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Platinum Priority – Kidney Cancer
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Genetic Variants Related to Longer Telomere Length are Associated with Increased Risk of Renal Cell Carcinoma

Mitchell J. Machiela [a], Jonathan N. Hofmann [a], Robert Carreras-Torres [b], Kevin M. Brown [a], Mattias Johansson [b], Zhaoming Wang [c], Matthieu Foll [b], Peng Li [b], Nathaniel Rothman [a], Sharon A. Savage [a], Valerie Gaborieau [b], James D. McKay [b], Yuanqing Ye [d], Marc Henrion [e], Fiona Bruinsma [f], Susan Jordan [g,h], Gianluca Severi [f,i,j,k], Kristian Hveem [l], Lars J. Vatten [m], Tony Fletcher [n], Kvetoslava Koppova [o], Susanna C. Larsson [p], Alicja Wolk [p], Rosamonde E. Banks [q], Peter J. Selby [q], Douglas F. Easton [r], Paul Pharoah [r], Gabriella Andreotti [a], Laura E. Beane Freeman [a], Stella Koutros [a], Demetrius Albanes [a], Satu Mannisto [s], Stephanie Weinstein [a], Peter E. Clark [t], Todd E. Edwards [t], Loren Lipworth [t], Susan M. Gapstur [u], Victoria L. Stevens [u], Hallie Carol [v], Matthew L. Freedman [v], Mark M. Pomerantz [v], Eunyoung Cho [w], Peter Kraft [x], Mark A. Preston [y], Kathryn M. Wilson [x], J. Michael Gaziano [y,z], Howard S. Sesso [x], Amanda Black [a], Neal D. Freedman [a], Wen-Yi Huang [a], John G. Anema [aa], Richard J. Kahnoski [aa], Brian R. Lane [aa,bb], Sabrina L. Noyes [cc], David Petillo [cc], Leandro M. Colli [a], Joshua N. Sampson [a], Celine Besse [dd], Helene Blanche [ee], Anne Boland [dd], Laurie Burdette [a], Egor Prokhortchouk [ff,gg], Konstantin G. Skryabin [ff,gg], Meredith Yeager [a], Mirjana Mijuskovic [hh], Miodrag Ognjanovic [ii], Lenka Foretova [ii], Ivana Holcatova [jj], Vladimir Janout [kk], Dana Mates [ll], Anush Mukeriya [mm], Stefan Rascu [nn], David Zaridze [mm], Vladimir Bencko [oo], Cezary Cybulski [pp], Eleonora Fabianova [o], Viorel Jinga [oo], Jolanta Lissowska [rr], Jan Lubinski [qq], Marie Navratilova [jj], Peter Rudnai [ss], Neonila Szeszenia-Dabrowska [tt], Simone Benhamou [uu,vv], Geraldine Cancel-Tassin [ww,xx], Olivier Cussenot [ww,xx,yy], H. Bas Bueno-de-Mesquita [zz,aaa,bbb,ccc], Federico Canzian [ddd], Eric J. Duell [eee], Börje Ljungberg [fff], Raviprakash T. Sitaram [fff], Ulrike Peters [ggg], Emily White [ggg], Garnet L. Anderson [ggg], Lisa Johnson [ggg], Juhua Luo [hhh], Julie Buring [x], I-Min Lee [x,y], Wong-Ho Chow [d], Lee E. Moore [a], Christopher Wood [iii], Timothy Eisen [jjj], James Larkin [kkk], Toni K. Choueiri [v], G. Mark Lathrop [lll], Bin Tean Teh [cc], Jean-Francois Deleuze [dd,ee], Xifeng Wu [d], Richard S. Houlston [mmm], Paul Brennan [b], Stephen J. Chanock [a], Ghislaine Scelo [b], Mark P. Purdue [a,]*

[a] *Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department Health and Human Services, Bethesda, MS, USA;* [b] *International Agency for Research on Cancer (IARC), Lyon, France;* [c] *St. Jude Children's Research Hospital, Memphis, TN, USA;* [d] *Department of Epidemiology, Division of Cancer Prevention and Population Sciences, The University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [e] *Icahn School of Medicine, New York, NY, USA;* [f] *Cancer Epidemiology and Intelligence Division, Cancer Council Victoria, Melbourne, Australia;* [g] *QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia;* [h] *School of Public Health, The University of Queensland, Brisbane, Australia;* [i] *Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Carlton, Australia;* [j] *Human Genetics Foundation (HuGeF),*

* Corresponding author. 9609 Medical Center Drive, Room 6E140, Bethesda, MD 20892-9776, USA. Tel. +1 240 276 7265.
E-mail address: purduem@mail.nih.gov (M.P. Purdue).

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Torino, Italy; [k] Centre de Recherche en Épidémiologie et Santé des Populations, Université Paris-Saclay, UPS, USQ, Gustave Roussy, Villejuif, France; [l] HUNT Research Centre, Department of Public Health and General Practice, Norwegian University of Science and Technology, Levanger, Sweden; [m] Department of Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway; [n] London School of Hygiene and Tropical Medicine, University of London, London, UK; [o] Regional Authority of Public Health in Banska Bystrica, Banska Bystrica, Slovakia; [p] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [q] Leeds Institute of Cancer and Pathology, University of Leeds, Cancer Research Building, St James's University Hospital, Leeds, UK; [r] Department of Oncology, and Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; [s] National Institute for Health and Welfare, Helsinki, Finland; [t] Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [u] American Cancer Society, Atlanta, GA, USA; [v] Dana-Farber Cancer Institute, Boston, MA, USA; [w] Brown University, Providence, RI, USA; [x] Harvard T.H. Chan School of Public Health, Boston, MA, USA; [y] Brigham and Women's Hospital, Boston, MA, USA; [z] Veterans Administration, Boston, MA, USA; [aa] Division of Urology, Spectrum Health, Grand Rapids, MI, USA; [bb] College of Human Medicine, Michigan State University, Grand Rapids, MI, USA; [cc] Van Andel Research Institute, Center for Cancer Genomics and Quantitative Biology, Grand Rapids, MI, USA; [dd] Centre National de Recherche en Genomique Humaine (CNRGH), Institut de biologie François Jacob, Commissariat à l'Energie Atomique et aux Energies Alternatives, Evry, France; [ee] Fondation Jean Dausset-Centre d'Etude du Polymorphisme Humain, Paris, France; [ff] Center 'Bioengineering' of the Russian Academy of Sciences, Moscow, Russian Federation; [gg] Kurchatov Scientific Center, Moscow, Russian Federation; [hh] Clinic for Nephrology, Military Medical Academy, Belgrade, Serbia; [ii] International Organization for Cancer Prevention and Research (IOCPR), Belgrade, Serbia; [jj] Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute, Brno, Czech Republic; [kk] Second Faculty of Medicine, Institute of Public Health and Preventive Medicine, Charles University, Prague, Czech Republic; [ll] Department of Preventive Medicine, Faculty of Medicine, Palacky University, Czech Republic; [mm] National Institute of Public Health, Bucharest, Romania; [nn] Russian N.N. Blokhin Cancer Research Centre, Moscow, Russian Federation; [oo] Carol Davila University of Medicine and Pharmacy, Th. Burghele Hospital, Bucharest, Romania; [pp] First Faculty of Medicine, Institute of Hygiene and Epidemiology, Charles University, Prague, Czech Republic; [qq] International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland; [rr] The M Sklodowska-Curie Cancer Center and Institute of Oncology, Warsaw, Poland; [ss] National Public Health Center, National Directorate of Environmental Health, Budapest, Hungary; [tt] Department of Epidemiology, Institute of Occupational Medicine, Lodz, Poland; [uu] INSERM U946, Paris, France; [vv] CNRS UMR8200, Institute Gustave Roussy, Villejuif, France; [ww] CeRePP, Paris, France; [xx] UPMC Univ Paris 06, Institut Universitaire de Cancérologie, Paris, France; [yy] AP-HP, Department of Urology, Hopitaux Universitaires Est Parisien Tenon, Paris, France; [zz] Department for Determinants of Chronic Diseases (DCD), National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands; [aaa] Department of Gastroenterology and Hepatology, University Medical Centre, Utrecht, The Netherlands; [bbb] Department of Epidemiology and Biostatistics, The School of Public Health, Imperial College London, St Mary's Campus, Norfolk Place, London, UK; [ccc] Department of Social & Preventive Medicine, Faculty of Medicine, University of Malaya, Pantai Valley, Kuala Lumpur, Malaysia; [ddd] Genomic Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany; [eee] Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO-IDIBELL), Barcelona, Spain; [fff] Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden; [ggg] Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [hhh] Department of Epidemiology and Biostatistics, School of Public Health Indiana University Bloomington, Bloomington, IN, USA; [iii] Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [jjj] University of Cambridge, Cambridge, UK; [kkk] Royal Marsden NHS Foundation Trust, London, UK; [lll] McGill University and Genome Quebec Innovation Centre, Montreal, QC, Canada; [mmm] The Institute of Cancer Research, London, UK

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Abstract

Background: Relative telomere length in peripheral blood leukocytes has been evaluated as a potential biomarker for renal cell carcinoma (RCC) risk in several studies, with conflicting findings.
Objective: We performed an analysis of genetic variants associated with leukocyte telomere length to assess the relationship between telomere length and RCC risk using Mendelian randomization, an approach unaffected by biases from temporal variability and reverse causation that might have affected earlier investigations.
Design, setting, and participants: Genotypes from nine telomere length-associated variants for 10 784 cases and 20 406 cancer-free controls from six genome-wide association studies (GWAS) of RCC were aggregated into a weighted genetic risk score (GRS) predictive of leukocyte telomere length.
Outcome measurements and statistical analysis: Odds ratios (ORs) relating the GRS and RCC risk were computed in individual GWAS datasets and combined by meta-analysis.
Results and limitations: Longer genetically inferred telomere length was associated with an increased risk of RCC (OR = 2.07 per predicted kilobase increase, 95% confidence interval [CI]: = 1.70–2.53, $p < 0.0001$). As a sensitivity analysis, we excluded two telomere length variants in linkage disequilibrium ($R^2 > 0.5$) with GWAS-identified RCC risk variants (rs10936599 and rs9420907) from the telomere length GRS; despite this exclusion, a statistically significant association between the GRS and RCC risk persisted (OR = 1.73, 95% CI = 1.36–2.21, $p < 0.0001$). Exploratory analyses for individual histologic subtypes suggested comparable associations with the telomere length GRS for clear cell ($N = 5573$, OR = 1.93, 95% CI = 1.50–2.49, $p < 0.0001$), papillary ($N = 573$, OR = 1.96, 95% CI = 1.01–3.81, $p = 0.046$), and chromophobe RCC ($N = 203$, OR = 2.37, 95% CI = 0.78–7.17, $p = 0.13$).
Conclusions: Our investigation adds to the growing body of evidence indicating some aspect of longer telomere length is important for RCC risk.
Patient summary: Telomeres are segments of DNA at chromosome ends that maintain chromosomal stability. Our study investigated the relationship between genetic variants associated with telomere length and renal cell carcinoma risk. We found evidence suggesting individuals with inherited predisposition to longer telomere length are at increased risk of developing renal cell carcinoma.

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