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1. JAMA Oncol. 2017 May 1;3(5):636-651. doi: 10.1001/jamaoncol.2016.5945.

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

Telomeres Mendelian Randomization Collaboration, Haycock PC[1], Burgess S[2], Nounu A[1], Zheng J[1], Okoli GN[3], Bowden J[1], Wade KH[1], Timpson NJ[1], Evans DM[4], Willeit P[5], Aviv A[6], Gaunt TR[1], Hemani G[1], Mangino M[7], Ellis HP[8], Kurian KM[8], Pooley KA[9], Eeles RA[10], Lee JE[11], Fang S[11], Chen WV[12], Law MH[13], Bowdler LM[14], Iles MM[15], Yang Q[16], Worrall BB[17], Markus HS[18], Hung RJ[19], Amos CI[20], Spurdle AB[21], Thompson DJ[9], O'Mara TA[21], Wolpin B[22], Amundadottir L[23], Stolzenberg-Solomon R[24], Trichopoulou A[25], Onland-Moret NC[26], Lund E[27], Duell EJ[28], Canzian F[29], Severi G[30], Overvad K[31], Gunter MJ[32], Tumino R[33], Svenson U[34], van Rij A[35], Baas AF[36], Bown MJ[37], Samani NJ[37], van t'Hof FNG[38], Tromp G[39], Jones GT[35], Kuivaniemi H[39], Elmore JR[40], Johansson M[41], Mckay J[42], Scelo G[41], Carreras-Torres R[41], Gaborieau V[41], Brennan P[41], Bracci PM[43], Neale RE[14], Olson SH[44], Gallinger S[45], Li D[46], Petersen GM[47], Risch HA[48], Klein AP[49], Han J[50], Abnet CC[51], Freedman ND[51], Taylor PR[51], Maris JM[52], Aben KK[53], Kiemeney LA[54], Vermeulen SH[54], Wiencke JK[55], Walsh KM[55], Wrensch M[55], Rice T[56], Turnbull C[57], Litchfield K[58], Paternoster L[1], Standl M[59], Abecasis GR[60], SanGiovanni JP[61], Li Y[62], Mijatovic V[63], Sapkota Y[14], Low SK[64], Zondervan KT[65], Montgomery GW[14], Nyholt DR[66], van Heel DA[67], Hunt K[67], Arking DE[68], Ashar FN[68], Sotoodehnia N[69], Woo D[70], Rosand J[71], Comeau ME[72], Brown WM[72], Silverman EK[73], Hokanson JE[74], Cho MH[73], Hui J[75], Ferreira MA[14], Thompson PJ[76], Morrison AC[77], Felix JF[78], Smith NL[79], Christiano AM[80], Petukhova L[81], Betz RC[82], Fan X[83], Zhang X[83], Zhu C[83], Langefeld CD[72], Thompson SD[84], Wang F[85], Lin X[85], Schwartz DA[86], Fingerlin T[87], Rotter JI[88], Cotch MF[89], Jensen RA[90], Munz M[91], Dommisch H[92], Schaefer AS[92], Han F[93], Ollila HM[94], Hillary RP[94], Albagha O[95], Ralston SH[96], Zeng C[97], Zheng W[97], Shu XO[97], Reis A[98], Uebe S[98], Hüffmeier U[98], Kawamura Y[99], Otowa T[100], Sasaki T[101], Hibberd ML[102], Davila S[103], Xie G[104], Siminovitch K[104], Bei JX[105], Zeng YX[106], Försti A[107], Chen B[108], Landi S[109], Franke A[110], Fischer A[111], Ellinghaus D[112], Flores C[113], Noth I[114], Ma SF[114], Foo JN[115], Liu J[115], Kim JW[116], Cox DG[117], Delattre O[118], Mirabeau O[118], Skibola CF[119], Tang CS[120], Garcia-Barcelo M[120], Chang KP[121], Su WH[122], Chang YS[123], Martin NG[14], Gordon S[14], Wade TD[124], Lee C[125], Kubo M[126], Cha PC[127], Nakamura Y[128], Levy D[129], Kimura M[6], Hwang SJ[129], Hunt

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Abstract

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.

PMID: 28241208

Similar articles

2. Carcinogenesis. 2016 Jun;37(6):576-82. doi: 10.1093/carcin/bgw037. Epub 2016 Apr 1.

Common genetic variants associated with telomere length confer risk for neuroblastoma and other childhood cancers.

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Abstract

Aberrant telomere lengthening is an important feature of cancer cells in adults and children. In addition to somatic mutations, germline polymorphisms in telomere maintenance genes impact telomere length. Whether these telomere-associated polymorphisms affect risk of childhood malignancies remains largely unexplored. We collected genome-wide data from three groups with pediatric malignancies [neuroblastoma (N = 1516), acute lymphoblastic leukemia (ALL) (N = 958) and osteosarcoma (N = 660)] and three control populations (N = 6892). Using case-control comparisons, we analyzed eight single nucleotide polymorphisms (SNPs) in genes definitively associated with interindividual variation in leukocyte telomere length (LTL) in prior genome-wide association studies: ACYP2, TERC, NAF1, TERT, OBFC1, CTC1,

ZNF208 and RTEL1 Six of these SNPs were associated (P < 0.05) with neuroblastoma risk, one with leukemia risk and one with osteosarcoma risk. The allele associated with longer LTL increased cancer risk for all these significantly associated SNPs. Using a weighted linear combination of the eight LTL-associated SNPs, we observed that neuroblastoma patients were predisposed to longer LTL than controls, with each standard deviation increase in genotypically estimated LTL associated with a 1.15-fold increased odds of neuroblastoma (95%CI = 1.09-1.22; P = 7.9×10(-7)). This effect was more pronounced in adolescent-onset neuroblastoma patients (OR = 1.46; 95%CI = 1.03-2.08). A one standard deviation increase in genotypically estimated LTL was more weakly associated with osteosarcoma risk (OR = 1.10; 95%CI = 1.01-1.19; P = 0.017) and leukemia risk (OR = 1.07; 95%CI = 1.00-1.14; P = 0.044), specifically for leukemia patients who relapsed (OR = 1.19; 95%CI = 1.01-1.40; P = 0.043). These results indicate that genetic predisposition to longer LTL is a newly identified risk factor for neuroblastoma and potentially for other cancers of childhood.

PMCID: PMC4876988 [Available on 2017-06-01]
PMID: 27207662 [Indexed for MEDLINE]
Similar articles

3. Cancer Epidemiol Biomarkers Prev. 2016 Jul;25(7):1043-9. doi: 10.1158/1055-9965.EPI-15-1329. Epub 2016 May 13.

Genetic Variation Associated with Longer Telomere Length Increases Risk of Chronic Lymphocytic Leukemia.

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Abstract

BACKGROUND:

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world. Shorter mean telomere length in leukemic cells has been associated with more aggressive disease. Germline polymorphisms in telomere maintenance genes affect telomere length and may contribute to CLL susceptibility.

METHODS:

We collected genome-wide data from two groups of patients with CLL (N = 273) and two control populations (N = 5,725). In ancestry-adjusted case-control comparisons, we analyzed eight SNPs in genes definitively associated with inter-individual variation in leukocyte telomere length (LTL) in prior genome-wide association studies: ACYP2, TERC, NAF1, TERT, OBFC1, CTC1, ZNF208, and RTEL1 RESULTS: Three of the eight LTL-associated SNPs were associated with CLL risk at $P < 0.05$, including those near: TERC [OR, 1.46; 95% confidence interval (CI), 1.15-1.86; $P = 1.8 \times 10(-3)$], TERT (OR = 1.23; 95% CI, 1.02-1.48; P = 0.030), and OBFC1 (OR, 1.36; 95% CI, 1.08-1.71; $P = 9.6 \times 10(-3)$). Using a weighted linear combination of the eight LTL-associated SNPs, we observed that CLL patients were predisposed to longer LTL than controls in both case-control sets ($P = 9.4 \times 10(-4)$ and 0.032, respectively). CLL risk increased monotonically with increasing quintiles of the weighted linear combination.

CONCLUSIONS:

Genetic variants in TERC, TERT, and OBFC1 are associated with both longer LTL and increased CLL risk. Because the human CST complex competes with shelterin for telomeric DNA, future work should explore the role of OBFC1 and other CST complex genes in leukemogenesis.

IMPACT:

A genetic predisposition to longer telomere length is associated with an increased risk of CLL, suggesting that the role of telomere length in CLL etiology may be distinct from its role in disease progression. Cancer Epidemiol Biomarkers Prev; 25(7); 1043-9. ©2016 AACR.

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Conflict of interest statement

The authors report no conflicts of interest.

4. Hum Mol Genet. 2016 Apr 15;25(8):1663-76. doi: 10.1093/hmg/ddw027. Epub 2016 Feb 9.

Genetically predicted longer telomere length is associated with increased risk of B-cell lymphoma subtypes.

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Abstract

Evidence from a small number of studies suggests that longer telomere length measured in peripheral leukocytes is associated with an increased risk of non-Hodgkin lymphoma (NHL). However, these studies may be biased by reverse causation, confounded by unmeasured environmental exposures and might miss time points for which prospective telomere measurement would best reveal a relationship between telomere length and NHL risk. We performed an analysis of genetically inferred telomere length and NHL risk in a study of 10 102 NHL cases of the four most common B-cell histologic types and 9562 controls using a genetic risk score (GRS) comprising nine telomere length-associated single-nucleotide polymorphisms. This approach uses existing genotype data and estimates telomere length by weighing the number of telomere length-associated variant alleles an individual carries with the published change in kb of telomere length. The analysis of the telomere length GRS resulted in an association between longer telomere length and increased NHL risk [four B-cell histologic types combined; odds ratio (OR) = 1.49, 95% CI 1.22-1.82,P-value = 8.5 × 10(-5)]. Subtype-specific analyses indicated that chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) was the principal NHL subtype contributing to this association (OR = 2.60, 95% CI 1.93-3.51,P-value = 4.0 × 10(-10)). Significant interactions were observed across strata of sex for CLL/SLL and marginal zone lymphoma subtypes as well as age for the follicular lymphoma subtype. Our results indicate that a genetic background that favors longer telomere length may increase NHL risk, particularly risk of CLL/SLL, and are consistent with earlier studies relating longer telomere length with increased NHL risk.

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Longer genotypically-estimated leukocyte telomere length is associated with increased adult glioma risk.

Walsh KM[1,2], Codd V[3,4], Rice T[1], Nelson CP[3,4], Smirnov IV[5], McCoy LS[1], Hansen HM[1], Elhauge E[1], Ojha J[1], Francis SS[5], Madsen NR[1], Bracci PM[6], Pico AR[7], Molinaro AM[5], Tihan T[8], Berger MS[5], Chang SM[5], Prados MD[5], Jenkins RB[9], Wiemels JL[1,6,10], ENGAGE Consortium Telomere Group, Samani NJ[3,4], Wiencke JK[1,10], Wrensch MR[1,10].

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Abstract

Telomere maintenance has emerged as an important molecular feature with impacts on adult glioma susceptibility and prognosis. Whether longer or shorter leukocyte telomere length (LTL) is associated with glioma risk remains elusive and is often confounded by the effects of age and patient treatment. We sought to determine if genotypically-estimated LTL is associated with glioma risk and if inherited single nucleotide polymorphisms (SNPs) that are associated with LTL are glioma risk factors. Using a Mendelian randomization approach, we assessed differences in genotypically-estimated relative LTL in two independent glioma case-control datasets from the UCSF Adult Glioma Study (652 patients and 3735 controls) and The Cancer Genome Atlas (478 non-overlapping patients and 2559 controls). LTL estimates were based on a weighted linear combination of subject genotype at eight SNPs, previously associated with LTL in the ENGAGE Consortium Telomere Project. Mean estimated LTL was 31bp (5.7%) longer in glioma patients than controls in discovery analyses (P = 7.82x10-8) and 27bp (5.0%) longer in glioma patients than controls in replication analyses (1.48x10-3). Glioma risk increased monotonically with each increasing septile of LTL (O.R.=1.12; P = 3.83x10-12). Four LTL-associated SNPs were significantly associated with glioma risk in pooled analyses, including those in the telomerase component genes TERC (O.R.=1.14; 95% C.I.=1.03-1.28) and TERT (O.R.=1.39; 95% C.I.=1.27-1.52), and those in the CST complex genes OBFC1 (O.R.=1.18; 95% C.I.=1.05-1.33) and CTC1 (O.R.=1.14; 95% C.I.=1.02-1.28). Future work is needed to characterize the role of the CST complex in gliomagenesis and further elucidate the complex balance between ageing, telomere length, and molecular carcinogenesis.

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Genetic determinants of telomere length and risk of common cancers: a Mendelian randomization study.

Zhang C[1], Doherty JA[2], Burgess S[3], Hung RJ[4], Lindström S[5], Kraft P[5], Gong J[6], Amos CI[7], Sellers TA[8], Monteiro AN[8], Chenevix-Trench G[9], Bickeböller H[10], Risch A[11], Brennan P[12], Mckay JD[12], Houlston RS[13], Landi MT[14], Timofeeva MN[12], Wang Y[13], Heinrich J[15], Kote-Jarai Z[16], Eeles RA[17], Muir K[18], Wiklund F[19], Grönberg H[19], Berndt SI[14], Chanock SJ[14], Schumacher F[20], Haiman CA[20], Henderson BE[20], Amin Al Olama A[21], Andrulis IL[22], Hopper JL[23], Chang-Claude J[24], John EM[25], Malone KE[6], Gammon MD[26], Ursin G[27], Whittemore AS[28], Hunter DJ[5], Gruber SB[29], Knight JA[30], Hou L[31], Le Marchand L[32], Newcomb PA[33], Hudson TJ[34], Chan AT[35], Li L[36], Woods MO[37], Ahsan H[38], Pierce BL[39]; GECCO and GAME-ON Network: CORECT, DRIVE, ELLIPSE, FOCI, and TRICL.

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Abstract

Epidemiological studies have reported inconsistent associations between telomere length (TL) and risk for various cancers. These inconsistencies are likely attributable, in part, to biases that arise due to post-diagnostic and post-treatment TL measurement. To avoid such biases, we used a Mendelian randomization approach and estimated associations between nine TL-associated SNPs and risk for five common cancer types (breast, lung, colorectal, ovarian and prostate cancer, including subtypes) using data on 51 725 cases and 62 035 controls. We then used an inverse-variance weighted average of the SNP-specific associations to estimate the association between a genetic score representing long TL and cancer risk. The long TL genetic score was significantly associated with increased risk of lung adenocarcinoma ($P = 6.3 \times 10(-15)$), even after exclusion of a SNP residing in a known lung cancer susceptibility region (TERT-CLPTM1L) $P = 6.6 \times 10(-6)$). Under Mendelian randomization assumptions, the association estimate [odds ratio (OR) = 2.78] is interpreted as the OR for lung adenocarcinoma corresponding to a 1000 bp increase in TL. The weighted TL SNP score was not associated with other cancer types or subtypes. Our finding that genetic determinants of long TL increase lung adenocarcinoma risk avoids issues with reverse causality and residual confounding that arise in observational studies of TL and disease risk. Under Mendelian randomization assumptions, our finding suggests that longer TL increases lung adenocarcinoma risk. However, caution regarding this causal interpretation is warranted in light of the potential issue of pleiotropy, and a more general interpretation is that SNPs influencing telomere biology are

also implicated in lung adenocarcinoma risk.

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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.

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Abstract

Recent evidence from several relatively small nested case-control studies in prospective cohorts shows an association between longer telomere length measured phenotypically in peripheral white blood cell (WBC) DNA and increased lung cancer risk. We sought to further explore this relationship by examining a panel of seven telomere-length associated genetic variants in a large study of 5,457 never-smoking female Asian lung cancer cases and 4,493 never-smoking female Asian controls using data from a previously reported genome-wide association study. Using a group of 1,536 individuals with phenotypically measured telomere length in WBCs in the prospective Shanghai Women's Health study, we demonstrated the utility of a genetic risk score (GRS) of seven telomere-length associated variants to predict telomere length in an Asian population. We then found that GRSs used as instrumental variables to predict longer telomere length were associated with increased lung cancer risk (OR = 1.51 (95% CI = 1.34-1.69) for upper vs. lower quartile of the weighted GRS, p value = 4.54 × 10(-14)) even after removing rs2736100 (p value = 4.81 × 10(-3)), a SNP in the TERT locus robustly associated with lung cancer risk in prior association studies. Stratified analyses suggested the effect of the telomere-associated GRS is strongest among younger individuals. We found no difference in GRS effect between adenocarcinoma and squamous cell subtypes. Our results indicate that a genetic background that favors longer telomere length may increase lung cancer risk, which is consistent with earlier prospective studies relating longer telomere length with increased lung cancer risk.

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