Association Between Telomere Length and Risk of Cancer and Non-Neoplastic Diseases
A Mendelian Randomization Study

The Telomeres Mendelian Randomization Collaboration

**IMPORTANCE** The causal direction and magnitude of the association between telomere length and incidence of cancer and non-neoplastic diseases is uncertain owing to the susceptibility of observational studies to confounding and reverse causation.

**OBJECTIVE** To conduct a Mendelian randomization study, using germline genetic variants as instrumental variables, to appraise the causal relevance of telomere length for risk of cancer and non-neoplastic diseases.

**DATA SOURCES** Genomewide association studies (GWAS) published up to January 15, 2015.

**STUDY SELECTION** GWAS of noncommunicable diseases that assayed germline genetic variation and did not select cohort or control participants on the basis of preexisting diseases. Of 163 GWAS of noncommunicable diseases identified, summary data from 103 were available.

**DATA EXTRACTION AND SYNTHESIS** Summary association statistics for single nucleotide polymorphisms (SNPs) that are strongly associated with telomere length in the general population.

**MAIN OUTCOMES AND MEASURES** Odds ratios (ORs) and 95% confidence intervals (CIs) for disease per standard deviation (SD) higher telomere length due to germline genetic variation.

**RESULTS** Summary data were available for 35 cancers and 48 non-neoplastic diseases, corresponding to 420,081 cases (median cases, 2,526 per disease) and 1,093,105 controls (median, 6,789 per disease). Increased telomere length due to germline genetic variation was generally associated with increased risk for site-specific cancers. The strongest associations (ORs [95% CIs] per 1-SD change in genetically increased telomere length) were observed for glioma, 5.27 (3.15-8.81); serous low-malignant-potential ovarian cancer, 4.35 (2.39-7.94); lung adenocarcinoma, 3.19 (2.40-4.22); neuroblastoma, 2.98 (1.92-4.62); bladder cancer, 2.19 (1.32-3.66); melanoma, 1.87 (1.55-2.26); testicular cancer, 1.76 (1.02-3.04); kidney cancer, 1.55 (1.08-2.23); and endometrial cancer, 1.31 (1.07-1.61). Associations were stronger for rarer cancers and at tissue sites with lower rates of stem cell division. There was generally little evidence of association between genetically increased telomere length and risk of psychiatric, autoimmune, inflammatory, diabetic, and other non-neoplastic diseases, except for coronary heart disease (OR, 0.78 [95% CI, 0.67-0.90]), abdominal aortic aneurysm (OR, 0.63 [95% CI, 0.49-0.81]), celiac disease (OR, 0.42 [95% CI, 0.28-0.61]) and interstitial lung disease (OR, 0.09 [95% CI, 0.05-0.15]).

**CONCLUSIONS AND RELEVANCE** It is likely that longer telomeres increase risk for several cancers but reduce risk for some non-neoplastic diseases, including cardiovascular diseases.
At the ends of chromosomes, telomeres are DNA-protein structures that protect the genome from damage, shorten progressively over time in most somatic tissues, and are proposed physiological markers of aging. Shorter leukocyte telomeres are correlated with older age, male sex, and other known risk factors for noncommunicable diseases and are generally associated with higher risk for cardiovascular diseases, type 2 diabetes, and nonvascular, non-neoplastic causes of mortality. Whether these associations are causal, however, is unknown. Telomere length has also been implicated in risk of cancer, but the direction and magnitude of the association is uncertain and contradictory across observational studies. The uncertainty reflects the considerable difficulty of designing observational studies of telomere length and cancer incidence that are sufficiently robust to reverse causation, confounding, and measurement error.

The aim of the present report was to conduct a Mendelian randomization study, using germline genetic variants as instrumental variables for telomere length, to help clarify the nature of the association between telomere length and risk of cancer and non-neoplastic diseases. The approach, which mimics the random allocation of individuals to the placebo and intervention arms of a randomized clinical trial, allowed us to: (1) estimate the direction and broad magnitude of the association of telomere length with risk of multiple cancer and non-neoplastic diseases; (2) appraise the evidence for causality in the estimated etiological associations; (3) investigate potential sources of heterogeneity in findings for site-specific cancers; and (4) compare genetic estimates with findings based on directly measured telomere length in prospective observational studies.

Methods

Study Design

The design of our study, illustrated in eFigure 1 in Supplement 1, had 3 key components: (1) the identification of genetic variants to serve as instruments for telomere length; (2) the acquisition of summary data for the genetic instruments from genomewide association studies (GWASs) of diseases and risk factors for noncommunicable diseases; and (3) the classification of diseases and risk factors into primary or secondary outcomes based on a priori statistical power. As a first step, we searched the GWAS catalog on January 15, 2015, to identify single-nucleotide polymorphisms (SNPs) associated with telomere length. To supplement the list with additional potential instruments, we also searched the original study reports curated by the GWAS catalog (using a P value threshold of $5 \times 10^{-8}$). We acquired summary data for all SNPs identified by our search from a meta-analysis of GWASs of telomere length, involving 9,190 participants of European ancestry.

The second key component of our design strategy involved the acquisition of summary data, corresponding to the selected genetic instruments for telomere length, from GWASs of noncommunicable diseases and risk factors (eFigure 1 in Supplement 1). As part of this step, we invited principal investigators of noncommunicable disease studies curated by the GWAS catalog to share summary data for our study. We also downloaded summary data for diseases and risk factors from publically available sources, including study-specific websites, dbGAP, ImmunoBase, and the GWAS catalog (eFigure 1 in Supplement 1).

The third key component of our design strategy was the classification of diseases and risk factors into either primary or secondary outcomes, which we defined on the basis of a priori statistical power to detect associations with telomere length. Primary outcomes were defined as diseases with sufficient numbers of cases and controls for greater than 50% statistical power, and secondary outcomes were defined as diseases with 50% or less statistical power to detect odds ratios (ORs) of 2.0 or higher per standard deviation (SD) change in genetically increased telomere length (α assumed to be .01). All risk factors were defined as secondary outcomes. Risk factors with less than 50% statistical power were excluded.

Further details on our design strategy can be found in Supplement 1.

Comparison With Prospective Observational Studies

We searched PubMed for prospective observational studies of the association between telomere length and disease (see eTables 3 and 4 in Supplement 1 for details of the search strategy and inclusion criteria). Study-specific relative risks for disease per unit change or quantile comparison of telomere length were transformed to an SD scale using previously described methods. Hazard ratios, risk ratios, and ORs were assumed to approximate the same measure of relative risk. Where multiple independent studies of the same disease were identified, these were combined by fixed effects meta-analysis, unless there was strong evidence of between-study heterogeneity (Cochran Q $P < .001$), in which case they were kept separate.

Statistical Analysis

We combined summary data across SNPs into a single instrument, using maximum likelihood to estimate the slope of the relationship between $\beta_{GD}$ and $\beta_{GP}$ and a variance-covariance matrix to make allowance for linkage disequilibrium between SNPs, where $\beta_{GD}$ is the change in disease log odds or risk factor levels per copy of the effect allele, and $\beta_{GP}$ is the SD
change in telomere length per copy of the effect allele (see eAppendix 1 in Supplement 1 for technical details). The slope from this approach can be interpreted as the log OR for binary outcomes, or the unit change for continuous risk factors, per SD change in genetically increased telomere length. P values for heterogeneity among SNPs in the estimated associations of genetically increased telomere length with disease and risk factors were estimated by likelihood ratio tests. Associations between genetically increased telomere length and continuous risk factors were transformed into SD units. For 5 secondary disease outcomes where only a single SNP was available for analysis, we estimated associations using the Wald ratio: $\beta_{e+\delta}/\beta_{e}$, with standard errors approximated by the delta method.

Inference of causality in the estimated etiological associations between telomere length and disease depends on satisfaction of Mendelian randomization assumptions (eFigure 7 in Supplement 1; also see eTable 5 in Supplement 1 for a glossary of terms). The assumptions are that (1) the selected SNPs are associated with telomere length; (2) the selected SNPs are not associated with confounders; and (3) the selected SNPs are associated with disease exclusively through their effect on telomere length. If these assumptions are satisfied, the selected SNPs are valid instrumental variables, and their association with disease can be interpreted as a causal effect of telomere length. We modeled the impact of violations of these assumptions through 2 sets of sensitivity analyses: a weighted median function and MR-Egger regression (see eAppendix 1 in Supplement 1 for technical details). We restricted our sensitivity analyses to diseases with strong evidence of association with genetically increased telomere length (defined as Bonferroni $P \leq .05$).

We used meta-regression to appraise potential sources of heterogeneity in our findings for cancer. The association of genetically increased telomere length with the log odds of cancer was regressed on cancer incidence, survival time, and median age at diagnosis (downloaded from the National Cancer Institute Surveillance, Epidemiology, and End Results [SEER] Program), and tissue-specific rates of stem cell division from Tomasetti and Vogelstein. As the downloaded cancer characteristics from SEER correspond to the United States population, 77% of which was of white ancestry in 2015, the meta-regression analyses excluded genetic studies conducted in East Asian populations.

All analyses were performed in R, version 3.1.2, and Stata release 13.1 (StataCorp LP). P values were 2-sided, and evidence of association was declared at $P < .05$. Where indicated, Bonferroni corrections were used to make allowance for multiple testing, although this is likely to be overly conservative given the nonindependence of many of the outcomes tested.

### Results

We selected 16 SNPs as instruments for telomere length (eFigure 1 in Supplement 1 and Table 1). The selected SNPs correspond to 10 independent genomic regions that collectively account for 2% to 3% of the variance in leukocyte telomere length, which would be equivalent to an F statistic of 18 to 28 in the sample used to define the instruments (Table 1). This indicates that the genetic instrument constructed from these 10 independent genomic regions is strongly associated with telomere length (details in eAppendix 1 in Supplement 1). Summary data for the genetic instruments were available for 83 noncommunicable diseases, corresponding to 420,081 cases (median, 2526 per disease), 1,093,105 controls (median, 6,789 per disease), and 44 risk factors (eFigure 1 and eTable 1 in Supplement 1). The median number of SNPs available across diseases was 11 (minimum, 1; maximum, 13) and across risk factors was 12 (minimum, 11; maximum, 13). Of the 83 diseases, 56 were classified as primary outcomes and 27 as secondary outcomes (Table 2; eFigure 1 and eTable 1 in Supplement 1). For 9 of the 83 noncommunicable diseases, additional summary data were available from 10 independent studies for replication analyses, corresponding to 40,465 cases (median, 1,416 per disease) and 52,306 controls (median, 3,537 per disease) (eTable 1 in Supplement 1).

The results from primary analyses of noncommunicable diseases are presented in Figure 1 and the eTable in Supplement 1; results from secondary analyses of risk factors and diseases with low a priori power are presented in eFigures 2, 5, and 6 in Supplement 1. Genetically increased telomere length was associated with higher ORs (95% CIs) of disease for 9 of 22 primary cancers ($P < .05$): glioma (5.27 [3.15-8.81]), endometrial cancer (1.31 [1.07-1.61]), kidney cancer (1.55 [1.08-2.23]), testicular germ-cell cancer (1.76 [1.02-3.04]), melanoma (1.87 [1.55-2.26]), bladder cancer (2.19 [1.32-3.66]), neuroblastoma (2.98 [1.92-4.62]), lung adenocarcinoma (3.19 [2.40-4.22]) and serous low-malignancy-potential (LMP) ovarian cancer (4.35 [2.39-7.94]) (Figure 1). The associations were, however, highly variable across cancer types, varying from an OR (95% CI) of 0.86 (0.57-1.30) for head and neck cancer to 5.27 (3.15-8.81) for glioma. Substantial variability was also observed within tissue sites. For example, the OR (95% CI) for lung adenocarcinoma was 3.19 (2.40-4.22) compared with 1.07 (0.82-1.39) for squamous cell lung cancer. For serous LMP ovarian cancer, the OR (95% CI) was 4.35 (2.39-7.94) compared with 1.21 (0.87-1.68) for endometrioid ovarian cancer, 1.12 (0.94-1.34) for serous invasive ovarian cancer, 1.04 (0.66-1.63) for clear-cell ovarian cancer, and 1.04 (0.73-1.47) for mucinous ovarian cancer. The strongest evidence of association was observed for glioma, lung adenocarcinoma, neuroblastoma, and serous LMP ovarian cancer (Figure 1). Results for glioma and bladder cancer showed evidence for replication in independent data sets (independent data sets were not available for other cancers) (eFigure 3 in Supplement 1).

Genetically increased telomere length was associated with lower ORs (95% CIs) of disease for 6 of 32 primary nonneoplastic diseases ($P < .05$): coronary heart disease (0.78 [0.67-0.91]), abdominal aortic aneurysm (0.63 [0.49-0.81]), Alzheimer disease (0.84 [0.71-0.98]), celiac disease (0.42 [0.28-0.61]), interstitial lung disease (0.09 [0.05-0.15]) and type 1 diabetes (0.71 [0.51-0.98]) (Figure 1). The strongest evidence of association was observed for coronary heart disease, abdominal aortic aneurysm, celiac disease, and interstitial lung disease (Figure 1). The associations with coronary heart disease and interstitial lung disease showed evidence for replication in independent data sets (eFigure 3 in Supplement 1).
Our genetic findings were generally similar in direction and magnitude to estimates based on observational prospective studies of leukocyte telomere length and disease (Figure 2). In sensitivity analyses, we appraised the potential impact of confounding by pleiotropic pathways on our results. Associations estimated by the weighted median and MR-Egger were broadly similar to the main results for glioma, lung adenocarcinoma, serous LMP ovarian cancer, neuroblastoma, abdominal aortic aneurysm, coronary heart disease, and interstitial lung disease (eFigure 4 in Supplement 1). We found little evidence for the presence of pleiotropy, as indicated by the MR-Egger intercept test (eFigure 4 in Supplement 1). The MR-Egger analyses were, however, generally underpowered, as reflected by the wide confidence intervals in the estimated odds ratios (eFigure 4 in Supplement 1).

In meta-regression analyses, we observed that genetically increased telomere length tended to be more strongly associated with rarer cancers and cancers at tissue sites with lower rates of stem cell division (Figure 3). The associations showed little evidence of varying by percentage survival 5 years after diagnosis or median age at diagnosis.

**Discussion**

In this report, we show that genetically increased telomere length is associated with increased risk of several cancers and with reduced risk of some non-neoplastic diseases. Given the random distribution of genotypes in the general population with respect to lifestyle and other environmental factors, as well as the fixed nature of germline genotypes, these results should be less susceptible to confounding and reverse causation than those generated by observational studies. Our results could, however, reflect violations of Mendelian randomization assumptions, such as confounding by pleiotropy, population stratification, or ancestry. Although we cannot entirely rule out this possibility, the majority of our results persisted in sensitivity analyses that made allowance for violations of Mendelian randomization assumptions. Confounding by population stratification or ancestry is also unlikely, given the adjustments made for ancestry in the original disease GWASs (see eAppendix 1 in Supplement 1). Our results are therefore compatible with causality.

**Comparison With Previous Studies**

Our findings for cancer are generally contradictory to those based on retrospective studies, which tend to report increased...
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<th>Disease</th>
<th>Cases, No.</th>
<th>Controls, No.</th>
<th>SNPs, No.</th>
<th>Statistical Power</th>
<th>Population</th>
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<td>Eye Disease</td>
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<tr>
<td>Age-related macular degeneration</td>
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<td>51,177</td>
<td>13</td>
<td>1.00</td>
<td>EUR</td>
<td>AMD Gene 81</td>
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<tr>
<td>Retinopathy</td>
<td>1,122</td>
<td>18,289</td>
<td>12</td>
<td>0.75</td>
<td>EUR</td>
<td>Jensen et al 82</td>
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</table>

(continued)
ponent genes germline loss-of-function mutations in the telomerase complex in individuals with dyskeratosis congenita, a disease caused by over the entire telomere length distribution. For example, the association with cancer may not, however, be linear over the entire telomere length distribution. For example, individuals with dyskeratosis congenita, a disease caused by germline loss-of-function mutations in the telomerase component genes TERC and TERT have chronically short telomeres and are at increased risk of some cancers, particularly acute myeloid leukemia and squamous cell carcinomas arising at sites of leukoplakia,125,126 presumably due to increased susceptibility to genome instability and chromosomal end-to-end fusions.127 Our results should therefore be interpreted as reflecting the average association at the population level and may not be generalizable to the extreme ends of the telomere length distribution.

Mechanisms of Association
Our cancer findings are compatible with known biology.127 By limiting the proliferative potential of cells, telomere shortening may serve as a tumor suppressor, and individuals with longer telomeres may be more likely to acquire somatic mutations owing to increased proliferative potential.127 Rates of cell division are, however, highly variable among tissues,34 and thus the relative gain in cell proliferative potential, conferred by having longer telomeres, may also be highly variable across tissues. This could explain the approximately 6-fold variation in ORs observed across cancer types in the present study as well as the tendency of our results to be stronger at tissue sites with lower rates of stem cell division. For example, the association was strongest for glioma (OR, 5.27) and comparatively weak for colorectal cancer (OR, 1.09), and the rates of stem cell division in the tissues giving rise to these cancers differ by several orders of magnitude. In neural stem cells, which give rise to gliomas, the number of divisions is about 270 million, and for colorectal stem cells it is about 1.2 trillion over the average lifetime.
### Figure 1. The Association Between Genetically Increased Telomere Length and Odds of Primary Noncommunicable Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Tumor/Disease</th>
<th>Cases</th>
<th>SNPs</th>
<th>OR (95% CI)</th>
<th>Lower Risk</th>
<th>Higher Risk</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td><strong>Cancer</strong></td>
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<tr>
<td>Glioma</td>
<td>NA</td>
<td>1130</td>
<td>12</td>
<td>5.27 (1.58-16.81)</td>
<td>&lt;.001</td>
<td>.001</td>
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<tr>
<td>Ovarian cancer</td>
<td>Serous LMP</td>
<td>972</td>
<td>13</td>
<td>4.35 (2.39-7.94)</td>
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<td>&lt;.001</td>
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<tr>
<td>Lung cancer</td>
<td>Adenocarcinoma</td>
<td>3442</td>
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<td>3.19 (2.04-4.22)</td>
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<td></td>
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<td>&lt;.001</td>
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<td>Bladder cancer</td>
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<td>1601</td>
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<td>2.19 (1.32-3.66)</td>
<td>&lt;.01</td>
<td>&lt;.001</td>
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<tr>
<td>Skin cancer</td>
<td>Melanoma</td>
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<td>13</td>
<td>1.87 (1.55-2.26)</td>
<td>&lt;.01</td>
<td>&lt;.001</td>
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<td>Testicular germ-cell cancer</td>
<td>NA</td>
<td>986</td>
<td>11</td>
<td>1.76 (1.02-3.04)</td>
<td>&lt;.01</td>
<td>&lt;.001</td>
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<td>Kidney cancer</td>
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<td>2461</td>
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<td>1.55 (1.08-2.23)</td>
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<td>Endometrial cancer</td>
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<td>6608</td>
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<td>1.31 (1.07-1.61)</td>
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<td>Basal cell carcinoma</td>
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<td><strong>Cardiovascular diseases</strong></td>
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<tr>
<td>Heart failure&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>2526</td>
<td>13</td>
<td>1.02 (0.77-1.35)</td>
<td>&lt;.01</td>
<td>&lt;.001</td>
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<tr>
<td>Ischemic stroke</td>
<td>Small vessel disease</td>
<td>1894</td>
<td>13</td>
<td>0.94 (0.66-1.33)</td>
<td>&lt;.01</td>
<td>&lt;.001</td>
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<tr>
<td>Sudden cardiac arrest</td>
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<td>3954</td>
<td>13</td>
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<td>&lt;.01</td>
<td>&lt;.001</td>
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<tr>
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<td>NA</td>
<td>2963</td>
<td>13</td>
<td>0.92 (0.61-1.37)</td>
<td>&lt;.01</td>
<td>&lt;.001</td>
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<tr>
<td>Ischemic stroke</td>
<td>Cardiembolic</td>
<td>2365</td>
<td>13</td>
<td>0.88 (0.64-1.22)</td>
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<td>&lt;.001</td>
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<td>&lt;.001</td>
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<tr>
<td>Ischemic stroke</td>
<td>Large vessel disease</td>
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<td>&lt;.001</td>
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<td><strong>Neurological/psychiatric diseases</strong></td>
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<td>&lt;.001</td>
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<td>Bipolar disorder</td>
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<td>7481</td>
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<td>&lt;.001</td>
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<td>Tourette syndrome</td>
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<td>Major depressive disorder</td>
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<td>8</td>
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<td>&lt;.001</td>
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<td><strong>Autoimmune/inflammatory diseases</strong></td>
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<td>7</td>
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<td>3</td>
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<td>5538</td>
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<td>0.87 (0.65-1.15)</td>
<td>&lt;.01</td>
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<td>&lt;.001</td>
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<td>&lt;.001</td>
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<td><strong>Other diseases</strong></td>
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<tr>
<td>Retinopathy</td>
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<td>1122</td>
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<td>&lt;.01</td>
<td>&lt;.001</td>
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<td>Age-related macular degeneration</td>
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<td>7473</td>
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<td>1.19 (0.96-1.48)</td>
<td>&lt;.01</td>
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<td>Type 2 diabetes</td>
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<td>10415</td>
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<td>&lt;.01</td>
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<td>COPD</td>
<td>NA</td>
<td>2812</td>
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<td>0.90 (0.64-1.27)</td>
<td>&lt;.01</td>
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<td>Asthma</td>
<td>NA</td>
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<td>4</td>
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<td>Type 1 diabetes</td>
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<td>Interstitial lung disease</td>
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<td>0.09 (0.05-0.15)</td>
<td>&lt;.01</td>
<td>&lt;.001</td>
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</table>

COPD indicates chronic obstructive pulmonary disease; ER, estrogen receptor; LMP, low malignancy potential; NA, not applicable; SNP, single-nucleotide polymorphism.

* P value for association between genetically increased telomere length and disease from maximum likelihood.

* P value for heterogeneity among SNPs within the instrument.

* The effect estimate for heart failure is a hazard ratio (all others are odds ratios).
### Figure 2. Comparison of the Present Mendelian Randomization (MR) Study and Prospective Observational Studies of the Association Between Telomere Length and Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of Cases</th>
<th>OR (95% CI)</th>
<th>Lower Risk of Disease</th>
<th>Higher Risk of Disease</th>
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<tbody>
<tr>
<td><strong>Cancer</strong></td>
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<td></td>
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</tr>
<tr>
<td>Breast cancer</td>
<td>48,155</td>
<td>1.08 (0.99-1.19)</td>
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<tr>
<td>Observational study</td>
<td>1716</td>
<td>1.02 (0.99-1.05)</td>
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<tr>
<td>Prostate cancer</td>
<td>22,297</td>
<td>1.12 (0.96-1.30)</td>
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<tr>
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<td>1.07 (1.01-1.14)</td>
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</tr>
<tr>
<td>Ovarian cancer</td>
<td>15,397</td>
<td>1.09 (0.94-1.27)</td>
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<tr>
<td>Observational study</td>
<td>96</td>
<td>1.13 (0.98-1.32)</td>
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<tr>
<td>Colorectal cancer</td>
<td>14,537</td>
<td>1.09 (0.91-1.31)</td>
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<tr>
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<td>1.04 (0.97-1.11)</td>
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<tr>
<td>Lung cancer</td>
<td>11,348</td>
<td>1.71 (1.44-2.04)</td>
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<tr>
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<td>522</td>
<td>0.94 (0.87-1.02)</td>
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<tr>
<td>Ovarian cancer</td>
<td>847</td>
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<td>1.31 (1.07-1.61)</td>
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<td>1.06 (0.95-1.19)</td>
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<td>Pancreatic cancer</td>
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<td>0.86 (0.56-1.32)</td>
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<tr>
<td>Observational study</td>
<td>648</td>
<td>1.05 (0.95-1.17)</td>
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<td><strong>Non-Neoplastic Diseases</strong></td>
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<td>Coronary heart disease</td>
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<td>0.94 (0.81-1.10)</td>
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<td>Head and neck cancer</td>
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<tr>
<td>Melanoma</td>
<td>12,814</td>
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<td>1.17 (1.06-1.29)</td>
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<tr>
<td>Bladder cancer</td>
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<tr>
<td>Testicular cancer</td>
<td>986</td>
<td>1.76 (1.02-3.04)</td>
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<td>Observational study</td>
<td>10</td>
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<tr>
<td>Glioma cancer</td>
<td>11,130</td>
<td>5.27 (3.15-8.81)</td>
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<td>0.90 (0.68-1.18)</td>
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</table>

Search strategy and characteristics for observational studies are described in eTables 3 and 4 in Supplement 1.

* From fixed-effects meta-analysis of independent observational studies described in eTable 3 in Supplement 1.

* From the combination of Copenhagen City Heart Study (CCHS) and Copenhagen General Population Study (CGPS).10

* From the combination of Prostate, Lung, Colorectal, and Ovarian (PLCO), Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), and Shanghai Women's Health Study (SWHS).97
The observation that genetically increased telomere length was more strongly associated with rarer cancers potentially reflects the same mechanism, since rarer cancers also tend to show lower rates of stem cell division. For example, the incidence of glioma per 100,000 people per year in the United States is 0.4, and for colorectal cancer it is 42.4.33

The inverse associations observed for some non-neoplastic diseases may reflect the impact of telomere shortening on tissue degeneration and an evolutionary trade-off for greater resistance to cancer at the cost of greater susceptibility to degenerative diseases, particularly cardiovascular diseases.128,129

A-D, The plotted data show how the strength of the relationship between genetically increased telomere length and cancer varies by the selected characteristic: the $R^2$ statistic indicates how much of the variation between cancers can be explained by the selected characteristic; $P$ values are from meta-regression models; circle sizes are proportional to the inverse of the variance of the log OR. A, Data for average lifetime number of stem cell divisions were downloaded from Tomasetti and Vogelstein.34 B-D, Data for percentage survival 5 years after diagnosis, cancer incidence and median age at diagnosis were downloaded from the Surveillance, Epidemiology, and End Results Program.33 Not all cancers had information available for the selected characteristics (hence the number of cancers varies across the subplots). Information was available for 9 cancers for tissue-specific rates of stem cell division, 13 cancers for percentage surviving 5 years after diagnosis, 17 cancers for cancer incidence, and 13 cancers for median age at diagnosis. OR indicates odds ratio; SD, standard deviation.
Clinical Relevance of Findings
Our findings suggest that potential clinical applications of telomere length, eg, as a tool for risk prediction or as an intervention target for disease prevention, may be subject to a trade-off in risk between cancer and non-neoplastic diseases. For example, a number of companies have been established that offer telomere length measurement services to the public (via a requesting physician) under the claim that shorter telomeres are a general indicator of poorer health status and older biological age and that such information can be used to motivate healthy lifestyle choices in individuals. However, the conflicting direction of association between telomere length and risk of cancer and non-neoplastic diseases indicated by our findings suggests that such services to the general public may be premature.

Study Limitations
Our study is subject to some limitations, in addition to the Mendelian randomization assumptions already considered. First, our method assumes that the magnitude of the association between SNPs and telomere length is consistent across tissues. Second, our study assumed a linear shape of association between telomere length and disease risk, whereas the shape could be “J” or “U” shaped.104,117,125 Third, our results assume that the samples used to define the genetic instrument for telomere length18 and the various samples used to estimate the SNP-disease associations are representative of the same general population, practically defined as being of similar ethnicity, age, and sex distribution.130 This assumption would, for example, not apply in the case of the SNP-disease associations derived from East Asian or pediatric populations. Generally speaking, violation of these assumptions could bias the magnitude of the association between genetically increased telomere length and disease but would probably not increase the likelihood of false positives (ie, incorrectly inferring an association when none exists).131 Our results should therefore remain informative for the direction and broad magnitude of the average association at the population level, even in the presence of such violations. Fourth, we cannot rule out chance in explaining some of the weaker findings. Fifth, our results may not be fully representative of noncommunicable diseases (since not all studies shared data, and our analyses were underpowered for the secondary disease outcomes). The diseases represented in our primary analyses probably account for more than 60% of all causes of death in American adults.132

Conclusions
It is likely that longer telomeres increase risk for several cancers but reduce risk for some non-neoplastic diseases, including cardiovascular diseases. Further research is required to resolve whether telomere length is a useful predictor of risk that can help guide therapeutic interventions, to clarify the shape of any dose-response relationships, and to characterize the nature of the association in population subgroups.


Telomere Length and Risk of Cancer and Non-Neoplastic Diseases


