

Association Between Telomere Length and Risk of Cancer and Non-Neoplastic Diseases

A Mendelian Randomization Study

The Telomeres Mendelian Randomization Collaboration

 Supplemental content

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, 2526 per disease) and 1 093 105 controls (median, 6789 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.

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At the ends of chromosomes, telomeres are DNA-protein structures that protect the genome from damage, shorten progressively over time in most somatic tissues,¹ and are proposed physiological markers of aging.^{2,3} Shorter leukocyte telomeres are correlated with older age, male sex, and other known risk factors for noncommunicable diseases⁴⁻⁶ and are generally associated with higher risk for cardiovascular diseases,^{7,8} type 2 diabetes,⁹ and nonvascular, non-neoplastic causes of mortality.⁸ 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.¹⁰⁻¹⁴ 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 (GWASes) 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^{15,16} 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 5×10^{-8}).¹⁷⁻²⁵ We acquired summary data for all SNPs identified by our search from a meta-analysis of GWASes of telomere length, involving 9190 participants of European ancestry.¹⁸

The second key component of our design strategy involved the acquisition of summary data, corresponding to the selected genetic instruments for telomere length, from GWASes of noncommunicable diseases and risk factors (eFigure 1 in Supplement 1). As part of this step, we invited principal inves-

Key Points

Question What is the causal relevance of telomere length for risk of cancer and non-neoplastic diseases?

Findings In this Mendelian randomization study, genetically longer telomeres were associated with higher odds of disease for 9 of 22 primary cancers tested but with reduced odds of disease for 6 of 32 primary non-neoplastic diseases, including cardiovascular diseases.

Meaning It is likely that longer telomeres increase risk for several cancers but reduce risk for some non-neoplastic diseases, including cardiovascular diseases. This trade-off in risk should be carefully considered in any diagnostic, prognostic, or therapeutic applications based on telomere length.

tigators of noncommunicable disease studies curated by the GWAS catalog^{15,26} 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 comparisons of telomere length were transformed to an SD scale using previously described methods.²⁷ 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 β_{GD} and β_{GB} and a variance-covariance matrix to make allowance for linkage disequilibrium between SNPs,²⁸ where β_{GD} is the change in disease log odds or

risk factor levels per copy of the effect allele, and β_{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.²⁸ 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: β_{GD}/β_{GP} , with standard errors approximated by the delta method.²⁹

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).^{30,31} 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 function³² and MR-Egger regression (see eAppendix 1 in Supplement 1 for technical details).³⁰ We restricted our sensitivity analyses to diseases showing the strongest 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] Program³³), and tissue-specific rates of stem cell division from Tomasetti and Vogelstein.³⁴ As the downloaded cancer characteristics from SEER correspond to the United States population, 77% of which was of white ancestry in 2015,³⁵ **[Please provide exact URL at which data for this specific report were found at ref 35 rather than the US Census home page.]** the meta-regression analyses excluded genetic studies conducted in East Asian populations.

All analyses were performed in R, version 3.1.2,³⁶ 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 is equivalent to an *F* statistic of approximately 18. 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).³⁷ 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, 6789 per disease), and 44 risk factors (eFigure 1 and eTable 1 in Supplement 1; Table 2). The median number of SNPs available across diseases was 11 (minimum, 1; maximum, 13) and across risk factors was 12 (minimum, 1; 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, 1416 per disease) and 52 306 controls (median, 3537 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 2; 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 (0.50-1.48) 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 reduced OR (95% CI) of disease for 6 of 32 primary non-neoplastic diseases ($P < .05$): coronary heart disease (0.78 [0.67-0.9]), abdominal aortic aneurysm (0.63 [0.49-0.81]), Alzhei-

Table 1. Single Nucleotide Polymorphisms Associated With Telomere Length

SNP	Chr	Pos	Gene	EA	OA	EAF ^a	β ^a	SE ^a	P Value ^a	P _{het} ^a	No. Studies ^a	Sample Size ^a	Discovery P Value	Variance Explained, %	Discovery Study
rs11125529	2	54248729	ACYP2	A	C	0.16	0.065	0.012	6.06 × 10 ⁻³	0.313	6	9177	8.00 × 10 ⁻¹⁰	0.080	Codd et al ²¹
rs6772228	3	58390292	PXK	T	A	0.87	0.041	0.014	.0497	0.77	6	8630	3.91 × 10 ⁻¹⁰	0.200	Pooley et al ¹⁷
rs12696304	3	169763483	TERC	C	G	0.74	0.090	0.011	5.41 × 10 ⁻⁸	0.651	6	9012	4.00 × 10 ⁻¹⁴	0.319	Codd et al ²²
rs10936599	3	169774313	TERC	C	T	0.76	0.100	0.011	1.76 × 10 ⁻⁹	0.087	6	9190	3.00 × 10 ⁻³¹	0.319	Codd et al ²¹
rs1317082	3	169779797	TERC	A	G	0.71	0.097	0.011	4.57 × 10 ⁻⁹	0.029	6	9176	1.00 × 10 ⁻⁸	0.319	Mangino et al ¹⁸
rs10936601	3	169810661	TERC	C	T	0.74	0.087	0.011	8.64 × 10 ⁻⁸	0.433	6	9150	4.00 × 10 ⁻¹⁵	0.319	Pooley et al ¹⁷
rs7675998	4	163086668	NAF1	G	A	0.80	0.048	0.012	.01	0.077	6	9161	4.35 × 10 ⁻¹⁶	0.190	Codd et al ²¹
rs2736100	5	1286401	TERT	C	A	0.52	0.085	0.013	2.14 × 10 ⁻⁵	0.54	4	5756	4.38 × 10 ⁻¹⁹	0.310	Codd et al ²¹
rs9419958	10	103916188	OBFC1	T	C	0.13	0.129	0.013	5.26 × 10 ⁻¹¹	0.028	6	9190	9.00 × 10 ⁻¹¹	0.171	Mangino et al ¹⁸
rs9420907	10	103916707	OBFC1	C	A	0.14	0.142	0.014	1.14 × 10 ⁻¹¹	0.181	6	9190	7.00 × 10 ⁻¹¹	0.171	Codd et al ²¹
rs4387287	10	103918139	OBFC1	A	C	0.14	0.120	0.013	1.40 × 10 ⁻⁹	0.044	6	8541	2.00 × 10 ⁻¹¹	0.171	Levy et al ²⁵
rs3027234	17	8232774	CTC1	C	T	0.83	0.103	0.012	2.75 × 10 ⁻⁸	0.266	6	9108	2.00 × 10 ⁻⁸	0.292	Mangino et al ¹⁸
rs8105767	19	22032639	ZNF208	G	A	0.25	0.064	0.011	<.001	0.412	6	9096	1.11 × 10 ⁻⁹	0.090	Codd et al ²¹
rs412658	19	22176638	ZNF676	T	C	0.35	0.086	0.010	1.83 × 10 ⁻⁸	0.568	6	9156	1.00 × 10 ⁻⁸	0.484	Mangino et al ¹⁸
rs6028466	20	39500359	DHX35	A	G	0.17	0.058	0.013	.004	0.533	6	9190	2.57 × 10 ^{-8b}	0.041	Mangino et al ¹⁸ and Gu et al ²⁰
rs755017	20	63790269	ZBTB46	G	A	0.17	0.019	0.0129	.34	0.757	5	8026	6.71 × 10 ⁻⁹	0.090	Codd et al ²¹

Abbreviations: β, standard deviation change in telomere length per copy of the effect allele; Chr, chromosome; EA, effect allele; EAF, EA frequency; OA, other allele; P_{het}, P value for between-study heterogeneity in association between SNP and telomere length; Pos, base-pair position (GRCh38.p3); SE, standard error; SNP, single-nucleotide polymorphism.

^a Summary data from Mangino et al.¹⁸
^b From a meta-analysis of Mangino¹⁸ and Gu²⁰ performed in the present study.

Table 2. Study Characteristics for Primary Noncommunicable Diseases

Disease	Cases, No.	Controls, No.	SNPs, No.	Statistical Power	Pop	Source
Cancer						
Bladder cancer	1601	1819	10	0.62	EUR	NBCS ³⁸
Breast cancer	48 155	43 612	13	1.00	EUR	BCAC ^{17,39}
ER-	7465	42 175	13	1.00	EUR	BCAC ^{17,39}
ER+	27 074	41 749	13	1.00	EUR	BCAC ^{17,39}
Colorectal cancer	14 537	16 922	9	1.00	EUR	CORECT/GECCO ^{40,41}
Endometrial cancer	6608	37 925	12	1.00	EUR	ECAC ^{42,43}
Esophageal SCC	1942	2111	11	0.64	EA	Abnet et al ⁴⁴
Glioma	1130	6300	12	0.72	EUR	Wrensch et al ⁴⁵ and Walsh et al ⁴⁶
Head & neck cancer	2082	3477	12	1.00	EUR	McKay et al ⁴⁷
Kidney cancer	2461	5081	12	0.99	EUR	KIDRISK ⁴⁸
Lung cancer	11 348	15 861	13	1.00	EUR	ILCCO ⁴⁹
Adenocarcinoma	3442	14 894	13	1.00	EUR	ILCCO ⁴⁹
SCC	3275	15 038	13	1.00	EUR	ILCCO ⁴⁹
Skin cancer						
Melanoma	12 814	23 203	13	1.00	EUR	MC ⁵⁰
Basal cell carcinoma	3361	11 518	13	1.00	EUR	NHS/HPFS ⁵¹
Neuroblastoma	2101	4202	12	0.87	EUR	Diskin ⁵²
Ovarian cancer	15 397	30 816	13	1.00	EUR	OCAC ^{17,53}
Clear cell	1016	30 816	13	0.76	EUR	OCAC ^{17,53}
Endometrioid	2154	30 816	13	0.98	EUR	OCAC ^{17,53}
Mucinous	1643	30 816	13	0.94	EUR	OCAC ^{17,53}
Serous invasive	9608	30 816	13	1.00	EUR	OCAC ^{17,53}
Serous LMP	972	30 816	13	0.73	EUR	OCAC ^{17,53}
Pancreatic cancer	5105	8739	12	1.00	EUR	PanScan (incl. EPIC) ⁵⁴
Prostate cancer	22 297	22 323	11	1.00	EUR	PRACTICAL ^{55,56}
Testicular germ-cell cancer	986	4946	11	0.52	EUR	Turnbull et al ⁵⁷ and Rapley et al ⁵⁸
Autoimmune/inflammatory diseases						
Alopecia areata	2332	5233	7	0.60	EUR	Betz ⁵⁹
Atopic dermatitis	10 788	30 047	13	1.00	EUR	EAGLE ⁶⁰
Celiac disease	4533	10 750	3	0.82	EUR	Dubois ⁶¹
Inflammatory bowel disease						
Crohn disease	5956	14 927	11	1.00	EUR	IIBDGC ⁶²
Ulcerative colitis	6968	20 464	12	1.00	EUR	IIBDGC ⁶²
Juvenile idiopathic arthritis	1866	14 786	11	0.87	EUR	Thompson et al ^{63a}
Multiple sclerosis	14 498	24 091	3	1.00	EUR	IMSGC ⁶⁴
Aggressive periodontitis	888	6789	13	0.63	EUR	Schaefer et al ⁶⁵
Rheumatoid arthritis	5538	20 163	11	1.00	EUR	Stahl et al ⁶⁶
Cardiovascular diseases						
Abdominal aortic aneurysm	4972	99 858	13	1.00	EUR	AC ⁶⁷⁻⁷²
Coronary heart disease	22 233	64 762	13	1.00	EUR	CARDIoGRAM ⁷³
Heart failure	2526	20 926	13	0.99	EUR	CHARGE-HF ⁷⁴
Hemorrhagic stroke	2963	5503	12	0.96	EUR	METASTROKE/ISGC ⁷⁵
Ischemic stroke	12 389	62 004	13	1.00	EUR	METASTROKE/ISGC ^{76,77}
Large-vessel disease	2167	62 004	13	0.99	EUR	METASTROKE/ISGC ^{76,77}
Small-vessel disease	1894	62 004	13	0.97	EUR	METASTROKE/ISGC ⁷⁶
Cardioembolic disease	2365	62 004	13	0.99	EUR	METASTROKE/ISGC ⁷⁶
Sudden cardiac arrest	3954	21 200	13	1.00	EUR	Unpublished
Diabetes						
Type 1	7514	9045	6	0.95	EUR	T1DBase ^{78,79}

(continued)

Table 2. Study Characteristics for Primary Noncommunicable Diseases (continued)

Disease	Cases, No.	Controls, No.	SNPs, No.	Statistical Power	Pop	Source
Type 2	10 415	53 655	11	1.00	EUR	DIAGRAM ⁸⁰
Eye disease						
AMD	7473	51 177	13	1.00	EUR	AMD Gene ⁸¹
Retinopathy	1122	18 289	12	0.75	EUR	Jensen et al ⁸²
Lung disease						
Asthma	13 034	20 638	4	1.00	EUR	GABRIEL / Ferreira et al ^{83,84}
COPD	2812	2534	12	0.85	EUR	COPDGene ⁸⁵
Interstitial lung disease	1616	4683	9	0.60	EUR	Fingerlin ⁸⁶
Neurological/psychiatric disease						
ALS	6100	7125	12	1.00	EUR	SLAGEN/ALSGEN ⁸⁷
Alzheimer disease	17 008	37 154	12	1.00	EUR	IGAP ⁸⁸
Anorexia nervosa	2907	14 860	9	0.93	EUR	GCAN ⁸⁹
Autism	4949	5314	7	0.82	EUR	PGC ⁹⁰
Bipolar disorder	7481	9250	9	1.00	EUR	PGC ⁹¹
Major depressive disorder	9240	9519	8	0.99	EUR	PGC ⁹²
Schizophrenia	35 476	46 839	12	1.00	EUR	PGC ⁹³
Tourette syndrome	1177	4955	13	0.74	EUR	TICG/TSAICG ⁹⁴
Other						
Chronic kidney disease	5807	56 430	13	1.00	EUR	CKDGen ⁹⁵
Endometriosis	4604	9393	11	1.00	Mix	Nyholt et al ⁹⁶

Abbreviations: ALS, amyotrophic lateral sclerosis; AMD, age-related macular degeneration; COPD, chronic obstructive pulmonary disease; EA, East Asian; ER, estrogen receptor; EUR, European; LMP, low malignant potential; Pop., population; SCC, squamous cell carcinoma; SNP, single-nucleotide polymorphism.

Study acronyms: AC, the Aneurysm Consortium; ALSGEN, the International Consortium on Amyotrophic Lateral Sclerosis Genetics; AMD Gene, Age-related Macular Degeneration Gene Consortium; BCAC, Breast Cancer Association Consortium; CARDIoGRAM, Coronary ARtery Disease Genome wide Replication and Meta-analysis; CHARGE-HF, Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium - Heart Failure Working Group; COPDGene, The Genetic Epidemiology of Chronic Obstructive Pulmonary Disease; CKDGen, Chronic Kidney Disease Genetics consortium; CORECT, ColoRectal Transdisciplinary Study; DIAGRAM, DIAbetes Genetics Replication And Meta-analysis; EAGLE, EARly Genetics & Lifecourse Epidemiology Eczema Consortium (excluding 23andMe); ECAC, Endometrial Cancer Association Consortium; EPIC, European Prospective Investigation into Cancer and Nutrition study; GABRIEL, Multidisciplinary Study to Identify the Genetic and

Environmental Causes of Asthma in the European Community; GCAN, Genetic Consortium for Anorexia Nervosa; GECCO, Genetics and Epidemiology of Colorectal Cancer Consortium; IGAP, International Genomics of Alzheimer Project; HPFS, Health Professionals Follow-Up Study; ILCCO, International Lung Cancer Consortium; IMSGC, International Multiple Sclerosis Genetic Consortium; IIBDGC, International Inflammatory Bowel Disease Genetics Consortium; KIDRISK, Kidney cancer consortium; MC, the melanoma meta-analysis consortium; METASTROKE/ISGC, METASTROKE project of the International Stroke Genetics Consortium; NBCS, Nijmegen Bladder Cancer Study; NHS, Nurses' Health Study; OCAC, Ovarian Cancer Association Consortium; PanScan, Pancreatic Cancer Cohort Consortium; PGC, Psychiatric Genomics Consortium; PRACTICAL, Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome; SLAGEN, Italian Consortium for the Genetics of Ayotrophic Lateral Sclerosis; TIDBase, type 1 diabetes database; TICG (Tourette International Collaborative-Genetics); TSAICG (Tourette Syndrome Association International Consortium for Genetics).

^a Plus previously unpublished data.

mer 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).

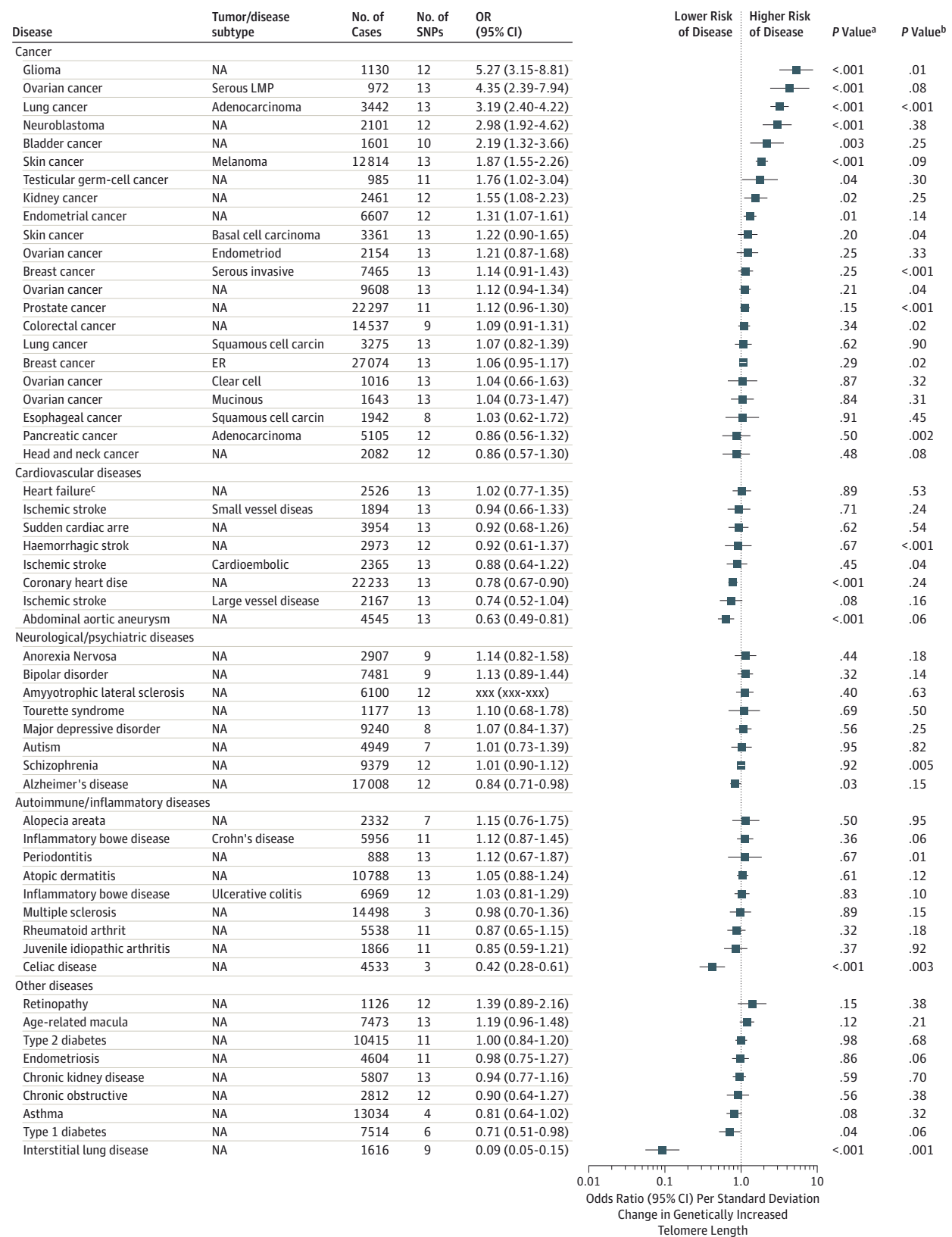
Our genetic findings were generally similar in direction and magnitude to estimates based on observational prospective studies of leukocyte telomere length and disease (Figure 2).^{10,97} Our genetic estimates for lung adenocarcinoma, melanoma, kidney cancer, and glioma were, however, stronger than the observational estimates.

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). In the second set of sensitivity analyses, implemented by MR-Egger regression, we found little evidence for the presence of pleiotropy (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.

Figure 1. The Association Between Genetically Increased Telomere Length and Odds of Primary Noncommunicable Diseases



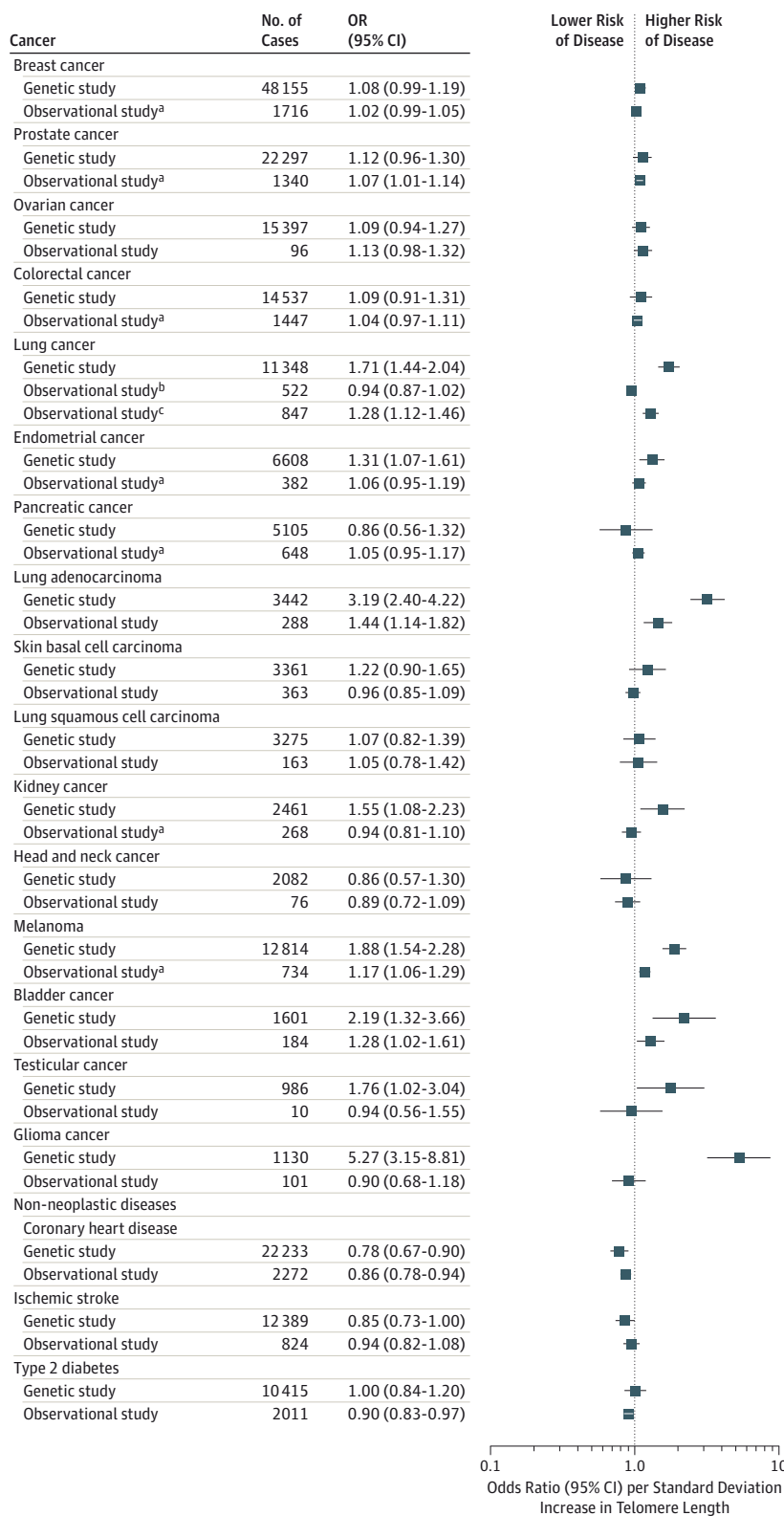
CPD indicates chronic obstructive pulmonary disease; ER, estrogen receptor; LMP, low malignancy potential; NA, not applicable; SNP, single-nucleotide polymorphism.

^b P value for heterogeneity among SNPs within the instrument.

^c The effect estimate for heart failure is a hazard ratio (all others are odds ratios).

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

Figure 2. Comparison of the Present Genetic Study and Prospective Observational Studies of the Association Between Telomere Length and Disease



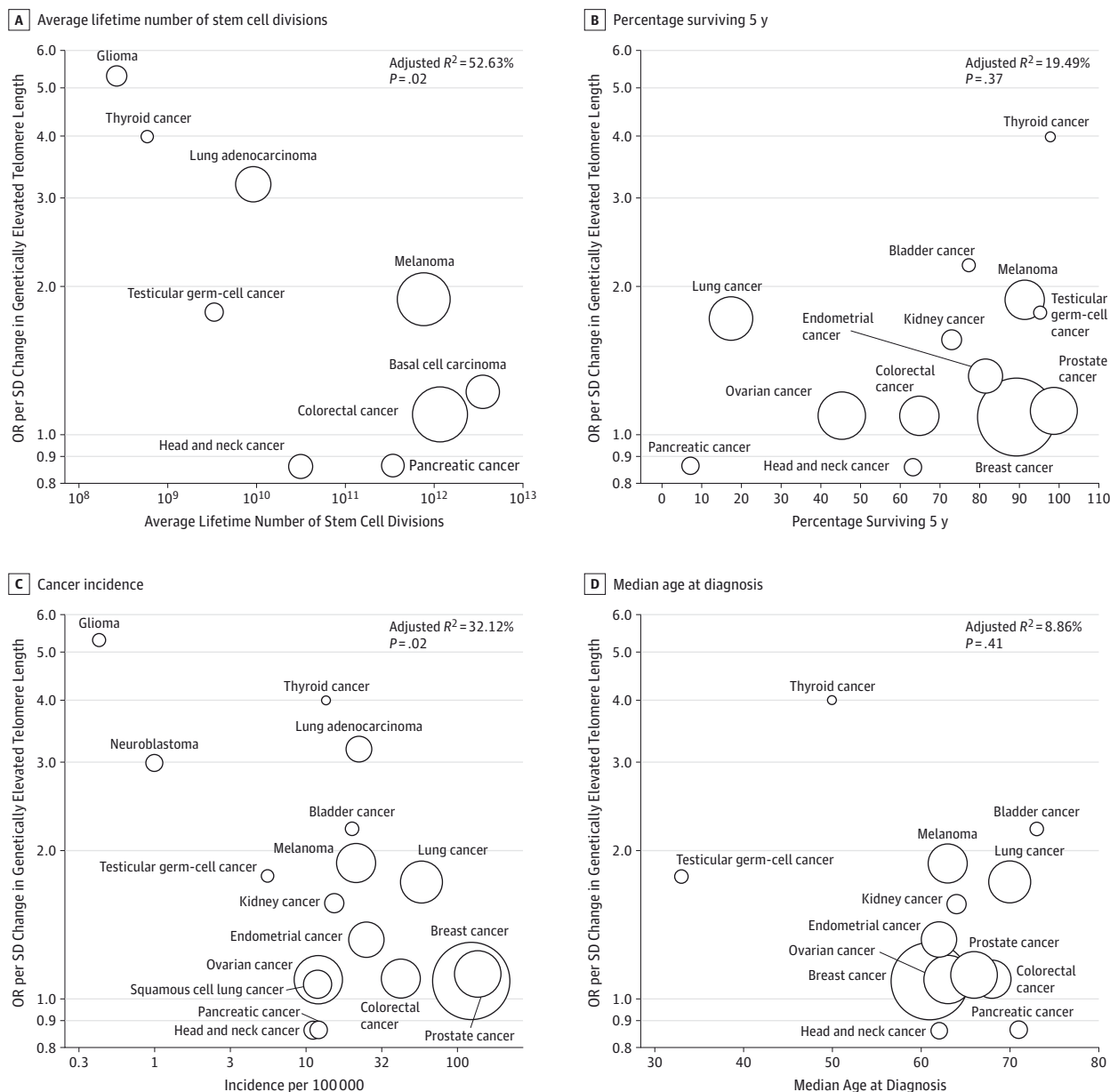
Search strategy and characteristics for observational studies are described in eTables 3 and 4 in Supplement 1.

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

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

^c 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

Figure 3. The Association Between Genetically Increased Telomere Length and Odds of Cancer as a Function of Selected Characteristics



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; the hashed line indicates the null of no association between telomere length and cancer (ie, an OR of 1). 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.

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.⁹⁸ 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 GWASes (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 risk for cancer in individuals with shorter telomeres.^{11,12,99-102} The contradictory findings may reflect reverse causation in the retrospective studies, whereby shorter telomeres arise as a result of disease, or of confounding effects, eg, due to case patients being slightly older than controls even in age-matched analyses. Our findings for cancer are generally more consistent with those based on prospective observational studies, which tend to report weak or null associations of longer leukocyte telomeres with overall and site-specific risk of cancer,^{10-13,97,101,103-121} with some exceptions.¹²² Our results are also similar to previously reported Mendelian randomization studies of telomere length and risk of melanoma, lung cancer, chronic lymphocytic leukemia, and glioma.^{40,46,123,124} The shape of 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 of an individual.³⁴ 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.³⁴ 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}

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, includ-

ing 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.

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