The Causal Relationship between Telomere Length and Cancer Risk: A Two-Sample Mendelian Randomization

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ABSTRACT

Background: Telomere length (TL) shortens with age and is associated with an increased risk of numerous chronic diseases. However, the causal direction of the association between TL and cancer risk remains uncertain. This study aimed to assess the causal impact of TL on cancer risk using Mendelian randomization (MR) analysis.

Methods: Genome-wide association studies from Singapore and China data, the Korean Cancer Prevention Study II (KCPS-II), the Korean Genome Epidemiologic Study, and the Biobank of Japan were utilized. A two-sample MR study was performed using summary-level genome-wide association study data from individuals of East Asian ancestry. SNPs associated with TL were used as instrumental variables.

Results: Longer TL per 1-SD increase due to germline genetic variants was associated with a higher risk of site-specific cancer. In the KCPS-II and Korean Genome Epidemiologic Study, the strongest association was observed with thyroid cancer {OR, 2.49 [95% confidence interval (CI), 1.79–3.47] and 2.27 (1.49–3.46)}, followed by lung cancer [OR, 2.19 (95% CI, 1.60–3.08) and 1.45 (1.12–1.87)]. Similar results were observed in the Biobank of Japan, with OR, 2.92 (95% CI, 1.75–4.88) for thyroid cancer and 2.04 (1.41–2.94) for lung cancer. In histologic subgroup analysis of KCPS-II, a significant relationship was found with lung adenocarcinoma [OR, 2.26 (95% CI, 1.55–3.31)] but not with lung squamous cell carcinoma (1.21, 0.47–3.06). After removing outlier SNPs in the radial MR analysis, significant associations were identified for both lung adenocarcinoma [OR, 1.88 (95% CI, 1.25–2.82)] and lung squamous cell carcinoma (2.29, 1.05–4.98).

Conclusions: Our findings suggest that longer TL increases the risk of various cancers in East Asian populations.

Impact: Genetically determined longer TL may contribute to a risk of certain cancers.

Introduction

Telomeres are nucleoprotein complexes located at the ends of linear chromosomes, playing a crucial role in maintaining chromosomal integrity (1). They shorten with each cell cycle, reflecting cellular aging and organismal aging (2). The critical functions of telomeres and telomerase in carcinogenesis have led to the hypothesis that short telomere length (TL) is a risk factor for cancer (3). Epidemiologic studies have shown that relatively short TLs are associated with an increased risk of various cancers, including lung (4, 5), ovarian, colorectal (6), and breast cancers (7, 8). However, causal inferences from observational studies are often hindered by potential confounding bias and reverse causation, leaving uncertainties about the direction and strength of the associations observed.

Gene-based Mendelian randomization (MR) is a recently developed method that addresses these issues by allowing for conclusions about causal associations under the assumption that genes are randomly assigned, thereby circumventing the influence of confounding variables (9, 10).

In causal MR studies, short TLs have been associated with an increased risk of glioma, ovarian cancer, lung adenocarcinoma (11), neuroblastoma, bladder cancer, melanoma, testicular cancer, kidney cancer, and endometrial cancer (12). Notably, these MR studies have primarily been conducted in European populations, limiting the generalizability of their findings to East Asian populations. Furthermore, there is a significant lack of research on cancers prevalent in Asians, such as stomach and thyroid cancers.

Against the backdrop of the rapid advancement of large-scale genome-wide association studies (GWAS), MR analysis leverages genetic variants strongly associated with exposure as instrumental variables to investigate causal relationships between exposures and outcomes (13). Although research evidence on genetic susceptibility to various cancer types from large-scale biobank studies in Asia remains limited, this study utilized biobank data from Korea, Japan, and Singapore.

Materials and Methods

Genetic instruments for TL

Genetic instrumental variables for TL were identified using data from 16,759 Southern Han Chinese samples and 6,407,959 SNPs from the Singapore Chinese Health Study (14). The selection of instrumental variables for MR analysis followed these criteria: First,

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Cancer Epidemiol Biomarkers Prev 2025;34:737–43

doi: 10.1158/1055-9965.EPI-24-1168

genome-wide significance: SNPs with a P value less than the genome-wide significance threshold ($P < 5 \times 10^{-8}$) were selected. Second, minor allele frequency (MAF): SNPs with an MAF greater than 0.01 were selected. Third, linkage disequilibrium: SNPs in linkage disequilibrium were excluded based on a clump threshold of $r^2 < 0.01$. Finally, palindromic SNPs: Palindromic SNPs with an MAF >0.42 were excluded (15).

Genetic associations of SNPs with cancer risk

We utilized only summary-level data analyzed through PLINK for this study. The summary data for MR analysis were obtained from three biobanks (**Fig. 1**): the Korean Cancer Prevention Study-II (KCPS-II; ref. 16), the Korean Genome Epidemiology Study (KoGES; ref. 17), and the Biobank of Japan (BBJ; ref. 18). KCPS-II: This biobank includes data from 159,844 individuals collected from 18 health examination centers across South Korea between 2004 and 2013. KoGES: This biobank comprises data from 211,285 individuals, including participants from local communities (n = 10,006), urban areas (n = 172,968), and rural areas (n = 28,311), collected during the same period (2004–2013). Both KCPS-II and KoGES are linked to cancer registration data from the National Cancer Center to track cancer occurrence. BBJ: This biobank contains data from 201,800 patients collected from 66 hospitals across Japan between 2003 and 2008 (**Fig. 1**).

MR

In MR, G-X represents the exposure GWAS, referring to the association between genotype and exposure, whereas G-Y represents the outcome GWAS, referring to the association between genotype and outcome. For this study, G-X data on exposure for two-sample MR were derived from the Singapore Chinese Health Study, whereas G-Y outcome data were obtained from KCPS-II, KoGES, and BBJ (**Fig. 1**). The β values were estimated using the inverse-variance weighted (IVW) method under the assumption that all selected SNPs were valid instrumental variables. The β value for each SNP was first calculated using the Wald ratio method and then combined using the IVW method. Finally, a meta-analysis was performed to determine the overall effect sizes by combining the results from the three datasets.

Sensitivity analysis

Several MR methods were applied to conduct sensitivity analyses in MR. For single-variable MR in two-sample MR (19), weighted median (20), weighted mode (21), and MR-Egger approaches were used (22).

MR-Egger: Under the Instrument Strength Independence of Direct Effect (InSIDE) assumption, this method estimates β values even if all SNPs are invalid instruments (23). Weighted median regression: This method does not require the InSIDE assumption and estimates β values under the assumption that at least 50% of SNPs are valid instruments. Weighted mode: This approach estimates causal effects based on subsets of SNPs, allowing for heterogeneity in the validity of instrumental variables.

Additionally, radial MR (24) and MR-PRESSO were performed to detect and account for horizontal pleiotropy (7). Heterogeneity was assessed using the Cochran Q test to determine whether a single instrumental variable (IV) was driving the outcome and to evaluate the consistency of MR assumptions and analyses. All analyses were conducted using the RadialMR, TwoSampleMR, and MR-PRESSO packages in R (version 3.6.0, R Project for Statistical Computing). To account for multiple comparisons, the Bonferroni correction was applied. A P value less than 0.0036 (0.05/14) was considered strong evidence for causal relationships.

Data availability

This study was conducted using the KCPS-II biobank resource under proposal number 202301, with access granted to S.H. Lee and S.H. Jee. The BBJ data are publicly available upon application via the BBJ Biobank website (https://pheweb.jp/phenotypes). Summary statistics for GWAS results will be made available to download from the GWAS Catalog (14).

Ethics statement

All participants in the Korean dataset provided written informed consent. This study complies with all relevant ethical regulations and was approved by the Severance Hospital Ethics Committee (reference number: 4-2011-0277).

Results

Table 1 presents the association between TL and the risk of all cancers and site-specific cancers in KCPS-II and KoGES cohorts, both of which are Korean biobanks. In both datasets, longer TL was positively associated with an increased risk of all cancers. Specifically, the corresponding OR [95% confidence interval (CI)] for a 1-SD increase in TL for all cancers was 1.51 (1.28–1.77) in KCPS-II and 1.25 (1.13–1.37) in KoGES. For site-specific cancers, positive

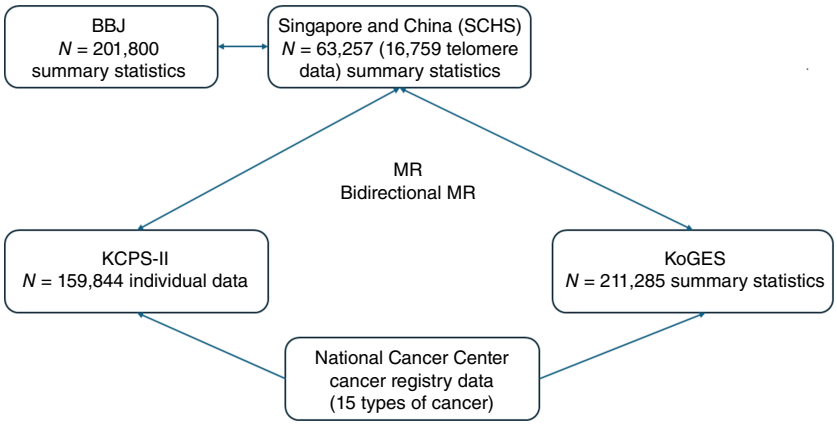

Figure 1.
MR design overview. The summary data for MR analysis were obtained from three biobanks. SCHS, Singapore Chinese Health Study.

Table 1. MR results of TL with cancer in KCPS-II and KoGES.

	KCPS-II (*N* = 159,844)			KoGES (*N* = 211,285)		
Cancer type	**Cases**	**OR (95% CI)**	***P* value**	**Cases**	**OR (95% CI)**	***P* value**
All cancers	14,239	1.51 (1.28–1.77)	4.55×10^{-7}	23,471	1.25 (1.13–1.37)	3.06×10^{-6}
Thyroid	3,761	2.49 (1.79–3.47)	7.08×10^{-8}	4,176	2.27 (1.49–3.46)	0.0001
Lung	892	2.19 (1.60–3.08)	6.13×10^{-6}	1,799	1.45 (1.12–1.87)	0.0004
Bladder	222	1.89 (1.01–3.56)	0.0481	458	1.72 (1.01–2.96)	0.0011
Kidney	425	1.84 (1.06–3.19)	0.0298	524	2.45 (1.53–3.91)	0.0001
Cervical	201	1.83 (0.95–3.52)	0.0705	751	1.01 (0.69–1.52)	0.4217
Larynx	57	1.68 (0.43–6.57)	0.4582	124	1.71 (0.69–4.19)	0.2451
Breast	1,361	1.34 (0.99–1.81)	0.0619	2,782	1.04 (0.72–1.49)	0.8165
Colorectal	1,170	1.25 (0.98–1.60)	0.0662	2,764	0.97 (0.75–0.1.26)	0.8564
Prostate	849	1.08 (0.69–1.67)	0.7195	1,190	1.37 (0.93–2.03)	0.1056
Ovarian	117	1.08 (0.70–1.68)	0.7195	345	0.94 (0.53–1.64)	0.8293
Liver	562	0.94 (0.62–1.42)	0.7757	1,197	0.94 (0.59–1.51)	0.8195
Stomach	1,750	0.85 (0.67–1.08)	0.1827	3,564	0.77 (0.63–0.94)	0.0099
Pancreatic	244	0.78 (0.37–1.63)	0.5039	529	0.61 (0.35–1.02)	0.0635
Gallbladder	122	0.24 (0.07–0.83)	0.0241	591	0.41 (0.24–0.66)	0.0003

associations were observed for thyroid, lung, bladder, and kidney cancers in both cohorts. Additionally, borderline significant associations were identified for cervical, breast, and colorectal cancers in KCPS-II. Interestingly, negative associations were noted for stomach and gallbladder cancers in certain cases.

Table 2 presents the results of the sensitivity analyses. In the KCPS-II cohort, all intercept tests for evaluating pleiotropy were nonsignificant and none of the MR-Egger results reached significance, suggesting no evidence of pleiotropy. Conversely, for cancers that showed significant associations in **Table 1**—specifically all cancers, thyroid cancer, and lung cancer—both weighted median and weighted mode methods yielded significant results. Similarly, in the KoGES cohort, the intercept term was significant for colorectal cancer but nonsignificant for all other cancers. Sensitivity analyses demonstrated significant findings for all cancers (Supplementary Fig. S1), whereas some analyses also revealed significant associations for thyroid, colorectal, and prostate cancers.

Table 3 presents the validation of the Korean analysis results from **Tables 1** and **2** using Japanese data from the BBJ cohort. Similar findings were observed in BBJ for thyroid and lung cancers (Supplementary Fig. S2). The intercept test and MR-Egger results were nonsignificant, indicating no evidence of pleiotropy. Furthermore, sensitivity analyses also yielded significant results. In addition to thyroid and lung cancers, BBJ data revealed positive associations for colorectal and prostate cancers using the IVW method in the sensitivity analyses.

Figure 2 illustrates meta-analysis results combining data from three biobanks (the Korean data KCPS-II and KoGES and the Japanese cohort BBJ). Overall, longer TL was associated with a 1.36-fold increase in the risk of all cancers. By cancer type, significant increases in risk were observed for thyroid (2.50-fold), kidney (2.43-fold), lung (1.83-fold), bladder (1.70-fold), prostate (1.48-fold), breast (1.20-fold), and colon cancers (1.14-fold). Notably, for most cancer sites, the I^2 value was 0%, indicating no heterogeneity across studies, except for lung and pancreatic cancers.

This study conducted additional analyses based on histologic subtypes of lung cancer (Supplementary Tables S1). In the KCPS-II data, lung adenocarcinoma showed a significant OR of 2.26 (95% CI, 1.55–3.31) using the IVW method. For lung squamous cell carcinoma, the IVW method results were not significant; however, after excluding two extreme values in the radial MR analysis, the OR became significant at 2.29 (95% CI, 1.05–4.98). Across both histologic types, the OR for the association between long TL and lung cancer was approximately twofold higher. In the KoGES data (Supplementary Table S2), only lung adenocarcinoma showed a significant OR of 1.79 (95% CI, 1.21–2.68) using the IVW method, whereas lung squamous cell carcinoma remained nonsignificant in the IVW analysis (Supplementary Fig. S3).

Additionally, the relationship between long TL and lung cancer was analyzed based on the Surveillance, Epidemiology, and End Results (SEER) stage (Supplementary Table S3). In the KCPS-II data, the OR was highest for localized-stage lung cancer at 3.83 (95% CI, 2.16–6.81), followed by distant-stage lung cancer with an OR of 2.67 (95% CI, 1.45–4.92). Regional-stage lung cancer did not show a significant association.

A similar analysis was conducted using KoGES data. The OR for localized-stage lung cancer was the highest at 2.26 (95% CI, 1.51–3.39), and regional-stage lung cancer also showed a significant association with an OR of 1.67 (95% CI, 1.06–2.65; Supplementary Table S4). Additionally, bidirectional MR analysis revealed no significant associations for any type of cancer (Supplementary Table S5).

Discussion

This study provides robust evidence that long TL is associated with an increased risk of site-specific cancers, including thyroid, lung, and colorectal cancers, based on data from large Korean and Japanese biobanks. These findings highlight the potential role of TL as a biomarker and a causal factor in cancer development.

This study utilized the Korean biobanks KCPS-II ($n = 159,844$; Supplementary Figs S4–S18) and KoGES ($n = 211,285$), along with the Japanese biobank BBJ ($n = 201,800$; Supplementary Figs. S19–S31), to explore the relationship between long TL and site-specific cancer development using two-sample MR.

Table 2. MR results (sensitivity analysis) of the association of TL (SCHS East Asian individuals) with cancer (KCPS-II).

Cancer type	Number of SNPs	MR-Egger	Weighted median	Weighted mode	Intercept test
		OR (95% CI)	OR (95% CI)	OR (95% CI)	*P* value
KCPS-II					
All cancers	10	1.36 (0.86–2.16)	1.39 (1.21–1.61)	1.32 (1.08–1.62)	0.6593
Thyroid	10	2.61 (0.99–6.84)	2.17 (1.68–2.82)	1.95 (1.41–2.72)	0.9202
Lung	10	2.05 (0.81–5.21)	2.08 (1.35–3.22)	2.15 (1.26–3.68)	0.8909
Bladder	10	1.46 (0.26–8.24)	1.76 (0.81–3.82)	1.66 (0.62–4.43)	0.7641
Kidney	10	2.25 (0.45–11.28)	1.82 (0.91–3.67)	1.32 (0.46–3.82)	0.7989
Cervical	10	2.18 (0.36–13.11)	1.79 (0.76–4.25)	1.49 (0.41–5.42)	0.8396
Larynx	10	0.97 (0.01–51.95)	1.18 (0.21–6.68)	0.88 (0.11–7.26)	0.7804
Breast	10	1.61 (0.67–3.81)	1.41 (0.97–2.03)	1.25 (0.71–2.18)	0.6678
Colorectal	10	1.27 (0.65–2.47)	1.32 (0.97–1.78)	1.33 (0.91–1.98)	0.9592
Prostate	10	0.86 (0.24–3.06)	1.11 (0.71–1.75)	1.11 (0.61–2.01)	0.7201
Ovarian	10	0.86 (0.24–3.06)	1.11 (0.71–1.76)	1.11 (0.61–2.02)	0.7201
Liver	10	0.81 (0.26–2.52)	1.08 (0.64–1.81)	1.03 (0.46–2.29)	0.7963
Stomach	10	0.78 (0.41–1.51)	0.81 (0.61–1.11)	0.83 (0.58–1.19)	0.8068
Pancreatic	10	3.17 (0.48–20.94)	1.05 (0.45–2.42)	1.16 (0.47–2.88)	0.1546
Gallbladder	10	0.52 (0.14–1.95)	0.55 (0.11–2.82)	0.78 (0.02–25.91)	0.5032
KoGES					
All cancers	10	1.25 (1.12–1.41)	1.29 (1.11–1.49)	1.42 (1.11–1.84)	0.3114
Thyroid	10	1.81 (1.27–2.55)	1.13 (0.49–2.59)	2.17 (0.63–7.42)	0.9421
Lung	10	0.24 (0.88–1.74)	1.18 (0.74–1.88)	0.94 (0.47–1.87)	0.2226
Bladder	10	1.12 (0.25–4.99)	1.71 (0.84–3.46)	1.74 (0.69–4.39)	0.5662
Kidney	10	4.55 (1.27–16.29)	2.45 (1.28–4.65)	2.13 (0.85–5.31)	0.3335
Cervical	10	1.14 (0.67–1.94)	1.19 (0.61–2.31)	1.06 (0.36–3.13)	0.9429
Larynx	10	0.41 (0.03–5.02)	1.39 (0.43–4.48)	1.36 (0.31–6.05)	0.2662
Breast	10	1.11 (0.81–1.53)	1.14 (0.73-1.78)	1.41 (0.51–3.91)	0.5434
Colorectal	10	1.11 (0.84–1.46)	1.17 (0.87–1.58)	1.93 (1.09–3.41)	0.0364
Prostate	10	1.63 (1.05–2.54)	1.83 (0.92–3.67)	1.79 (0.56–5.41)	0.6277
Ovarian	10	2.51 (0.55–11.34)	1.01 (0.48–2.08)	1.13 (0.49–2.62)	0.2101
Liver	10	1.02 (0.64–1.64)	1.21 (0.66–2.19)	1.23 (0.32–4.69)	0.6866
Stomach	10	0.86 (0.67–1.11)	0.91 (0.68–1.22)	1.09 (0.65–1.81)	0.1977
Pancreatic	10	0.59 (0.29–1.21)	0.58 (0.22–1.55)	0.78 (0.16–3.68)	0.7264
Gallbladder	10	0.35 (0.18–0.67)	0.33 (0.15–0.72)	0.35 (0.08–1.38)	0.8381

Abbreviation: SCHS, Singapore Chinese Health Study.

This study used SNPs associated with TL, as identified by the Singapore biobank, as instrumental variables (Supplementary Table S6; Supplementary Fig. S3) and conducted two-sample MR analyses with cancer incidence as the outcome in Korean and Japanese datasets (**Fig. 1**).

The results consistently demonstrated OR ranging from 1.4 to 2.5 for overall, thyroid, and lung cancers. For lung cancer, histologic subtype analysis showed a consistent relationship only for lung adenocarcinoma, with an OR of 2.26 in KCPS-II and 1.79 in KoGES.

In the SEER stage analysis, a consistent association was observed only for localized-stage lung cancer, with an OR of 3.83 in KCPS-II and 2.26 in KoGES. Sensitivity analysis further supported this relationship, showing no evidence of horizontal pleiotropy.

Our study is notable for being the largest to date conducted on an Asian population to investigate the relationship between telomeres and cancer occurrence using two-sample MR, and it aligns with previous findings from predominantly Western populations. Additionally, a meta-analysis was performed on the ORs derived from three independent biobank datasets, resulting in a combined OR. The meta-analysis revealed an I^2 value of 0% across all cancer types except lung and pancreatic cancers, indicating minimal heterogeneity in the genetic influence of TL across Asian biobanks. These findings are unique and not commonly observed in meta-analyses of observational studies.

TL plays a crucial role in cellular replication, influencing cancer risk through mechanisms involving telomere-regulating genes such as *TERT* and *TERC*. Excessively long telomeres can facilitate uncontrolled cell division, a hallmark of cancer cells (25). Notably, East Asian populations exhibit a higher prevalence of certain telomere-associated genetic mutations, which may increase susceptibility to lung cancer (26). Environmental factors also play a significant role in telomere maintenance. Variables such as physical activity, body mass index, hormone replacement therapy, smoking, chronic inflammation, oxidative stress, dietary antioxidants, and vitamin intake can all affect TL (27). This interplay between genetic predisposition and environmental exposures profoundly shapes cancer susceptibility in East Asian populations (28, 29).

Based on our results, comparisons with Western studies reveal notable differences. First, an observational study conducted in Western populations reported that shorter TL increases cancer risk (6), which is entirely inconsistent with our results. A 2019 review of observational studies (1) by Smith and colleagues included a meta-analysis of 50 outcomes. Of these, only stomach cancer showed a significant association with short TL [OR, 1.95 (95% CI, 1.68–2.26)].

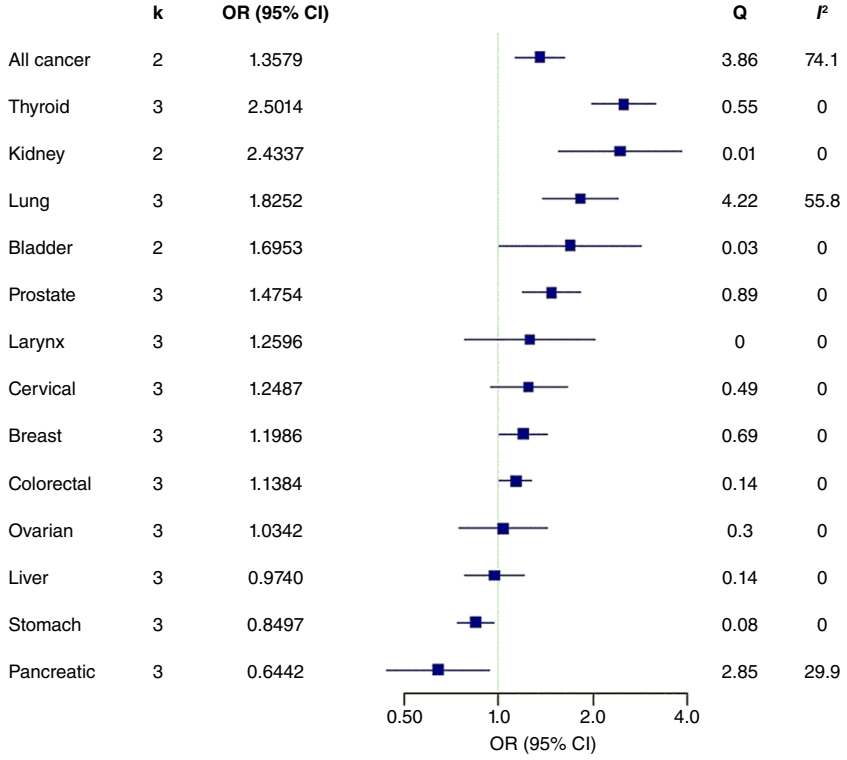

Figure 2.
Combined effect of TL with cancer in three biobanks (KCPS-II, KoGES and BBJ). Results of the meta-analysis combining data from three biobanks are illustrated. Overall, longer TL was associated with a 1.36-fold increase in the risk of all cancers.

As these findings are based on observational studies, they likely reflect residual confounding effects. A key factor that may explain the discrepancy between previous observational studies and our MR results is the influence of age. TL typically shortens with age, and cancer risk increases with advancing age. Therefore, the confounding effect of age may partially account for the association observed in observational studies.

In 2013, Lan and colleagues reported that longer TL in peripheral white blood cells was associated with an increased risk of lung cancer in women. However, the study had a limited sample size, with only 215 patients and 215 controls (5). Subsequently, in 2015, a meta-analysis involving participants from China, Korea, Japan, Singapore, Taiwan, and Hong Kong synthesized the results of 14 studies. This analysis found that the upper quartile compared with lower quartile of weighted TL genetic risk scores was associated with an increased OR for female lung cancer [OR, 1.51 (95% CI, 1.34–1.17); ref. 9]. The genetic risk score used in the study included seven SNPs: *rs10936599*, *rs2736100*, *rs7675998*, *rs9420907*, *rs8105767*, *rs755017*, and *rs11125529*. Of these, rs2736100 (*TERT*) had already been implicated in previous studies (5, 8), whereas the *TERC* locus (*rs10936599*) was reported in the study by Machiela and colleagues However, these studies did not explore associations with histologically classified subtypes of lung cancer.

Table 3. MR results and sensitivity analysis of TL with cancer in BBJ ($N = 201{,}800$).

		IVW method		MR-Egger	Weighted median	Weighted mode	Intercept test
Cancer type	**Cases**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	***P* value**
Thyroid	361	2.92 (1.75–4.88)	4.18×10^{-5}	2.34 (0.55–9.85)	2.46 (1.19–5.06)	2.13 (0.75–6.05)	0.7531
Lung	4,444	2.04 (1.41–2.94)	1.55×10^{-4}	1.09 (0.41–2.95)	1.54 (1.24–1.92)	1.54 (1.24–1.92)	0.2258
Cervical	967	1.27 (0.91–1.78)	0.8661	1.38 (0.51–3.77)	1.09 (0.69–1.73)	0.89 (0.41–1.93)	0.8661
Larynx	300	1.12 (0.63–1.97)	0.6923	1.11 (0.22–5.44)	1.02 (0.48–2.17)	0.95 (0.31–2.94)	0.9919
Breast	6,325	1.22 (0.98–1.52)	0.0682	0.72 (0.43–1.22)	1.15 (0.93–1.43)	1.01 (0.68–1.46)	0.0705
Colorectal	8,305	1.14 (1.01–1.31)	0.0292	1.45 (1.05–2.01)	1.21 (1.03–1.42)	1.29 (0.99–1.69)	0.1587
Prostate	5,672	1.46(1.15–1.87)	1.87×10^{-3}	1.62 (0.79–3.32)	1.64 (1.32–2.03)	1.63 (1.23–2.17)	0.7823
Ovarian	843	1.11 (0.73–1.67)	0.6251	0.85 (0.25–2.89)	1.21 (0.75–1.93)	1.22 (0.62–2.38)	0.6676
Liver	2,122	0.97 (0.75–1.24)	0.8196	1.06 (0.51–2.21)	1.05 (0.77–1.43)	1.21 (0.73–2.01)	0.7361
Stomach	7,921	0.85 (0.73–1.01)	0.0604	0.66 (0.43–1.02)	0.91 (0.75–1.07)	0.93 (0.67–1.31)	0.2436
Pancreatic	499	0.61 (0.39–0.95)	0.0301	0.49 (0.14–1.69)	0.61 (0.34–1.04)	0.63 (0.31–1.29)	0.7172
Hepatic bile duct	418	2.26 (1.55–3.31)	2.36×10^{-5}	1.94 (1.16–3.26)	1.85 (0.93–3.69)	2.64 (0.88–7.88)	0.7772

In 2017, the Telomeres Mendelian Randomization Collaboration published a study based on large-scale Western population data, including 420,081 patients with cancer and 1,093,104 controls (12). This study performed MR analysis using summary data for 35 cancers and 48 nonneoplastic diseases. A strong association was reported for lung adenocarcinoma [OR, 3.19 (95% CI, 2.40–4.22)], which aligns closely with the findings of our study. Conversely, lung squamous cell carcinoma was not significant [OR, 1.07 (95% CI, 0.82–1.39)]. In our KCPS-II analysis, lung squamous cell carcinoma was also not significant using the IVW method. However, after removing two extreme Q10 SNPs in radial MR analysis, lung squamous cell carcinoma was significant [OR, 2.29 (95% CI, 1.05–4.98)]. The Telomeres Mendelian Randomization Collaboration study also reported significant associations for glioma [OR, 5.27 (95% CI, 3.15–8.81)] and ovarian cancer [OR, 4.35 (95% CI, 2.39–7.94); ref. 12]. However, no associations with these cancers were observed in our study, suggesting that further research is needed to clarify these relationships. Overall, the Telomeres Mendelian Randomization Collaboration study concluded that genetically increased telomeres is associated with a heightened risk of site-specific cancers. Among the 23 carcinomas analyzed, increased TL significantly elevated the risk of several cancers, with none showing a significantly reduced risk (11).

In 2022, the results of a systematic review of 190 MR studies were published (13). Among these, 13 studies focused on telomeres, but the findings were inconsistent, particularly with regard to their relationship with cancer. According to figure 5 of that review, TL was associated with an increased risk of overall cancer and lung adenocarcinoma but a decreased risk of thyroid cancer, skin cancer, and leukemia. The review also highlighted that 68.6% of the included studies did not perform sensitivity analysis. Compared with our study, the observed increase in lung adenocarcinoma risk is consistent. However, the reported decrease in thyroid cancer risk is inconsistent with our findings. Among the studies concluded to date, particularly in Western populations, TL and lung cancer have been extensively studied, and the results have been largely consistent.

However, in an MR review article published in 2022, the claim that long TL reduces the risk of thyroid cancer is inconsistent with our findings (13). On the contrary, multiple studies have reported that longer telomeres are associated with an increased risk of thyroid cancer. For example, a 2022 study by Lulu Huang found that longer TL increased the risk of thyroid cancer by 4.68 times (95% CI, 2.35–9.31; ref. 30). Similarly, a phenome-wide MR study (MR-PheWAS) published in 2023 reported a 2.55-fold increase in thyroid cancer risk (95% CI, 1.66–3.92; ref. 31). In our study, the risk of thyroid cancer increased approximately twofold with longer TL, findings that were validated in both Japanese (BBJ) and Korean (KoGES) data. Furthermore, the analysis included a total of 12,381 thyroid cancer cases: 3,761 from KCPS-II, 4,176 from KoGES, and 4,444 from BBJ, derived from a combined population of 572,929 individuals across the three biobanks. These results underscore the need for further research to comprehensively evaluate the relationship between TL and thyroid cancer, particularly given the discrepancies across studies.

In this study, the relationship between long TL and lung cancer was analyzed according to SEER stage. The results showed that the localized-stage lung cancer had the highest OR of 3.83 (95% CI, 2.16–6.81) in the KCPS-II data, with similar findings observed in the KoGES data. However, neither KCPS-II nor KoGES provided evidence that TL consistently influences the degree of metastasis. These findings suggest that long TL likely contributes to the development of lung cancer, whereas the progression or metastasis of lung cancer may be influenced by other clinical characteristics or genetic factors.

The mechanism by which long TL increases cancer occurrence remains underexplored. In the Telomeres Mendelian Randomization Collaboration (12), the authors proposed a mechanism whereby increased stem cell differentiation lowers cancer risk, whereas reduced differentiation—resulting in long telomeres—elevates cancer risk. In other words, low stem cell differentiation is associated with a higher likelihood of cancer. Furthermore, it has been suggested that stem cell differentiation occurs less frequently in rare cancers. According to a related theory of cell proliferation, shorter telomeres can suppress cancer, but as somatic mutations drive increased cell proliferation, telomere elongation may occur through relative telomere gain. Notably, these mechanisms are reported to vary significantly depending on the tissue type.

Telomeres, the protective caps at the ends of chromosomes, are essential for cellular aging and maintaining genomic stability. Although long telomeres can facilitate uncontrolled cell division and elevate cancer risk (32), specific mutations in telomere maintenance genes may further enhance cancer susceptibility (33). Conversely, longer telomeres are associated with a reduced risk of cardiovascular diseases, likely due to improved cellular repair mechanisms (34). However, they may also increase the risk of autoimmune diseases (35), highlighting the complex trade-offs in health risks associated with TL.

Individuals with short telomeres face an increased risk of cancer because of genomic instability. Conversely, those with long telomeres also exhibit a heightened cancer susceptibility, presenting a paradox in the relationship between TL and cancer risk. Previous studies have proposed a two-hit clonal expansion model, in which initial mutational hits create clones with a replicative advantage and subsequent hits transform these clones into malignant cells. This model highlights the complex regulatory role of telomeres in cancer development (36).

The strengths and limitations of this study are as follows: Although MR studies are less sensitive to confounding variables, reverse causality, and measurement error compared with observational studies, fully verifying whether the MR assumptions were adequately met remains challenging. Violations of key MR assumptions, such as pleiotropy, population stratification, and racial differences, are still possible and require careful interpretation. Fortunately, in the context of this study, population stratification is less likely to pose a significant issue, as the analysis primarily targeted Korean and Japanese populations with relatively homogeneous genetic backgrounds.

In conclusion, long TL shows potential as a predictor of cancer risk and may warrant careful consideration for clinical use. However, the risk varies by cancer type, and the trade-offs involving risks in noncancerous diseases make it premature to adopt TL prediction or prevention strategies at this stage. Nevertheless, the consistent evidence of increased risk for overall, lung, and thyroid cancers highlights an important association that cannot be overlooked.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

S.H. Lee: Data curation, writing–original draft. **D.S. Song:** Data curation, software, visualization. **U.C. Kim:** Formal analysis, methodology, project administration. **S.H. Jee:** Conceptualization, resources, supervision. **K. Lee:** Conceptualization, supervision.

Acknowledgments

S.H. Jee of Yonsei University College of Medicine conducted the study with research funding from the National Cancer Center. This work was supported by the National R&D Program for Cancer Control (HA21C0142) through the National Cancer Center funded by the Ministry of Health & Welfare. This study was supported by research funding from Basgen Bio for the years 2021-2026.

Note

Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Received August 11, 2024; revised November 2, 2024; accepted March 10, 2025; posted first March 13, 2025.

References

1. Smith L, Luchini C, Demurtas J, Soysal P, Stubbs B, Hamer M, et al. Telomere length and health outcomes: an umbrella review of systematic reviews and meta-analyses of observational studies. Ageing Res Rev 2019;51:1–10.
2. Blackburn EH, Epel ES, Lin J. Human telomere biology: a contributory and interactive factor in aging, disease risks, and protection. Science 2015;350:1193–8.
3. Samani NJ, van der Harst P. Biological ageing and cardiovascular disease. Heart 2008;94:537–9.
4. Haycock PC, Heydon EE, Kaptoge S, Butterworth AS, Thompson A, Willeit P. Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. BMJ 2014;349:g4227.
5. Lan Q, Cawthon R, Gao Y, Hu W, Hosgood HD 3rd, Barone-Adesi F, et al. Longer telomere length in peripheral white blood cells is associated with risk of lung cancer and the rs2736100 (CLPTM1L-TERT) polymorphism in a prospective cohort study among women in China. PLoS one 2013;8:e59230.
6. Sanchez-Espiridion B, Chen M, Chang JY, Lu C, Chang DW, Roth JA, et al. Telomere length in peripheral blood leukocytes and lung cancer risk: a large case–control study in Caucasians. Cancer Res 2014;74:2476–86.
7. Codd V, Wang Q, Allara E, Musicha C, Kaptoge S, Stoma S, et al. Polygenic basis and biomedical consequences of telomere length variation. Nat Genet 2021;53:1425–33.
8. McKay JD, Hung RJ, Han Y, Zong X, Carreras-Torres R, Christiani DC, et al. Large-scale association analysis identifies new lung cancer susceptibility loci and heterogeneity in genetic susceptibility across histological subtypes. Nat Genet 2017;49:1126–32.
9. Spiller W, Jung KJ, Lee J-Y, Jee SH. Precision medicine and cardiovascular health: insights from Mendelian randomization analyses. Korean Circ J 2020;50:91–111.
10. Lee SH, Lee J-Y, Kim GH, Jung KJ, Lee S, Kim HC, et al. Two-sample Mendelian randomization study of lipid levels and ischemic heart disease. Korean Circ J 2020;50:940–8.
11. Machiela MJ, Hsiung CA, Shu XO, Seow WJ, Wang Z, Matsuo K, et al. Genetic variants associated with longer telomere length are associated with increased lung cancer risk among never-smoking women in Asia: a report from the Female Lung Cancer Consortium in Asia. Int J Cancer 2015;137:311–9.
12. Telomeres Mendelian Randomization Collaboration. Haycock PC, Burgess S, Nounu A, Zheng J, Okoli GN, et al. Association between telomere length and risk of cancer and non-neoplastic diseases: a Mendelian randomization study. JAMA Oncol 2017;3:636–51.
13. Markozannes G, Kanellopoulou A, Dimopoulou O, Kosmidis D, Zhang X, Wang L, et al. Systematic review of Mendelian randomization studies on risk of cancer. BMC Med 2022;20:41.
14. Dorajoo R, Chang X, Gurung RL, Li Z, Wang L, Wang R, et al. Loci for human leukocyte telomere length in the Singaporean Chinese population and trans-ethnic genetic studies. Nat Commun 2019;10:2491.
15. Gibson MJ, Spiga F, Campbell A, Khouja JN, Richmond RC, Munafò MR. Reporting and methodological quality of studies that use Mendelian randomisation in UK Biobank: a meta-epidemiological study. BMJ Evid Based Med 2023;28:103–10.
16. Jee YH, Emberson J, Jung KJ, Lee SJ, Lee S, Back JH, et al. Cohort profile: the Korean Cancer Prevention Study-II (KCPS-II) biobank. Int J Epidemiol 2018;47:385–6f.
17. KoGES Group; Kim YJ, Han BG. Cohort profile: the Korean Genome and Epidemiology Study (KoGES) Consortium. Int J Epidemiol 2017;46:e20.
18. Nagai A, Hirata M, Kamatani Y, Muto K, Matsuda K, Kiyohara Y, et al. Overview of the BioBank Japan project: study design and profile. J Epidemiol 2017;27(Suppl_III):S2–8.
19. Chen D, Zhang Y, Yidilisi A, Xu Y, Dong Q, Jiang J. Causal associations between circulating adipokines and cardiovascular disease: a Mendelian randomization study. J Clin Endocrinol Metab 2022;107:e2572–80.
20. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol 2016;40:304–14.
21. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. Int J Epidemiol 2017;46:1985–98.
22. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. Eur J Epidemiol 2017;32:377–89.
23. Schmidt A, Dudbridge F. Mendelian randomization with Egger pleiotropy correction and weakly informative Bayesian priors. Int J Epidemiol 2018;47:1217–28.
24. Bowden J, Spiller W, Del Greco M F, Sheehan N, Thompson J, Minelli C, et al. Improving the visualization, interpretation and analysis of two-sample summary data Mendelian randomization via the Radial plot and Radial regression. Int J Epidemiol 2018;47:1264–78.
25. Trybek T, Kowalik A, Góźdź S, Kowalska A. Telomeres and telomerase in oncogenesis. Oncol Lett 2020;20:1015–27.
26. Teng Y, Huang DQ, Li RX, Yi C, Zhan YQ. Association between telomere length and risk of lung cancer in an asian population: a Mendelian randomization study. World J Oncol 2023;14:277–84.
27. Tsatsakis A, Oikonomopoulou T, Nikolouzakis TK, Vakonaki E, Tzatzarakis M, Flamourakis M, et al. Role of telomere length in human carcinogenesis. Int J Oncol 2023;63:1–24.
28. Cao X, Huang M, Zhu M, Fang R, Ma Z, Jiang T, et al. Mendelian randomization study of telomere length and lung cancer risk in East Asian population. Cancer Med 2019;8:7469–76.
29. Ruwali M, Shukla R. Interactions of environmental risk factors and genetic variations: association with susceptibility to cancer. In: Environmental microbiology and biotechnology. Volume 2: Bioenergy and environmental health. Singapore: Springer; 2021. pp. 211–34.
30. Huang L, Feng X, Yang W, Li X, Zhang K, Feng S, et al. Appraising the effect of potential risk factors on thyroid cancer: a Mendelian randomization study. J Clin Endocrinol Metab 2022;107:e2783–91.
31. Wang W, Huang N, Zhuang Z, Song Z, Li Y, Dong X, et al. Identifying potential causal effects of telomere length on health outcomes: a phenome-wide investigation and Mendelian randomization study. J Gerontol A Biol Sci Med Sci 2024;79:glad128.
32. Boccardi V, Marano L. Aging, cancer, and inflammation: the telomerase connection. Int J Mol Sci 2024;25:8542.
33. Gaspar TB, Sá A, Lopes JM, Sobrinho-Simões M, Soares P, Vinagre J. Telomere maintenance mechanisms in cancer. Genes 2018;9:241.
34. Yeh J-K, Wang C-Y. Telomeres and telomerase in cardiovascular diseases. Genes 2016;7:58.
35. Hohensinner PJ, Goronzy JJ, Weyand CM. Telomere dysfunction, autoimmunity and aging. Aging Dis 2011;2:524–37.
36. Aviv A, Anderson JJ, Shay JW. Mutations, cancer and the telomere length paradox. Trends Cancer 2017;3:253–8.