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Pre-Diagnostic Telomere Length and Colorectal Cancer Risk

Keming Yang[1,6], **Jennifer Prescott**[2], **Aditi Hazra**[3], **Jeffrey A. Meyerhardt**[4], **Xuehong Zhang**[1,2], **Immaculata De Vivo**[2,5], **Andrew T. Chan**[6,7], **Mengmeng Du**[8], **Edward L. Giovannucci**[1,5,*], **Hongmei Nan**[9,10,*,#]

[1]-Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA.

[2]-Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.

[3]-Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.

[4]-Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA.

[5]-Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA.

[6]-Clinical and Translational Epidemiology Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA.

[7]-Division of Gastroenterology, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA.

[8]-Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA.

[9]-Department of Global Health, Richard M. Fairbanks School of Public Health, Indiana University, Indianapolis, IN, USA.

[#]:Corresponding author: Telephone: 317-274-3120, hnan@iu.edu.

[*]:Contributed equally as co-senior/last authors

Authorship contribution: JP, AH, ID were involved in telomere length measurement and validation process. KY analyzed the data and drafted the manuscript. HN and ELG supervised the study. All authors (KY, JP, AH, JAM, XZ, ID, AC, MD, ELG, HN) contributed to the interpretation of the results and revision of the manuscript critically for important intellectual content. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Co-senior/last author:

Dr. Hongmei Nan (corresponding author): Department of Global Health, Richard M. Fairbanks School of Public Health, Indiana University, 1050 Wishard Blvd, RG 6086, IN 46202, USA.

Dr. Edward Giovannucci: Departments of Nutrition and Epidemiology, Harvard T.H. Chan School of Public Health, 665 Huntington Ave, SPH2-371A, Boston, MA 02115, USA.

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[10]Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University, Indianapolis, IN, USA.

Abstract

Background: Progressive telomere shortening may be related to genomic instability and carcinogenesis. Prospective evidence relating telomere length (TL) with colorectal cancer (CRC) risk has been limited and inconsistent.

Methods: We examined the association between pre-diagnostic peripheral blood leukocyte TL and CRC risk in two matched case-control studies nested within the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS). Relative leukocyte TL was measured using qPCR among 356 incident CRC cases and 801 controls (NHS: 186/465, HPFS: 170/336).

Results: We did not find a significant association between pre-diagnostic TL and CRC risk [in all participants, multivariable-adjusted odds ratio (OR) (95% CI) for TL Quartile 1 (shortest) vs. Quartile 4 (longest) = 1.36 (0.85, 2.17), P-trend=0.27; OR (95% CI) per 1 SD decrease in TL=1.12 (0.92, 1.36)].

Conclusions: Our prospective analysis did not support a significant association between pre-diagnostic leukocyte TL and CRC risk.

Keywords

telomere length; peripheral blood leukocyte; colorectal cancer; colon cancer; rectal cancer; nested case-control study

INTRODUCTION

Telomeres are repeated DNA sequences at chromosome ends that maintain genomic stability.[1] Telomere length (TL) shortens with cell divisions; progressive TL shortening may contribute to genomic instability, which is a hallmark of cancer.[2] Epidemiologic studies have associated TL with risks of many cancers (e.g., skin, ovarian, lung, bladder)[3, 4], including colorectal cancer (CRC). However, evidence on the relationship between TL and CRC risk has been limited and contradictory; positive, inverse, U-shaped as well as null associations have been reported.[5–10] Moreover, prospective evidence on TL/CRC relationship is still sparse. A recent meta-analysis of four prospective studies did not show a significant association [pooled estimate = 1.01 (0.77, 1.34)],[7] suggesting the need for additional prospective studies on this topic. Therefore, to further examine the association between pre-diagnostic TL and CRC risk, we conducted two nested case-control studies within the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS).

METHODS

Participants in our nested case-control studies were identified from NHS and HPFS.[11] In 1976, NHS enrolled 121,700 female nurses aged 30–55 at baseline. In 1986, HPFS enrolled 51,529 male health professionals aged 40–75 at baseline. In both cohorts, participants' dietary habits, lifestyles and disease status were updated every two to four years. A total of

32,826 NHS participants (1989–1990) and 18,225 HPFS participants (1993–1995) provided blood samples. A total of 356 incident CRC cases diagnosed after blood collection and 801 controls were included in our analysis (NHS: 186/465, HPFS: 170/336). One to three cancer-free controls from the same cohort were randomly selected and matched with cases based on age at blood collection, race, and fasting status (Supplementary Figure 1).

Genomic DNA was extracted using QIAmp 96-spin protocol from peripheral blood leukocytes. Relative TL was determined using qPCR and calculated as the ratio of telomere repeat copy number to a single gene (36B4) copy number (T/S). Details of the method were described elsewhere[12] and summarized in Supplementary Materials. TL was reported as the exponentiated T/S ratio corrected for a reference sample. The average coefficients of variation for the telomere assay and the single-gene assay were 0.54% and 0.53%, respectively. The average coefficient of variation for the exponentiated T/S of quality control samples was 14.6%. As expected, TL was inversely correlated with age at blood collection in our datasets ($P < 0.001$). Z-scores of log-transformed TL were calculated and used as the exposure of interest in our analyses.

Descriptive analyses for cases and controls at blood collection were conducted; means (standard deviation) for continuous variables and percentages for categorical variables were calculated. To examine the associations of TL quartiles with risks of CRC and subsite cancers, conditional logistic regression models were performed to estimate odds ratios (ORs) and 95% confidence intervals (CIs). We built two models: Model 1: Conditional logistic regression model conditioning on matching factors (age at blood draw, race, and fasting status), and Model 2: Model 1 + adjusting for body mass index, physical activity, smoking status, alcohol consumption, Alternate Health Eating Index (AHEI), regular aspirin and NSAIDs use, and CRC family history. ORs (95% CIs) were also estimated for cancer risk by one standard deviation (SD) decrease in TL. To minimize the potential for reverse influence of undetectable tumors at blood collection on TL, we conducted a sensitivity analysis by excluding cases diagnosed within 2 years after blood collection. Further, interaction and stratified analyses by pre-selected above-listed covariates were examined. All analyses were performed using SAS (Unix, 9.4).

RESULTS

Our analysis included 356 incident CRC cases and 801 controls; characteristics of cases and controls in NHS (186/465) and HPFS (170/336) are shown in Table 1. Mean age (SD) of cases was 60.1 (6.6) in NHS and 66.8 (8.0) in HPFS. We did not find a significant association between pre-diagnostic TL and CRC risk among NHS [multivariable adjusted OR (95% CI) for Quartile 1 (shortest) vs. 4 (longest) = 1.74 (0.91, 3.32), per 1 SD decrease in TL=1.23 (0.93, 1.61)], HPFS [multivariable adjusted OR (95% CI) for Quartile 1 (shortest) vs. 4 (longest) = 0.97 (0.48, 1.96), per 1 SD decrease in TL=0.99 (0.74, 1.31)] or the combined dataset [multivariable adjusted OR (95% CI) for Quartile 1 (shortest) vs. 4 (longest) = 1.36 (0.85, 2.17), per 1 SD decrease in TL=1.12 (0.92, 1.36)](Table 2). Results did not change materially in the sensitivity analysis among cases (n=288/632) diagnosed 2 years since blood collection [multivariable adjusted OR (95% CI) per 1 SD decrease in TL=1.17 (0.94, 1.46) among all participants]. The null association pattern did not differ

according to cancer subsites (Table 2) and subgroups stratified by pre-selected lifestyle factors including smoking, body mass index, physical activity, AHEI, alcohol intake and regular aspirin use (Supplementary Table S1).

DISCUSSION

Our nested case-control within two prospective cohorts did not find a significant association between pre-diagnostic peripheral blood leucocyte TL and risk of CRC. Our results were in line with prospective evidence from Women's Health Study (WHS)[9], Physicians' Health Study (PHS),[10] and European Prospective Investigation into Cancer (EPIC) cohort,[8] which reported similar null associations of TL and CRC risk. Interesting, longer TL was associated with higher CRC risk in Singapore Chinese Health Study (SCHS)[6] while Shanghai Women's Health Study (SWHS) reported a U-shaped association.[5] In comparison, a few retrospective studies where TL measurements were made after CRC was diagnosed reported that shorter TL was associated with increased risk of CRC;[8, 13] however, these estimates may be influenced by reverse causation.

The biological mechanisms underlying the TL/cancer relationship are complex. With each cell division, telomeres lose some sequences. Progressive telomere shortening below a critical length can trigger a DNA damage crisis featured by chromosomal instability, a characteristic of cancer. Subsequently, cells with telomere dysfunction may either enter a state of permanent growth arrest (senescence) or go through programmed cell death (apoptosis).[1, 2, 4] Rarely, some cells (i.e., preneoplastic/cancerous cells) may bypass senescence or apoptosis and continue to proliferate, which further exacerbates telomere erosion and genomic instability. Meanwhile, in these cells, telomerase (an enzyme that adds telomeric repeats to the end of chromosome) may be activated or there is an alternative lengthening of telomeres (ALT) mechanism, which stabilized telomeres; this process is thought to facilitate tumor initiation and progression.[1, 2, 4]

This bi-directional mechanism may help explain the inconsistent directions and small magnitudes of the TL/CRC associations (point estimates ~ 0.94 – 1.61) reported in previous studies.[3, 5–8] Because both telomere erosion and elongation may occur before/during tumorigenesis, an overall null association could be observed in epidemiological studies such as ours. The relationship between TL and cancer may also be cancer type specific.[12]

Our study has several advantages. First, our prospective design and the assessment of pre-diagnostic TL minimized potential reverse effect of undiagnosed CRC if any at blood collection on TL. The robustness of our finding was further supported by a sensitivity analysis among cases diagnosed ≥ 2 years since blood collection. Besides, detailed covariables information collected through NHS/HPFS cohort follow-ups provided the opportunities for multivariable adjustment and effect modification examinations in our study. We also acknowledge some limitations. First, we cannot fully rule out residual confounding due to the observational nature of our study although we have adopted a matched design and comprehensively adjusted a list of covariables. Also, the modest sample size of our study may limit the statistical power especially for subsite cancer/stratified analyses. Additionally, in our study, leukocyte TL was measured as a biomarker of interest. Although recent

research found that TL was in general positively correlated across various human tissues and leukocyte TL can be a proxy for TL in most tissues including human colon,[14] independent telomere events may occur in local tissues during CRC development.

Overall, based on our prospective analysis, leukocyte TL may not be a strong predictor of CRC risk. Future research may further examine the relationship of the changes of TL with CRC risk. Additionally, more basic research are needed to study the biology of telomere in the pathogenesis of different cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement:

The data of this study are available upon reasonable request. Further information including the procedures to obtain and access data from the Nurses' Health Studies and Health Professionals Follow-up Study is described at https://www.nurseshealthstudy.org/researchers (contact email: nhsaccess@channing.harvard.edu) and https://sites.sph.harvard.edu/hpfs/for-collaborators/.

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HIGHLIGHTS

- Basic research has shown both telomere erosion and elongation may occur before/during tumorigenesis
- Prospective epidemiologic evidence relating TL and CRC risk has been limited and inconsistent
- We examined the TL/CRC association using prospective data from two U.S. cohorts
- Our study did not support TL as a strong predictor of CRC risk

Table 1.

Characteristics of CRC cases and controls in two nested case-control studies within the NHS and HPFS

	NHS		HPFS	
Characteristic	**Cases**	**Controls**	**Cases**	**Controls**
Number of cases, n	186	465	170	336
Telomere length, z score	−0.05 (1.1)	0.008 (1.0)	0.03 (1.0)	0.02 (1.0)
Age at blood collection, yrs	60.1 (6.6)	60.1 (6.5)	66.8 (8.0)	66.7 (8.1)
Age at CRC diagnosis, yrs	65.7 (7.1)	-	71.1 (8.2)	-
Years from blood collection to diagnosis, yrs	5.6 (3.3)	-	4.3 (2.4)	-
Sex, female%	100	100	0	0
Race, white%	100	100	93.1	93.1
Body mass index, kg/m^2	25.6 (5.2)	25.4 (4.5)	25.9 (3.0)	25.4 (2.8)
Physical activity, MET-hours/week	17.2 (15.8)	19.7 (20.3)	30.8 (27.4)	30.3 (27.3)
Smoking status, %				
Never	42.5	45.6	40.6	44.4
Past	41.4	41.9	53.5	50.3
Current	16.1	12.5	5.9	5.4
Alternate Healthy Eating Index	48.1(9.3)	49.5 (10.2)	47.7 (10.9)	49.1 (10.4)
Alcohol consumption, g/d	6.6 (10.4)	5.5 (10.0)	12.0 (15.7)	12.2 (15.0)
Family history of CRC, %	18.8	15.5	21.2	13.1
Regular aspirin users, %	44.6	48.2	37.1	46.1
Regular non-aspirin NSAIDs users, %	14.5	18.1	10	11.3

Note: Abbreviations: CRC: colorectal cancer; NHS: Nurses' Health Study; HPFS: Health Professionals Follow-Up Study. Values are means (standard deviation, SD) for continuous variables and percentages for categorical variables. The alternative healthy eating index (AHEI) is an established dietary score that measures adherence to a diet pattern based on 10 components of foods and nutrients that are most predictive of disease risk in the literature, including vegetables, fruits, whole grains, sugar-sweetened beverages and fruit juice, nuts and legumes, red meat and processed meat, trans fat, long-chain (n-3) fats (EPA + DHA), poly-unsaturated fatty acids, and sodium intakes. Higher score indicates higher diet quality (score range: 0–100).

Table 2.

ORs (95% CIs) for the associations between pre-diagnostic TL and risks of CRC overall and by subsites

	Quartile 4 (longest)	Quartile 3	Quartile 2	Quartile 1 (shortest)	Per 1 SD decrease	P for trend
NHS	40/123	51/112	45/118	50/112		
Model 1	ref	1.48 (0.86, 2.54)	1.29 (0.73, 2.28)	1.70 (0.91, 3.18)	1.21 (0.93, 1.58)	0.16
Model 2	ref	1.45 (0.84, 2.52)	1.25 (0.69, 2.27)	1.74 (0.91, 3.32)	1.23 (0.93, 1.61)	0.15
HPFS	42/84	42/85	43/84	43/83		
Model 1	ref	0.99 (0.56, 1.75)	1.03 (0.57, 1.87)	1.07 (0.54, 2.10)	1.03 (0.78, 1.35)	0.83
Model 2	ref	0.97 (0.54, 1.77)	0.95 (0.51, 1.76)	0.97 (0.48, 1.96)	0.99 (0.74, 1.31)	0.92
NHS+HP FS	81/208	94/196	88/201	93/196		
Model 1	ref	1.27 (0.86, 1.89)	1.20 (0.79, 1.81)	1.40 (0.88, 2.22)	1.13 (0.93, 1.37)	0.21
Model 2	ref	1.24 (0.83, 1.85)	1.14 (0.74, 1.74)	1.36 (0.85, 2.17)	1.12 (0.92, 1.36)	0.27
Colon	55/137	66/129	62/152	72/143		
Model 1	ref	1.31 (0.81, 2.10)	1.10 (0.67, 1.80)	1.42 (0.83, 2.42)	1.12 (0.90, 1.41)	0.31
Model 2	ref	1.29 (0.80, 2.08)	1.07 (0.64, 1.77)	1.40 (0.81, 2.41)	1.12 (0.89, 1.41)	0.32
Proximal colon	27/74	32/70	37/73	38/77		
Model 1	ref	1.37 (0.70, 2.69)	1.55 (0.80, 3.00)	1.68 (0.80, 3.54)	1.24 (0.92, 1.68)	0.16
Model 2	ref	1.37 (0.67, 2.79)	1.39 (0.69, 2.80)	1.54 (0.71, 3.34)	1.18 (0.86, 1.61)	0.32
Distal colon	28/63	34/59	25/79	34/66		
Model 1	ref	1.23 (0.63, 2.38)	0.67 (0.32, 1.43)	1.07 (0.49, 2.32)	1.00 (0.71, 1.39)	0.97
Model 2	ref	1.21 (0.62, 2.36)	0.75 (0.35, 1.64)	1.15 (0.52, 2.58)	1.04 (0.74, 1.48)	0.82
Rectum	21/59	25/56	23/37	17/38		
Model 1	ref	1.37 (0.64, 2.93)	1.88 (0.80, 4.40)	1.55 (0.56, 4.28)	1.26 (0.84, 1.90)	0.26
Model 2	ref	1.33 (0.61, 2.92)	1.76 (0.71, 4.39)	1.38 (0.47, 4.04)	1.20 (0.78, 1.86)	0.41

Note: Abbreviation: OR: odds ratio, CI: confidence interval, TL: telomere length, CRC: colorectal cancer, ref: reference group, SD: standard deviation; Model 1: Conditional logistic regression model conditioning on matching factors (age at blood draw, race and fasting status); Model 2: Conditional logistic regression model conditioning on matching factors (age at blood collection, race and fasting status), and further adjusting for body mass index (continuous), physical activity (continuous), smoking status (never, former, or current smokers), alcohol consumption (continuous), Alternate Health Eating Index (continuous), regular aspirin use (yes/no), regular non-aspirin NSAIDs use (yes/no), and family history of colorectal cancer (yes/no); No significant heterogeneity was detected between NHS and HPFS (P for heterogeneity = 0.28). Associations between TL and cancers at subsites were examined among all participants (NHS+HPFS).