown).

Discussion

Recently, a few epidemiologic studies investigated the association between leukocyte telomere length and colorectal cancer risk, with conflicting results. Pooley and colleagues (17) conducted a retrospective study using data from the SEARCH colorectal cancer case–control study (2,249 cases; 2,161 controls) and a prospective study using data from the EPIC-Norfolk cohort (185 cases; 406 controls) and found a strong association between short telomeres and colorectal cancer risk in the retrospective study (OR, 2.14; 95% CI, 1.77–2.59; quartile 1 versus quartile 4; $P_{trend} < 0.0001$), but not in the prospective study (OR, 1.13; 95% CI, 0.54–2.36; $P_{trend} = 0.82$). No statistically significant association between mean telomere length and colorectal cancer risk was reported by 2 other relatively small prospective, nested case–control studies: among white men from the Physicians' Health Study (cases/controls = 191/306; OR, 1.25; 95% CI, 0.86–1.81; ref. 19), and among white women from the Women's Health Study (cases/controls = 134/357; OR, 0.94; 95% CI, 0.65–1.38; ref. 18). Intriguingly, in a most recent study examining a large white, European ancestry sample, (3,921 controls and 2,157 cases), Jones and colleagues found that carriers of the common allele at a SNP near the TERC had significantly longer telomeres in leukocytes and found the same allele to be associated with increased colorectal cancer risk (20). Differing from previous reports, our study found a U-shaped association between telomere length and colorectal cancer risk, indicating both long and short telomeres to be associated with increased risk of colorectal cancer. Discrepancies between our results and previous reports may be attributed partially to differences in study population (e.g., ethnicity, sex, and age), sample size, and analytical method used. In the prospective arm of the Pooley and colleagues study (17), colorectal cancer risk was shown to be lowest in the third quartile of telomere length, which is similar to our finding. However, Pooley and colleagues did not specifically evaluate the nonlinear association between telomere length and colorectal cancer risk.

The U-shaped association between telomere length and colorectal cancer risk observed in our study is unexpected, but it is biologically plausible. Experimental studies and animal models have shown that telomeres at the end of chromosomes play important roles in maintaining genomic integrity and stability (2). When telomeres become critically shortened, Rb and p53 signal pathways are triggered, and cells undergo either replicative senescence or apoptosis (5, 7). If such processes are bypassed, cells continue to proliferate through activation of telomeres, genetic lesions, and inactivated suppressor checkpoints, ultimately resulting in tumorigenesis (4–7, 13). In humans, it has been well documented that short telomeres are associated with multiple premature aging syndromes, including ataxia telangiectasia, ataxia-telangiectasia-like

Published OnlineFirst August 21, 2012; DOI: 10.1158/1055-9965.EPI-12-0657

Table 3. ORs and 95% confidence intervals for the association between telomere length and colorectal cancer risk

Telomere length (by quintile)	No. of cases	No. of controls	OR (95% CI)[a,b]
All subjects			
Q1 (short)	95	109	1.56 (0.92–2.64)
Q2	91	110	1.30 (0.86–1.97)
Q3	72	110	1.00 (reference)
Q4	92	110	1.38 (0.90–2.11)
Q5 (long)	91	110	1.61 (0.94–2.75)
Linear			$P = 0.1633$
Nonlinear			$P = 0.0122$
Overall			$P = 0.0152$
Excluding cases diagnosed within 1 year since blood collection			
Q1 (short)	90	98	1.59 (0.92–2.74)
Q2	83	105	1.21 (0.79–1.86)
Q3	68	101	1.00 (reference)
Q4	87	104	1.30 (0.84–2.02)
Q5 (long)	85	109	1.53 (0.88–2.65)
Linear			$P = 0.3229$
Nonlinear			$P = 0.0088$
Overall			$P = 0.0199$
Interval between blood collection and cancer diagnosis less than 5 years			
Q1 (short)	33	43	1.99 (0.82–4.80)
Q2	35	44	1.55 (0.82–2.92)
Q3	30	51	1.00 (reference)
Q4	37	50	1.35 (0.72–2.55)
Q5 (long)	43	48	2.02 (0.93–4.39)
Linear			$P = 0.2073$
Nonlinear			$P = 0.0208$
Overall			$P = 0.0312$
Interval between blood collection and cancer diagnosis 5 years or more			
Q1 (short)	62	66	1.33 (0.68–2.59)
Q2	56	66	1.16 (0.66–2.02)
Q3	42	59	1.00 (reference)
Q4	55	60	1.37 (0.77–2.45)
Q5 (long)	48	62	1.33 (0.63–2.82)
Linear			$P = 0.5166$
Nonlinear			$P = 0.2667$
Overall			$P = 0.4372$
Colon cancer			
Q1 (short)	65	75	1.50 (0.79–2.85)
Q2	61	70	1.35 (0.79–2.31)
Q3	44	69	1.00 (reference)
Q4	59	60	1.55 (0.90–2.68)
Q5 (long)	47	71	1.11 (0.55–2.26)
Linear			$P = 0.7558$
Nonlinear			$P = 0.0700$
Overall			$P = 0.1846$
Rectum cancer			
Q1 (short)	30	34	1.78 (0.69–4.65)
Q2	30	40	1.28 (0.66–2.74)
Q3	28	41	1.00 (reference)
Q4	33	50	1.16 (0.59–2.26)

(Continued on the following page)

Published OnlineFirst August 21, 2012; DOI: 10.1158/1055-9965.EPI-12-0657

Table 3. ORs and 95% confidence intervals for the association between telomere length and colorectal cancer risk (Cont'd)

Telomere length (by quintile)	No. of cases	No. of controls	OR (95% CI)[a,b]
Q5 (long)	44	39	2.54 (1.08–5.96)
Linear			$P = 0.0899$
Nonlinear			$P = 0.1478$
Overall			$P = 0.0833$

[a]Adjusted for matched sets.
[b]Subjects with telomere length in the third quintile (40th–60th percentiles) had the lowest risk of colorectal cancer and were used as reference.

disorder, aplastic anemia, Bloom syndrome, Fanconi anemia, Nijmegen breakage syndrome, and dyskeratosis congenita (4, 12). On the other hand, although short telomeres have been associated with cancer risk, it is evident that very long telomeres may also increase risk of carcinogenic transformation. In specimens from solid tumors, including colorectal cancer, histopathological studies have shown that telomeres were significantly shorter in most cases; however, tumors from a subset of patients showed elongated telomeres, compared with their adjacent noncancerous tissues (14). In epidemiologic studies analyzing telomeres in leukocytes and cancer risk, both short and long telomeres have been found to be associated with increased risk of several types of cancer (17), including breast cancer (17, 23, 25–27), colorectal cancer (17, 20), lung cancer (28–31), renal cell carcinoma (32, 33), and non-Hodgkin lymphoma (34, 35). It has been proposed that cells with long telomeres may favor a delayed cell senescence and apoptosis; therefore, these cells could have an increased chance of exposure to various genetic and environmental insults and acquirement/accumulation of genetic abnormalities, thus being at higher risk of carcinogenic transformation (11, 34). Our study is the first to provide evidence in the same study cohort that both short and long telomeres may contribute to increased risk of colorectal cancer. Our study, together with others, suggests that telomere length in an "appropriate range" may be necessary to maintain chromosomal stability and normal programmed cell death—functions that are protective against tumor development.

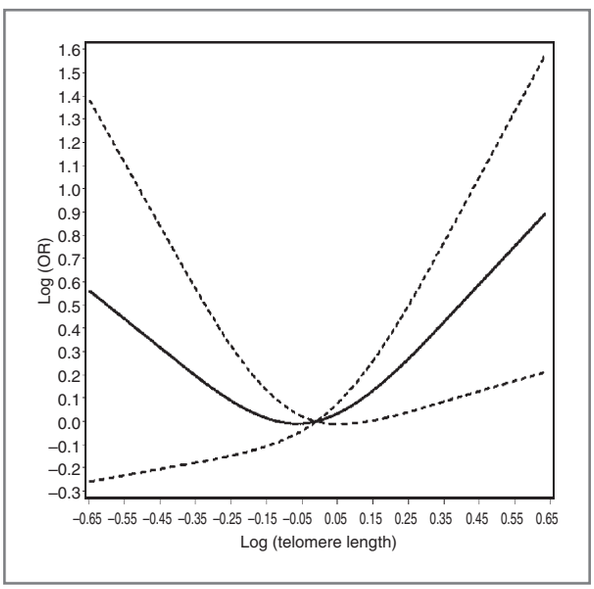

Figure 1. ORs (solid line) and their 95% CIs (dotted lines) for the association between telomere length and colorectal cancer risk (in all subjects). *P* values for tests of overall association, linearity, and nonlinearity are 0.0152, 0.1633, and 0.0122, respectively.

A major strength of our study is the use of prediagnostic blood samples. However, lifestyle changes over time could affect the association between telomere length and colorectal cancer risk. In particular, cigarette smoking and regular aspirin use could affect telomere length. However, less than 5% of study participants smoked cigarettes or used aspirin regularly and thus these 2 variables should not have any major impact on our study results. Similar to other studies, the precision of relative telomere measurement was not optimal, and a relatively large CV was observed. However, this measurement error should be random, which tends to attenuate the association between telomere length and breast cancer risk. To minimize the effect of interplate variation on study results, we used the same plate to analyze samples from each case–control set and used monochrome multiplex quantitative PCR method. Although our study is the largest prospective study conducted to date addressing the association of telomere length with colorectal cancer risk, the sample size for some analyses remains relatively small. Further research is warranted to evaluate the association in large prospective studies and by different racial/ethnic groups.

In conclusion, our prospective study revealed a U-shaped association between telomere length in peripheral blood cells and colorectal cancer risk. Our findings provide strong evidence that both very short and very long telomeres are associated with increased risk of colorectal cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Published OnlineFirst August 21, 2012; DOI: 10.1158/1055-9965.EPI-12-0657

Authors' Contributions

Conception and design: S. Qu, W. Wen, N. Rothman, X.-O. Shu, W. Zheng
Development of methodology: Q. Cai, S. Qu, W. Wen, J. Wu, W. Zheng
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Q. Cai, S. Qu, Y.-B. Xiang, J. Wu, N. Rothman, G. Yang, X.-O. Shu, Y.-T. Gao, W. Zheng
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Cui, S. Qu, W.-H. Chow, W. Wen, W. Zheng
Writing, review, and/or revision of the manuscript: Y. Cui, S. Qu, W.-H. Chow, W. Wen, Y.-B. Xiang, N. Rothman, G. Yang, X.-O. Shu, Y.-T. Gao, W. Zheng
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y.-B. Xiang, J. Wu, Y.-T. Gao, W. Zheng
Study supervision: Q. Cai, Y.-B. Xiang, X.-O. Shu, Y.-T. Gao, W. Zheng

Acknowledgments

The authors wish to thank Ms. Regina Courtney for her excellent laboratory assistance in sample handling and preparation. Sample preparations and telomere length assays were conducted at the Survey and Biospecimen Shared Resource, which is supported in part by the Vanderbilt-Ingram Cancer Center (P30 CA68485).

Grant Support

Funding support for this work was provided by NIH grant (R37 CA 070867).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received May 31, 2012; revised July 19, 2012; accepted August 9, 2012; published OnlineFirst August 21, 2012.

References

1. Blackburn EH. Telomere states and cell fates. Nature 2000;408:53–6.
2. Stewart SA, Weinberg RA. Telomeres: cancer to human aging. Annu Rev Cell Dev Biol 2006;22:531–57.
3. Greider CW, Blackburn EH. Tracking telomerease. Cell 2004;116:S83–S86 81p following S86.
4. Blasco MA. Telomeres and human disease: ageing, cancer and beyond. Nat Rev Genet 2005;6:611–22.
5. Gilley D, Herbert B, Huda N, Tanka H, Reed T. Factors impacting human telomere homeostasis and age-related disease. Mech Ageing Dev 2008;129:27–34.
6. Prescott J, Wentzensen IM, Savage SA, De Vivo I. Epidemiologic evidence for a role of telomere dysfunction in cancer etiology. Mutat Res 2012;730:75–84.
7. Mathon NF, Lloyd AC. Cell senescence and cancer. Nat Rev Cancer 2001;1:203–13.
8. Greider CW. Telomerase activity, cell proliferation, and cancer. Proc Natl Acad Sci USA 1998;95:90–2.
9. Mooi WJ, Peeper DS. Oncogene-induced cell senescence–halting on the road to cancer. N Engl J Med 2006;355:1037–46.
10. Stewart JA, Chaiken MF, Wang F, Price CM. Maintaining the end: Roles of telomere proteins in end-protection, telomere replication and length regulation. Mutat Res 2012;730:12–9.
11. Hou L, Zhang X, Gawron AJ, Liu J. Surrogate tissue telomere length and cancer risk: shorter or longer? Cancer Lett 2012;319:130–5.
12. Alter BP, Giri N, Savage SA, Rosenberg PS. Cancer in dyskeratosis congenita. Blood 2009;113:6549–57.
13. Lee HW, Blasco MA, Gottlieb GJ, Horner JW II, Greider CW, DePinho RA. Essential role of mouse telomerase in highly proliferative organs. Nature 1998;392:569–74.
14. Bisoffi M, Heaphy CM, Griffith JK. Telomeres: prognostic markers for solid tumors. Int J Cancer 2006;119:2255–60.
15. Ma H, Zhou Z, Wei S, Liu Z, Pooley KA, Dunning AM, et al. Shortened telomere length is associated with increased risk of cancer: a meta-analysis. PLoS One 2011;6:e20466.
16. Wentzensen IM, Mirabello L, Pfeiffer RM, Savage SA. The association of telomere length and cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2011;20:1238–50.
17. Pooley KA, Sandhu MS, Tyrer J, Shah M, Driver KE, Luben RN, et al. Telomere length in prospective and retrospective cancer case-control studies. Cancer Res 2010;70:3170–6.
18. Lee IM, Lin J, Castonguay AJ, Barton NS, Buring JE, Zee RY. Mean leukocyte telomere length and risk of incident colorectal carcinoma in women: a prospective, nested case-control study. Clin Chem Lab Med 2010;48:259–62.
19. Zee RY, Castonguay AJ, Barton NS, Buring JE. Mean telomere length and risk of incident colorectal carcinoma: a prospective, nested case-control approach. Cancer Epidemiol Biomarkers Prev 2009;18:2280–2.
20. Jones AM, Beggs AD, Carvajal-Carmona L, Farrington S, Tenesa A, Walker M, et al. TERC polymorphisms are associated both with susceptibility to colorectal cancer and with longer telomeres. Gut 2012;61:248–54.
21. Zheng W, Chow WH, Yang G, Jin F, Rothman N, Blair A, et al. The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. Am J Epidemiol 2005;162:1123–31.
22. Cawthon RM. Telomere length measurement by a novel monochrome multiplex quantitative PCR method. Nucleic Acids Res 2009;37:e21.
23. Qu S, Wen W, Shu XO, Chow WH, Xiang YB, Wu J, et al. Association of leukocyte telomere length with breast cancer risk: nested case-control findings from the Shanghai Women's Health Study. Am J Epidemiol. 2012 (In press).
24. Harrell F. Regression modeling strategies. New York, NY: Springer; 2001.
25. Svenson U, Nordfjall K, Stegmayr B, Manjer J, Nilsson P, Tavelin B, et al. Breast cancer survival is associated with telomere length in peripheral blood cells. Cancer Res 2008;68:3618–23.
26. Gramatges MM, Telli ML, Balise R, Ford JM. Longer relative telomere length in blood from women with sporadic and familial breast cancer compared with healthy controls. Cancer Epidemiol Biomarkers Prev 2010;19:605–13.
27. Levy T, Agoulnik I, Atkinson EN, Tong XW, Gause HM, Hasenburg A, et al. Telomere length in human white blood cells remains constant with age and is shorter in breast cancer patients. Anticancer Res 1998;18:1345–9.
28. Shen M, Cawthon R, Rothman N, Weinstein SJ, Virtamo J, Hosgood HD 3rd, et al. A prospective study of telomere length measured by monochrome multiplex quantitative PCR and risk of lung cancer. Lung Cancer 2011;54:482–9.
29. Jang JS, Choi YY, Lee WK, Choi JE, Cha SI, Kim YJ, et al. Telomere length and the risk of lung cancer. Cancer Sci 2008;99:1385–9.
30. Hosgood HD III, Cawthon R, He X, Chanock S, Lan Q. Genetic variation in telomere maintenance genes, telomere length, and lung cancer susceptibility. Lung Cancer 2009;66:157–61.
31. Wu X, Amos CI, Zhu Y, Zhao H, Grossman BH, Shay JW, et al. Telomere dysfunction: a potential cancer predisposition factor. J Natl Cancer Inst 2003;95:1211–8.
32. Svenson U, Ljungberg B, Roos G. Telomere length in peripheral blood predicts survival in clear cell renal cell carcinoma. Cancer Res 2009;69:2896–901.
33. Shao L, Wood CG, Zhang D, Tannir NM, Matin S, Dinney CP, et al. Telomere dysfunction in peripheral lymphocytes as a potential predisposition factor for renal cancer. J Urol 2007;178:1492–6.
34. Lan Q, Cawthon R, Shen M, Weinstein SJ, Virtamo J, Lim U, et al. A prospective study of telomere length measured by monochrome multiplex quantitative PCR and risk of non-Hodgkin lymphoma. Clin Cancer Res 2009;15:7429–33.
35. Widmann TA, Herrman M, Taha N, Konig J, Pfreundschuh M. Short telomeres in aggressive non-Hodgkin's lymphoma as a risk factor in lymphomagenesis. Exp Hematol 2007;35:939–46.