**Peer Review Information:**

Nature Genetics thanks Mark Rubin and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

**Editor summary**:

A multi-ancestry genome-wide association study of prostate cancer performed in 156 319 cases and 788 443 controls identifies 187 novel risk variants associated with the disease. Genetic risk scores associated with overall risk, and risk of aggressive disease in men of African ancestry.

# 1. Extended Data

| Figure or Table #<br>Please group Extended Data items by type, in sequential order. Total number of items (Figs. + Tables) must not exceed 10. | Figure/Table title<br>One sentence only | Filename<br>Whole original file name including extension. i.e.: Smith_ED_Fig1.jpg | Figure/Table Legend<br>If you are citing a reference for the first time in these legends, please include all new references in the main text Methods References section, and carry on the numbering from the main References section of the paper. If your paper does not have a Methods section, include all new references at the end of the main Reference list. |
|---|---|---|---|
| Extended Data Fig. 1 | Venn diagram of prostate cancer risk variants common (MAF>1%) among European, African, Asian and Hispanic populations. | eFig1.eps | The plot illustrates the distribution of 451 prostate cancer risk variants, highlighting the number of variants that are either unique to or shared among European, African, Asian, and Hispanic populations. Five variants with a minor allele frequency (MAF) of ≤1% across all populations are specifically included under the European population, where they have the highest MAF. Numbers in parentheses denote the total count of variants common to each respective population. |
| Extended Data Fig. 2 | The associations of $GRS_{451}$ and total prostate cancer risk in GWAS discovery and replication sub-studies and meta-analysis by ancestry. | eFig2.tiff | Odds ratios and 95% confidence intervals for one SD increase in $GRS_{451}$ and total prostate cancer risk were calculated from logistic regression. The columns 'case' and 'control' show the case and control sample sizes, respectively. 'META' refers to the meta-analyzed results using the inverse-variance weighted method. The y-axis shows each individual sub-studies (details of each sub-studies are available in Supplemental Table 1 and 2) and their |

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| | | | corresponding meta-analyzed results by ancestry and study phase (GWAS discovery or replication), as well as overall meta-analyzed results. |

# 1. Supplementary Information:

## A. PDF Files

| Item | Present? | Filename<br>Whole original file name including extension. i.e.: Smith_SI.pdf. The extension must be .pdf | A brief, numerical description of file contents.<br>i.e.: *Supplementary Figures 1-4, Supplementary Discussion, and Supplementary Tables 1-4.* |
|---|---|---|---|
| Supplementary Information | Yes | Supplementary_Note.pdf | Supplementary Figures 1-7 and Additional Acknowledgements. |
| Reporting Summary | Yes | NG-LE60828R2_Haiman_RS.pdf | |
| Peer Review Information | Yes | *NG-LE60828R2_Haiman_TPR.pdf* | |

## B. Additional Supplementary Files

| Type | Number<br>Each type of file (Table, Video, etc.) should be numbered from 1 onwards. Multiple files of the same type should be listed in sequence, i.e.: Supplementary Video 1, Supplementary Video 2, etc. | Filename<br>Whole original file name including extension. i.e.: *Smith_ Supplementary_Video_1.mov* | Legend or Descriptive Caption<br>Describe the contents of the file |
|---|---|---|---|
| Supplementary Table | Supplementary Tables 1-19 | Supplementary_Tables.xlsx | Supplementary Tables 1-19 |

**Characterizing prostate cancer risk through multi-ancestry genome-wide discovery of 187 novel risk variants**

Anqi Wang[1], Jiayi Shen[1], Alex A. Rodriguez[2], Edward J. Saunders[3], Fei Chen[1], Rohini Janivara[4], Burcu F. Darst[1,5], Xin Sheng[1], Yili Xu[1], Alisha J. Chou[1], Sara Benlloch[6], Tokhir Dadaev[3], Mark N. Brook[3], Anna Plym[7,8], Ali Sahimi[9], Thomas J. Hoffman[10,11], Atushi Takahashi[12,13], Koichi Matsuda[14], Yukihide Momozawa[15], Masashi Fujita[16], Triin Laisk[17],

Jéssica Figuerêdo[17], Kenneth Muir[18,19], Shuji Ito[20,21], Xiaoxi Liu[22], The Biobank Japan Project*, Yuji Uchio[20], Michiaki Kubo[21], Yoichiro Kamatani[22,23], Artitaya Lophatananon[24], Peggy Wan[9], Caroline Andrews[25], Adriana Lori[26], Parichoy P. Choudhury[27], Johanna Schleutker[28,29], Teuvo L.J. Tammela[30], Csilla Sipeky[28], Anssi Auvinen[31], Graham G. Giles[32,33,34], Melissa C. Southey[34], Robert J. MacInnis[32,33], Cezary Cybulski[35], Dominika Wokolorczyk[35], Jan Lubinski[35], Christopher T. Rentsch[36,37,38], Kelly Cho[39,40], Benjamin H. Mcmahon[41], David E. Neal[42,43,44], Jenny L. Donovan[45], Freddie C. Hamdy[46,47], Richard M. Martin[48,49,50], Borge G. Nordestgaard[51,52], Sune F. Nielsen[51,52], Maren Weischer[52], Stig E. Bojesen[51,52], Martin Andreas Røder[53,54], Hein V. Stroomberg[53], Jyotsna Batra[55,56], Suzanne Chambers[57], Lisa Horvath[58,59], Judith A. Clements[55,56], Wayne Tilly[60], Gail P. Risbridger[61,62], Henrik Gronberg[63], Markus Aly[63,64,65], Robert Szulkin[63,66], Martin Eklund[63], Tobias Nordstrom[63,67], Nora Pashayan[68,69,70], Alison M. Dunning[69], Maya Ghoussaini[71], Ruth C. Travis[72], Tim J. Key[72], Elio Riboli[73], Jong Y. Park[74], Thomas A. Sellers[74], Hui-Yi Lin[75], Demetrius Albanes[76], Stephanie Weinstein[76], Michael B. Cook[77], Lorelei A. Mucci[78], Edward Giovannucci[78], Sara Lindstrom[79], Peter Kraft[80], David J. Hunter[81], Kathryn L. Penney[82], Constance Turman[80], Catherine M. Tangen[83], Phyllis J. Goodman[83], Ian M. Thompson Jr.[84], Robert J. Hamilton[85,86], Neil E. Fleshner[85], Antonio Finelli[87], Marie-Élise Parent[88], Janet L. Stanford[5], Elaine A. Ostrander[89], Stella Koutros[76], Laura E. Beane Freeman[76], Meir Stampfer[82], Alicja Wolk[90,91], Niclas Håkansson[90], Gerald L. Andriole[92], Robert N. Hoover[76], Mitchell J. Machiela[76], Karina Dalsgaard Sørensen[93,94], Michael Borre[95,94], William J. Blot[96,97], Wei Zheng[96], Edward D. Yeboah[98], James E. Mensah[99,98], Yong-Jie Lu[100], Hong-Wei Zhang[101], Ninghan Feng[102], Xueying Mao[100], Yudong Wu[103], Shan-Chao Zhao[104], Zan Sun[105], Stephen N. Thibodeau[106], Shannon K. McDonnell[107], Daniel J. Schaid[107], Catharine M.L. West[108], Gill Barnett[109], Christiane Maier[110], Thomas Schnoeller[111], Manuel Luedeke[110], Adam S. Kibel[112], Bettina F. Drake[113], Olivier Cussenot[114,115], Geraldine Cancel-Tassin[114,115], Florence Menegaux[116], Thérèse Truong[116], Yves Akoli Koudou[117], Esther M. John[118], Eli Marie Grindedal[119], Lovise Maehle[119], Kay-Tee Khaw[120], Sue A. Ingles[121], Mariana C Stern[121], Ana Vega[122,123,124], Antonio Gómez-Caamaño[125], Laura Fachal[126,127,123,124], Barry S. Rosenstein[128,129], Sarah L. Kerns[130], Harry Ostrer[131], Manuel R. Teixeira[132,133,134], Paula Paulo[133], Andreia Brandão[133], Stephen Watya[135], Alexander Lubwama[135], Jeannette T. Bensen[136,137], Ebonee N. Butler[136], James L. Mohler[138,139], Jack A. Taylor[140,141], Manolis Kogevinas[142,143,144,145], Trinidad Dierssen-Sotos[146,145], Gemma Castaño-

Vinyals[142,143,144,145], Lisa Cannon-Albright[147,148], Craig C. Teerlink[147,148], Chad D. Huff[149], Patrick Pilie[150], Yao Yu[149], Ryan J. Bohlender[149], Jian Gu[149], Sara S. Strom[151], Luc Multigner[152], Pascal Blanchet[153], Laurent Brureau[153], Radka Kaneva[154], Chavdar Slavov[155], Vanio Mitev[154], Robin J. Leach[156], Hermann Brenner[157,158,159], Xuechen Chen[157], Bernd Holleczek[160], Ben Schöttker[157], Eric A. Klein[161,162], Ann W. Hsing[163], Rick A. Kittles[164], Adam B. Murphy[165], Christopher J. Logothetis[166], Jeri Kim[166], Susan L. Neuhausen[167], Linda Steele[167], Yuan Chun Ding[167], William B. Isaacs[168], Barbara Nemesure[169], Anselm J.M. Hennis[169,170], John Carpten[171], Hardev Pandha[172], Agnieszka Michael[172], Kim De Ruyck[173], Gert De Meerleer[174], Piet Ost[174], Jianfeng Xu[175], Azad Razack[176], Jasmine Lim[176], Soo-Hwang Teo[177], Lisa F. Newcomb[178,179], Daniel W. Lin[178,179], Jay H. Fowke[180], Christine M. Neslund-Dudas[181], Benjamin A. Rybicki[181], Marija Gamulin[182], Davor Lessel[183], Tomislav Kulis[184], Nawaid Usmani[185,186], Aswin Abraham[185,186], Sandeep Singhal[185], Matthew Parliament[185,186], Frank Claessens[187], Steven Joniau[188], Thomas Van den Broeck[187,188], Manuela Gago-Dominguez[189,190], Jose Esteban Castelao[191], Maria Elena Martinez[192], Samantha Larkin[193], Paul A. Townsend[194], Claire Aukim-Hastie[195], William S. Bush[196], Melinda C. Aldrich[197], Dana C. Crawford[196], Shiv Srivastava[198], Jennifer Cullen[199,196], Gyorgy Petrovics[199], Graham Casey[200], Ying Wang[26], Yao Tettey[201,99], Joseph Lachance[4], Wei Tang[202], Richard B. Biritwum[99], Andrew A. Adjei[203], Evelyn Tay[99], Ann Truelove[204], Shelley Niwa[204], Kosj Yamoah[205,74], Koveela Govindasami[3], Anand P. Chokkalingam[206], Jacob M. Keaton[96,207], Jacklyn N. Hellwege[96,208], Peter E. Clark[209], Mohamed Jalloh[210], Serigne M. Gueye[210], Lamine Niang[210], Olufemi Ogunbiyi[211], Olayiwola Shittu[212], Olukemi Amodu[213], Akindele O. Adebiyi[214], Oseremen I. Aisuodionoe-Shadrach[215], Hafees O. Ajibola[215], Mustapha A. Jamda[215], Olabode P. Oluwole[215], Maxwell Nwegbu[215], Ben Adusei[216], Sunny Mante[216], Afua Darkwa-Abrahams[99], Halimatou Diop[217], Susan M. Gundell[1], Monique J. Roobol[218], Guido Jenster[218], Ron H.N. van Schaik[219], Jennifer J. Hu[220], Maureen Sanderson[221], Linda Kachuri[222], Rohit Varma[223], Roberta McKean-Cowdin[9], Mina Torres[223], Michael H. Preuss[224], Ruth J.F. Loos[224], Matthew Zawistowski[225,226], Sebastian Zöllner[225,226,227], Zeyun Lu[9], Stephen K. Van Den Eeden[228], Douglas F. Easton[229], Stefan Ambs[202], Todd L. Edwards[96], Reedik Mägi[17], Timothy R. Rebbeck[230], Lars Fritsche[231], Stephen J. Chanock[232], Sonja I. Berndt[232], Fredrik Wiklund[7], Hidewaki Nakagawa[233], John S. Witte[222,234], J. Michael Gaziano[39,40], Amy C. Justice[36], Nick Mancuso[1], Chikashi

Terao[235,236,237], Rosalind A. Eeles[3,238], Zsofia Kote-Jarai[3], Ravi K. Madduri[2], David V. Conti[1], Christopher A. Haiman[1*]

[1]Center for Genetic Epidemiology,Department of Population and Public Health Sciences, Keck School of Medicine,University of Southern California, Los Angeles, CA, USA, [2]Argonne National Laboratory, Lemont, IL, USA, [3]The Institute of Cancer Research, London, UK, [4]School of Biological Sciences, Georgia Institute of Technology, Atlanta, GA, USA, [5]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [6]Department of Public Health and Primary Care, Centre for Cancer Genetic Epidemiology,University of Cambridge, Cambridge, UK, [7]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden, [8]Urology Division, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, [9]Department of Population and Public Health Sciences, Keck School of Medicine,University of Southern California, Los Angeles, CA, USA, [10]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA, [11]Institute for Human Genetics, University of California, San Francisco, San Francisco, CA, USA, [12]Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan, [13]Department of Genomic Medicine, National Cerebral and Cardiovascular Center Research Institute, Suita, Japan, [14]Department of Computational Biology and Medical Sciences, Laboratory of Clinical Genome Sequencing,Graduate school of Frontier Sciences,The University of Tokyo, Tokyo, Japan, [15]Laboratory for Genotyping Development, RIKEN Center of Integrative Medical Sciences, Yokohama, Japan, [16]Laboratory for Cancer Genomics, RIKEN Center of Integrative Medical Sciences, Yokohama, Japan, [17]Estonian Genome Centre, Institute of Genomics, University of Tartu, Tartu, Estonia, [18]Division of Population Health, Health Services Research and Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK, [19]Warwick Medical School, University of Warwick, Coventry, UK, [20]Department of Orthopaedics, Shimane University, Izumo, Shimane, Japan, [21]RIKEN Center for Integrative Medical Sciences, Yokohama, Japan, [22]Laboratory for Statistical and Translational Genetics, Center for Integrative Medical Sciences, RIKEN, Yokohama, Japan, [23]Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, Japan, [24]Division of Population Health, Health Services Research and

Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, Manchester, UK, [25]Harvard TH Chan School of Public Health and Division of Population Sciences,Dana Farber Cancer Institute, Boston, MA, USA, [26]Department of Population Science, American Cancer Society, Kennesaw, GA, USA, [27]Surveillance&Health Science Department, American Cancer Society, Kennesaw, GA, USA, [28]Institute of Biomedicine, University of Turku, Turku, Finland, [29]Department of Medical Genetics, Genomics, Laboratory Division, Turku University Hospital, Turku, Finland, [30]Department of Urology, Tampere University Hospital, Tampere, Finland, [31]Unit of Health Sciences, Faculty of Social Sciences, Tampere University, Tampere, Finland, [32]Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Australia, [33]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health,The University of Melbourne, Victoria, Australia, [34]Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia, [35]International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland, [36]Yale School of Medicine, New Haven, CT, USA, [37]Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK, [38]VA Connecticut Healthcare System, West Haven, CT, USA, [39]Division of Aging, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, [40]VA Boston Healthcare System, Boston, MA, USA, [41]Theoretical Biology Division, Los Alamos National Lab, Los Alamos, NM, USA, [42]Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Headington, Oxford, UK, [43]University of Cambridge, Department of Oncology, Addenbrooke's Hospital, Cambridge, UK, [44]Cancer Research UK, Cambridge Research Institute, Li Ka Shing Centre, Cambridge, UK, [45]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK, [46]Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK, [47]Faculty of Medical Science, University of Oxford, John Radcliffe Hospital, Oxford, UK, [48]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK, [49]NIHR Bristol Biomedical Research Centre at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol, Bristol, UK, [50]Medical Research Council (MRC) Integrative Epidemiology Unit, University of Bristol, Bristol, UK, [51]Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, [52]Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Copenhagen, Denmark, [53]Copenhagen Prostate Cancer

Center, Department of Urology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [54]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, [55]Australian Prostate Cancer Research Centre-Qld, Institute of Health and Biomedical Innovation and School of Biomedical Sciences, Queensland University of Technology, Brisbane, Australia, [56]Translational Research Institute, Brisbane, Queensland, Australia, [57]University of Technology, Sydney, Australia, [58]Chris O'Brien Lifehouse (COBLH), Camperdown, Sydney, NSW, Australia, Sydney, Australia, [59]Garvan Institute of Medical Research, Sydney, Australia, [60]Dame Roma Mitchell Cancer Research Laboratories, University of Adelaide, Adelaide, Australia, [61]Department of Anatomy and Developmental Biology, Biomedicine Discovery Institute, Monash University, Melbourne, Victoria, Australia, [62]Prostate Cancer Translational Research Program, Cancer Research Division, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia, [63]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden, [64]Department of Molecular Medicine and Surgery, Karolinska Institutet, and Department of Urology, Karolinska University Hospital, Solna, Stockholm, Sweden, [65]Department of Urology, Karolinska University Hospital, Stockholm, Sweden, [66]SDS Life Sciences, Stockholm, Sweden, [67]Department of Clinical Sciences at Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden, [68]University College London, Department of Applied Health Research, London, UK, [69]Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Strangeways Laboratory, Cambridge, UK, [70]Department of Applied Health Research, University College London, London, UK, [71]Open Targets, Wellcome Sanger Institute, Hinxton, Saffron Walden, Hinxton, UK, [72]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK, [73]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK, [74]Department of Cancer Epidemiology, Moffitt Cancer Center, Tampa, FL, USA, [75]School of Public Health, Louisiana State University Health Sciences Center, New Orleans, LA, USA, [76]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, MD, USA, [77]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH,, Bethesda, MD, USA, [78]Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA, USA, [79]Department of Epidemiology, University of Washington, Seattle, WA, USA, [80]Program in Genetic Epidemiology and Statistical Genetics, Department of Epidemiology, Harvard T. H. Chan School of Public Health,

Boston, MA, USA, [81]Nuffield Department of Population Health, University of Oxford, Oxford, UK, [82]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA, [83]SWOG Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [84]CHRISTUS Santa Rosa Hospital – Medical Center, San Antonio, TX, USA, [85]Dept. of Surgical Oncology, Princess Margaret Cancer Centre, Toronto, Canada, [86]Dept. of Surgery (Urology), University of Toronto, Toronto, Canada, [87]Division of Urology, Princess Margaret Cancer Centre, Toronto, Canada, [88]Epidemiology and Biostatistics Unit, Centre Armand-Frappier Santé Biotechnologie, Laval, QC, Canada, [89]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA, [90]Division of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [91]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden, [92]Brady Urological Institute in National Capital Region, Johns Hopkins University, Baltimore, MD, USA, [93]Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark, [94]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark, [95]Department of Urology, Aarhus University Hospital, Aarhus, Denmark, [96]Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA, [97]International Epidemiology Institute, Rockville, MD, USA, [98]University of Ghana Medical School, Accra, Ghana, [99]Korle Bu Teaching Hospital, Accra, Ghana, [100]Centre for Molecular Oncology, Barts Cancer Institute, Queen Mary University of London, John Vane Science Centre, London, UK, [101]Second Military Medical University, Shanghai, P.R.China, [102]Wuxi Second Hospital, Nanjing Medical University, Wuxi, Jiangzhu Province, China, [103]Department of Urology, First Affiliated Hospital, The Academy of Medical Sciences, Zhengzhou University, Zhengzhou, China, [104]Department of Urology, Nanfang Hospital, Southern Medical University, Guangzhou, China, [105]The People's Hospital of Liaoning Proviouce, The People's Hospital of China Medical University, Shenyang, China, Shenyang, China, [106]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA, [107]Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN, USA, [108]Division of Cancer Sciences, University of Manchester, Manchester Academic Health Science Centre, Radiotherapy Related Research, The Christie Hospital NHS Foundation Trust, Manchester, UK, [109]University of Cambridge Department of Oncology, Oncology Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK, [110]Humangenetik Tuebingen, Tuebingen,

Germany, [111]Department of Urology, University Hospital Ulm, Ulm, Germany, [112]Division of Urologic Surgery, Brigham and Womens Hospital, Boston, MA, USA, [113]Washington University School of Medicine, St. Louis, MO, USA, [114]GRC 5 Predictive Onco-Urology, Sorbonne Université, Paris, France, [115]CeRePP, Paris, France, [116]Exposome and Heredity, CESP (UMR 1018), Paris-Saclay Medical School, Paris-Saclay University, Inserm, Gustave Roussy, Villejuif, France, [117]Cancer & Environment Group, Center for Research in Epidemiology and Population Health (CESP), INSERM, University Paris-Sud, University Paris-Saclay, Villejuif Cédex, France, [118]Department of Medicine, Stanford Cancer Institute,Stanford University School of Medicine, Stanford, CA, USA, [119]Department of Medical Genetics, Oslo University Hospital, Oslo, Norway, [120]Clinical Gerontology Unit, University of Cambridge, Cambridge, UK, [121]Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [122]Fundación Pública Galega Medicina Xenómica, Santiago De Compostela, Spain, [123]Instituto de Investigación Sanitaria de Santiago de Compostela, Santiago De Compostela, Spain, [124]Centro de Investigación en Red de Enfermedades Raras (CIBERER), Spain, [125]Department of Radiation Oncology, Complexo Hospitalario Universitario de Santiago, SERGAS, Santiago de Compostela, Spain, [126]Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Cambridge, UK, [127]Fundación Pública Galega Medicina Xenómica, Santiago de Compostela, Spain, [128]Department of Radiation Oncology and Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [129]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [130]Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI, USA, [131]Professor of Pathology and Pediatrics, Albert Einstein College of Medicine, Bronx, NY, USA, [132]Department of Laboratory Genetics, Portuguese Oncology Institute of Porto (IPO Porto) / Porto Comprehensive Cancer Center, Porto, Portugal, [133]Cancer Genetics Group, IPO Porto Research Center (CI-IPOP) / RISE@CI-IPOP (Health Research Network), Portuguese Oncology Institute of Porto (IPO Porto) / Porto Comprehensive Cancer Center, Porto, Portugal, [134]School of Medicine and Biomedical Sciences (ICBAS), University of Porto, Porto, Portugal, [135]Uro Care, Kampala, Uganda, [136]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [137]Lineberger Comprehensive Cancer Center,

University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [138]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [139]Department of Urology, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA, [140]Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA, [141]Laboratory of Molecular Carcinogenesis, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA, [142]ISGlobal, Barcelona, Spain, [143]IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain, [144]Universitat Pompeu Fabra (UPF), Barcelona, Spain, [145]CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain, [146]University of Cantabria-IDIVAL, Santander, Spain, [147]Division of Epidemiology, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA, [148]George E. Wahlen Department of Veterans Affairs Medical Center, Salt Lake City, UT, USA, [149]Department of Epidemiology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA, [150]Department of Genitourinary Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA, [151]The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA, [152]Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail), Rennes, France, [153]CHU de Pointe-à-Pitre, Univ Antilles, Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail), Pointe-à-Pitre, France, [154]Molecular Medicine Center, Department of Medical Chemistry and Biochemistry, Medical University of Sofia, Sofia, Bulgaria, [155]Department of Urology and Alexandrovska University Hospital, Medical University of Sofia, Sofia, Bulgaria, [156]Department of Cell Systems and Anatomy and Mays Cancer Center, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA, [157]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany, [158]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany, [159]Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany, [160]Saarland Cancer Registry, Saarbrücken, Germany, [161]Cleveland Clinic Lerner Research Institute, Cleveland, OH, USA, [162]Glickman Urological & Kidney Institute, Cleveland Clinic, Cleveland, OH, USA, [163]Department of Medicine and Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA, USA, [164]City of Hope Comprehensive Cancer Center, Duarte, CA, USA, [165]Department of Urology, Northwestern University, Chicago, IL, USA, [166]The

University of Texas M. D. Anderson Cancer Center, Department of Genitourinary Medical Oncology, Houston, TX, USA, [167]Department of Population Sciences, Beckman Research Institute of the City of Hope, Duarte, CA, USA, [168]James Buchanan Brady Urological Institute, Johns Hopkins Hospital and Medical Institution, Baltimore, MD, USA, [169]Department of Family, Population and Preventive Medicine, Stony Brook University, Stony Brook, NY, USA, [170]Chronic Disease Research Centre and Faculty of Medical Sciences, University of the West Indies, Bridgetown, Barbados, [171]Department of Translational Genomics, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA, [172]The University of Surrey, Guildford, Surrey, UK, [173]Ghent University, Faculty of Medicine and Health Sciences, Basic Medical Sciences, Ghent, Belgium, [174]Ghent University Hospital, Department of Radiotherapy, Ghent, Belgium, [175]Program for Personalized Cancer Care and Department of Surgery, NorthShore University HealthSystem, Evanston, IL, USA, [176]Department of Surgery, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, [177]Cancer Research Malaysia (CRM), Outpatient Centre, Subang Jaya Medical Centre, Subang Jaya, Selangor, Malaysia, [178]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [179]Department of Urology, University of Washington, Seattle, WA, USA, [180]Department of Preventive Medicine, Division of Epidemiology,The University of Tennessee Health Science Center, Memphis, TN, USA, [181]Department of Public Health Sciences, Henry Ford Hospital, Detroit, Detroit, MI, USA, [182]Division of Medical Oncology, Urogenital Unit, Department of Oncology, University Hospital Centre Zagreb, Zagreb, Croatia, [183]Institute of Human Genetics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [184]Department of Urology, University Hospital Center Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia, [185]Department of Oncology, Cross Cancer Institute, University of Alberta, Edmonton, Alberta, Canada, [186]Division of Radiation Oncology, Cross Cancer Institute, Edmonton, Alberta, Canada, [187]Molecular Endocrinology Laboratory, Department of Cellular and Molecular Medicine, Leuven, Belgium, [188]Department of Urology, University Hospitals Leuven, Leuven, Belgium, [189]Genomic Medicine Group, Galician Foundation of Genomic Medicine, Instituto de Investigacion Sanitaria de Santiago de Compostela (IDIS), Complejo Hospitalario Universitario de Santiago, Servicio Galego de Saúde, SERGAS, Santiago de Compostela, Spain, [190]University of California San Diego, Moores Cancer Center, La Jolla, CA, USA, [191]Genetic Oncology Unit, CHUVI Hospital, Complexo Hospitalario Universitario de Vigo,

Instituto de Investigación Biomédica Galicia Sur (IISGS), Vigo (Pontevedra), Spain, [192]University of California San Diego, Moores Cancer Center, Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, USA, [193]Scientific Education Support, Thames Ditton, Surrey, Formerly Cancer Sciences, University of Southampton, Southampton, UK, [194]School of Biosciences and Medicine, Faculty of Health and Medical Sciences, University of Surrey, Surrey, UK, [195]Scientific Education Support, Thames Ditton, Surrey, Surrey, UK, [196]Department of Population and Quantitative Health Sciences, Cleveland Institute for Computational Biology, Case Western Reserve University, Cleveland, OH, USA, [197]Division of Genetic Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA, [198]Department of Biochemistry and Molecular & Cellular Biology, Georgetown University Medical Center, Washington, DC, USA, [199]Department of Surgery, Center for Prostate Disease Research,Uniformed Services University of the Health Sciences, Bethesda, MD, USA, [200]Department of Public Health Science, Center for Public Health Genomics,University of Virginia, Charlottesville, VA, USA, [201]Department of Pathology, University of Ghana, Accra, Ghana, [202]Laboratory of Human Carcinogenesis, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA, [203]Department of Pathology, University of Ghana Medical School, Accra, Ghana, [204]Westat, Rockville, MD, USA, [205]Department of Radiation Oncology, Moffitt Cancer Center, Tampa, FL, USA, [206]School of Public Health, University of California, Berkeley, Berkeley, CA, USA, [207]Center for Precision Health Research, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA, [208]Division of Genetic Medicine, Department of Medicine, Vanderbilt Genetics Institute, Nashville, TN, USA, [209]Atrium Health/Levine Cancer Institute, Charlotte, NC, USA, [210]Hôpital Général Idrissa Pouye, Dakar, Senegal, [211]Department of Pathology, College of Medicine, University of Ibadan, Ibadan, Nigeria, [212]Department of Surgery, College of Medicine, University of Ibadan and Univerity College Hospital, Ibadan, Nigeria, [213]Institute of Child Health, College of Medicine, University of Ibadan and University College Hospital, Ibadan, Nigeria, [214]Clinical Epidemiology Unit, Department of Community Medicine, College of Medicine, University of Ibadan, Ibadan, Nigeria, [215]College of Health Sciences, University of Abuja, University of Abuja Teaching Hospital and Cancer Science Center, Abuja, Nigeria, [216]37 Military Hospital, Accra, Ghana, [217]Laboratoires Bacteriologie et Virologie, Hôpital Aristide Le Dantec, Dakar, Senegal, [218]Department of Urology, Erasmus University Medical

Center, Rotterdam, Netherlands, [219]Department of Clinical Chemistry, Erasmus University Medical Center, Rotterdam, Netherlands, [220]The University of Miami School of Medicine, Sylvester Comprehensive Cancer Center, Miami, FL, USA, [221]Department of Family and Community Medicine, Meharry Medical College, Nashville, TN, USA, [222]Department of Epidemiology and Population Health, Stanford Cancer Institute, Stanford, CA, USA, [223]Southern California Eye Institute, CHA Hollywood Presbyterian Medical Center, Los Angeles, CA, USA, [224]The Charles Bronfman Institute for Personalized Medicine,Icahn School of Medicine at Mount Sinai, New York, NY, USA, [225]Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, MI, USA, [226]Center for Statistical Genetics, University of Michigan School of Public Health, Ann Arbor, MI, USA, [227]Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA, [228]Division of Research, Kaiser Permanente, Northern California, Oakland, CA, USA, [229]Department of Public Health and Primary Care, Centre for Cancer Genetic Epidemiology,, Cambridge, UK, [230]Harvard TH Chan School of Public Health and Division of Population Sciences, Dana Farber Cancer Institute, Boston, MA, USA, [231]Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, MI, USA, [232]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, MD, USA, [233]Laboratory for Cancer Genomics, RIKEN Center of Integrative Medical Sciences, Yokohama, Japan, [234]Departments of Biomedical Data Science, Stanford University, Stanford, CA, USA, [235]Laboratory for Statistical and Translational Genetics, Center for Integrative Medical Sciences, RIKEN, Yokohama, Japan, [236]Clinical Research Center, Shizuoka General Hospital, Shizuoka, Japan, [237]The Department of Applied Genetics, School of Pharmaceutical Sciences, Shizuoka, Japan, [238]Royal Marsden NHS Foundation Trust, London, UK

† Drs. Conti and Haiman contributed equally to this article.

*Corresponding Author: Christopher A. Haiman, Harlyne J. Norris Cancer Research Tower, USC Norris Comprehensive Cancer Center, 1450 Biggy Street, Rm 1504, Los Angeles, CA 90033 or haiman@usc.edu

## Introduction

The transferability and clinical value of genetic risk scores (GRS) across populations remains limited due to an imbalance in genetic studies across ancestrally diverse populations. We conducted a multi-ancestry genome-wide association study (GWAS) of 156,319 prostate cancer cases and 788,443 controls of European, African, Asian, and Hispanic men, reflecting a 57% increase in the number of non-European cases over previous prostate cancer GWAS. We identified 187 novel risk variants for prostate cancer, increasing the total number of risk variants to 451. An externally replicated multi-ancestry GRS was associated with risk that ranged from 1.8 (per standard deviation (SD)) in African ancestry men to 2.2 in European ancestry men. The GRS was associated with a greater risk of aggressive versus non-aggressive disease in men of African ancestry ($P$=0.03). Our study presents novel prostate cancer susceptibility loci and a GRS with effective risk stratification across ancestry groups.

In men, prostate cancer is the most frequently diagnosed non-skin cancer globally[1]. Variation in prostate cancer incidence is observed across populations globally, with the highest rates observed in men of African ancestry[1]. prostate cancer risk is heavily influenced by genetic factors, with 278 genetic risk variants identified through GWAS[2-13]. While the majority of samples in prostate cancer GWAS have been of European ancestry, multi-ancestry analysis has been demonstrated to improve discovery of novel risk variants[14] and enhance genetic risk prediction for prostate cancer across populations[2].

We conducted a multi-ancestry GWAS meta-analysis with 122,188/604,640 (cases/controls) of European ancestry, 19,391/61,608 of African ancestry, 10,809/95,790 of East Asian ancestry and 3,931/26,405 of Hispanic ethnicity. Studies, genotyping, quality control and association testing methods are described in **Supplementary Table 1 and 2 (Methods)**. Case sample size was increased by 43% in European, 87% in African, 26% in Asian and 45% in Hispanic groups (with a corresponding effective sample size ≥128% in each population accounting for controls), compared to previous multi-ancestry GWAS analyses[2]. We performed a fixed-effect meta-analysis within each ancestry group and meta-analyzed the ancestry-specific GWAS results. The genomic inflation statistic (λ) was 1.158 in the multi-ancestry GWAS and ranged from 1.053 in Asian to 1.169 in European ancestry studies (**Supplementary Table 3**); the corresponding meta-analysis $\lambda_{1000}$ (scaled to a sample size of 1,000 cases and 1,000 controls) was 1.001.

Overall, 42,428,922 variants with a minor allele frequency (MAF)>0.1% were examined for association with prostate cancer risk, with 55,241 variants reaching genome-wide significance ($P<5.0\times10^{-8}$). To identify independent risk variants, we implemented a forward-selection conditional analysis using multi-population Joint Analysis of Marginal summary statistics (mJAM; **Methods**)[2,15]. We identified 451 independent risk variants for prostate cancer that were genome-wide significant in multi-ancestry or ancestry-specific analyses (**Supplementary Table 4**), including 187 that were previously unreported (**Fig. 1, Supplementary Tables 4** and **5**). Of these, 61 were within 800 Kb of known variants but remained genome-wide significant after conditioning on nearby known variants. Of the 451 variants, 150 were known risk variants that were replaced by a more significant lead variant, while 114 remained the lead risk variant in the region. Eighteen variants previously reported as prostate cancer risk variants were dropped because they did not reach genome-wide significance (**Supplementary Table 4**).

The underlying rationale for conducting a cross-ancestry meta-analysis is based on the hypothesis that true causal variants are predominantly shared across populations. Of the 451 risk variants, 429 (95%) in European, 411 (91%) in African, 377 (84%) in Asian and 424 (94%) in Hispanic populations had MAF>1% (**Extended Data Fig. 1**), and 339 (75%), 47 (10%), 42 (9%) and 9 (2%) were genome-wide significant, respectively (**Fig. 2a**). Of these, nineteen (European), five (African) and three (Asian) were population-specific risk variants with MAF≤1% in all other populations (**Extended Data Fig. 1**). For variants with a MAF>1% in all populations (n=370), 369, 247, 208 and 125 were nominally significant in European, African, Asian and Hispanic populations, respectively **(Fig. 2b)**. The effect sizes for variants with a MAF>1% were correlated between populations, with an R=0.73 for European versus African ancestry (398 variants), R=0.58 for European versus Asian ancestry (371 variants) and R=0.72 for European ancestry versus Hispanic men (414 variants; **Fig. 2c, Supplementary Fig. 1**). Heterogeneity in effect size was statistically significant ($P_{heterogeneity}$<0.05) for 78 variants (21%), with the largest average effect size in Asian men (odds ratio $(OR)_{avg}$=1.11) followed by European ancestry ($OR_{avg}$ =1.09), African ancestry ($OR_{avg}$ =1.08) and Hispanic men ($OR_{avg}$ =1.08; **Supplementary Table 6**).

Of the 451 variants, 28 (6.2%) directly alter protein structure (**Supplementary Table 7**). We detected a novel association with a population-specific frameshift deletion in the *C9orf152* gene (European) and previously reported frameshift deletions in *ANO7* (African[16]) and *CHEK2* (European[2]) and a frameshift insertion in *FAM111A* (European[4]). The lead variants include 24 missense substitutions representing previously reported variants within *ANO7* (three lead variants[4]), *CDKN1B*, *CHEK2*, *COL23A1*, *HOXB13*, *INCENP*, *KLK3*, *POGLUT3*, *RASSF6*, *RFX7* and *SUN2,* replacement lead variants in *FAM118A*, *INHBB* and *SPDL1*, novel associations in *MMAB*, *PIM1*, *RPA1*, *SERPINA1*, *SIM2*, *SYTL1* and *ZBTB42,* and a second missense risk variant in *RASSF6* **Supplementary Table 7**). Among the new genes implicated in prostate cancer risk, expression of *SIM2*, a transcription factor, has been shown to discriminate prostate cancer and non-cancerous tumor tissue[17] and to be associated with poorer survival[18], while *PIM1* is a serine/threonine kinase overexpressed in prostate cancer[19], shown to modulate androgen receptor transcriptional activity through phosphorylation[20] and be a co-activator of c-MYC[21].

Many lead variants were also implicated in regulation of gene expression in prostate tissues and cell-lines (**Methods**). Seventy-four variants (16.4%), including 19 novel associations, were located within regions of open chromatin, chromatin modifications consistent with regulatory elements, situated within transcription factor binding sites overlapping an association for differential gene expression or splicing (**Supplementary Table 7**), providing strong support for biological functionality. Candidate functional variants include rs1858800, correlated with expression of *ZFXH3*, a gene frequently somatically mutated in prostate cancer[22]; rs10499188, correlated with expression of *SLC2A12*, a gene encoding a glucose transporter expressed in prostate cancer cell-lines but not benign prostatic hyperplasia[23] and regulated by androgen receptor signaling[24], and rs79186742, correlated with expression of *BARX2*, a homeobox transcription factor associated with poor prognosis for a range of solid tumors[25].

Overall, 219 of the 451 lead variants (48.6%) overlap with significant associations for differential expression in prostate tissues (**Methods, Supplementary Table 7**) of 439 distinct genes (eQTLs), while 69 (15.3%) correlate with significant associations for alternative splicing of 95 unique genes (sQTLs). Of the 439 differentially expressed genes, 204 (46.5%) had not been implicated as candidate mediators of prostate cancer risk by the previous panel of 269 prostate cancer risk variants[2] and were established through the identification of additional novel risk variants and replacement of lead variants. To assess the extent to which prostate cancer risk variants exhibit prostate-specific regulatory function compared with the genome-wide background, we performed a permutation test while controlling for MAF and linkage disequilibrium (LD) patterns (**Methods**). Overall, we found evidence for enrichment of prostate cancer risk variants in regions of prostate-specific regulatory activity across eQTLs, sQTLs and candidate *cis*-regulatory elements (≥2.9-fold enrichment, $P < 0.0017$; **Supplementary Table 8**).

To further explore the molecular mechanisms underlying prostate cancer risk, we performed transcriptome- (TWAS) and proteome-wide association studies (PWAS)[26-28] using predicted gene expression and protein levels from multiple prostate tissue[29-31] and plasma[32] studies (**Methods**). Across 19,352 tests performed, we identified 746 associations across 528 genes and 230 genomic regions (**Supplementary Tables 9** and **10**). Of the 746 associations, the greatest contribution was from predicted expression in histologically normal prostate tissue (351/746)[30]. However, this is likely due to the larger reference panel sample size and, thus, number of association tests performed

(**Supplementary Table 9;** ANOVA $P$>0.05). Of the 451 genomic risk regions identified through GWAS, 237 colocalized within 250Kb of transcriptome- or proteome-wide significant associations, which is consistent with previous large-scale TWAS investigations of prostate cancer risk[33,34]. Of the 230 TWAS/PWAS genomic risk regions identified, 45 did not colocalize within 250Kb of the 451 genome-wide significant variants, suggesting that increasing GWAS sample sizes will continue to identify novel risk regions (**Supplementary Table 11)**.

The predictive ability of the GRS for prostate cancer has improved with the identification of additional risk variants[2-6,8]. We compared the performance of GRSs based on past marker sets (n=100[8], 181[5,6,35], 269[2]) to the current set of 451 risk variants, with GRSs constructed by summing the risk allele dosage, weighted by the multi-ancestry per-allele log-ORs estimated from the current meta-analysis (**Methods**). With the discovery of more risk variants, there is greater stability in the assignment of unaffected men to GRS categories; 58% of men in the lowest or highest quintile remained in the same quintile between $GRS_{100}$ and $GRS_{181}$, whereas 69% to 70% remained between $GRS_{269}$ and $GRS_{451}$ (**Supplementary Fig. 2a-6a**). Likewise, the percentage of cases has increased for each population within higher GRS categories (e.g., from 40.5% in the highest quintile of $GRS_{100}$ to 51.2% in $GRS_{451}$) and decreased within lower GRS categories (e.g., from 7.5% in the lowest quintile of $GRS_{100}$ to 4.4% in $GRS_{451}$; **Fig. 3, Supplementary Fig. 2b-6b**). Risk classification with the GRS in addition to age was evaluated using the net reclassification index (NRI)[36] and showed substantial improvement from $GRS_{100}$ (range across populations: 30.2% in African to 49.5% in European) to $GRS_{451}$ (range across populations: 58.5% in African to 69.9% in European; **Supplementary Table 12**). Compared to a model with $GRS_{269}$, the population specific improvement for a model with $GRS_{451}$ resulted in a NRI ranging from 3.3% in Asian ancestry to 21.7% in Hispanics. The improvement in risk prediction of $GRS_{451}$ over previous GRS panels was confirmed in replication studies among men of European and African ancestry that were not included in the GWAS (**Fig. 4a-b, Supplementary Table 13** and **14**). Based on the high degree of variation in the association of $GRS_{451}$ with prostate cancer risk across sub-studies in the discovery and replication phases (**Extended Data Fig. 2**), a single summary OR per SD was estimated from the overall meta-analyzed sample: 2.32 [95%CI: 2.30-2.35], 2.04 [95%CI: 2.00-2.08], 2.15 [95%CI: 1.99-2.32] and 2.12 [95%CI: 2.03-2.23] for European, African, Asian and Hispanic men, respectively ($P_{heterogeneity}$ by population: $4.51 \times 10^{-50}$,

7.52x10$^{-4}$, 0.29 and 0.31, respectively). The ORs in the replication studies were 2.19 [95%CI: 2.12-2.25] in European and 1.79 [95%CI:1.69-1.90] in African ancestry men (**Fig. 4b**). In replication studies, comparing $GRS_{451}$ to a genome-wide polygenic risk score (PRS) derived by PRS-CSx (**Methods**), the effect estimates of the genome-wide PRS were smaller than those of $GRS_{451}$ in both men of European (OR per SD = 2.00, 95%CI: 1.92-2.10) and African ancestry (OR per SD = 1.54, 95%CI: 1.44-1.64; **Supplementary Table 15**).

As observed for $GRS_{269}$, age modifies the association of $GRS_{451}$ and prostate cancer risk (**Fig. 4c, Supplementary Table 16, Methods**)[37]. In men of European ancestry, $GRS_{451}$ was associated with an OR per SD of 2.90 [95 %CI: 2.80-3.00] for men ≤ 55 and 2.30 [95%CI: 2.27-2.32] for men > 55 years ($P_{heterogeneity}$ = 2.0x10$^{-37}$). Effect modification of $GRS_{451}$ by age was similarly observed in men of African ancestry: OR per SD = 2.45 [95 %CI: 2.33-2.58] for men ≤ 55 years and 2.00 [95%CI: 1.95-2.05] for men > 55 years ($P_{heterogeneity}$ = 3.3x10$^{-12}$) and was reproducible in the replication studies (**Supplementary Table 16**).

In men of European and Asian ancestry and in Hispanic men, the $GRS_{451}$ was equally associated with risk of aggressive prostate cancer (stage T3/T4, regional lymph node involvement, metastatic disease, Gleason score ≥ 8, prostate-specific antigen (PSA) level ≥ 20 ng/mL or prostate cancer as the underlying cause of death) and non-aggressive prostate cancer (no aggressive features; **Fig. 4d, Supplementary Table 17, Methods**). For men of African ancestry with prostate cancer, $GRS_{451}$ was associated with a greater risk of aggressive versus non-aggressive disease (OR per SD = 1.08, 95%CI: 1.04-1.12, $P$=1.1x10$^{-4}$; **Fig. 4d, Supplementary Fig. 7**). A weak nominally significant association of $GRS_{451}$ with aggressive disease in African ancestry men was also observed in the African prostate cancer MADCaP replication sample (OR per SD= 1.12, 95%CI: 1.01-1.23, $P$ = 0.03).

Fifty-one of the 451 prostate cancer risk variants have been directly or indirectly (LD $R^2$>0.8) associated in GWAS of PSA at $P$<5x10$^{-8}$ (**Supplementary Table 7, Methods**). To assess whether the prostate cancer risk signals for PSA-associated variants reflect an increased likelihood of prostate cancer detection due to screening, particularly for low-stage disease, we examined their aggregate association with disease aggressiveness (**Supplementary Table 18**). When removing the prostate cancer-PSA variants from the GRS analysis we found the GRS (with 400 markers) to be more strongly

associated with aggressive disease (versus $GRS_{451}$) in European ancestry men (OR per SD = 1.04, 95%CI: 1.03-1.06, $P = 3.2 \times 10^{-8}$), African ancestry men (OR per SD = 1.10, 95%CI: 1.06-1.14, $P = 7.0 \times 10^{-7}$) and Hispanic men (OR per SD = 1.05, 95%CI: 0.94-1.14, $P = 0.21$), which suggests that some prostate cancer risk variants may be over-represented in men with less aggressive disease as the result of their association with PSA levels.

A man's cumulative risk of developing prostate cancer, including aggressive disease, is profoundly influenced by the GRS. For men of European ancestry, 20% of men have a 2-fold or greater risk compared to men at the 50% of $GRS_{451}$, and these men achieve an absolute risk comparable to the median risk in the population 16 years earlier. Specifically, these men reach a level of absolute risk of at least 7.8% (the risk at age 85 for men with a 50% $GRS_{451}$) by age 69 or earlier (**Fig. 5**). For African ancestry men, 16% of men achieve a 2-fold or greater risk by age 66, with an absolute risk comparable to the risk reached by the average man by age 85 (11.6%), a full 19 years earlier. A GRS-informed approach to screening may improve early detection, as over 50% of cases, including those with aggressive and lethal disease, develop among men in the top GRS quintile, while fewer than 5% of cases develop among men in the bottom 20% (**Fig. 3**).

Increasing the size of genetic studies across ancestrally diverse populations is paramount for broad and equitable discovery of risk loci and clinical translation. The current multi-ancestry study reflects a 57% increase in the number of non-European cases over previous prostate cancer GWAS and resulted in the identification of 187 novel risk variants, which represents ~40% of all prostate cancer risk variants identified to date. We detected a 3% (Asian), 14% (European), 15% (Hispanic) and 23% (African) increase in the OR (per SD) for $GRS_{451}$ versus $GRS_{269}$ (**Fig. 4**), which supports previous work demonstrating the ability of multi-ancestry studies to identify prostate cancer risk variants that improve risk prediction across populations[2]. As shown previously in comparisons of $GRS_{269}$ with genome-wide approaches[38], the greater predictive performance observed for $GRS_{451}$ over a genome-wide PRS emphasizes our approach to select a limited set of multi-ancestry risk variants that capture risk across populations. The random selection of markers used for genome-wide PRS may not adequately capture risk across all risk regions resulting in poorer performance, particularly in some populations.

Of critical importance for clinical utility of GRS in prostate cancer is the ability to differentiate risk of aggressive/lethal versus non-aggressive disease. We demonstrated

that an understanding of the relationship between germline variants that influence both PSA levels and prostate cancer risk variants is needed to accurately estimate the GRS association with prostate cancer aggressiveness and prostate cancer outcomes. Evidence that GRS can differentiate risk of aggressive versus non-aggressive disease, albeit modestly, for men of African ancestry, an association that strengthened when accounting for PSA variants, suggests potential clinical utility of GRS in this high-risk population[16]. While GRS for prostate cancer is a highly effective tool for risk stratification and personalized risk assessment, how and when this information should be included in the decision-making process for prostate cancer screening and early detection needs to be determined.

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## Author Contributions

CAH, DVC, RAE and ZK-J contributed to study conception. AWang, CAH, DVC, EJS and NM wrote the manuscript. EJS, YX, XS, PW, MB, AAR, RKM and TD provided data management and bioinformatics support. AWang, JShen, AAR, DVC and CAH contributed to data analysis and interpretation. All authors contributed data to the study, revised, critically reviewed and approved the final version of the manuscript: AWang, JShen, AAR, EJS, FChen, RJanivara, BFDarst, XS, YX, AJC, SB, TD, MNB, AP, AS, TJH, ATakahashi, KMatsuda, YM, MF, TL, JF, KMuir, SI, XL, YU, MKubo, YK, ALophatananon, PW, CA, ALori, PPC, JSchleutker, TLT, CSipeky, AAuvinen, GGG, MCSouthey, RJM, CC, DW, JLubinski, CTR, KC, BHM, DEN, JLD, FCH, RMMartin, BGN, SFN, MW, SEB, MAR, HVS, JB, SC, LH, JAC, WTilly, GPR, HG, MA, RS, ME, TN, NP, AMD, MGhoussaini, RCT, TJK, ER, JYP, TAS, HYL, DA, SWeinstein, MBC, LAM, EG, SLindstrom, PK, DJH, KLP, CTurman, CMT, PJG, IMT, RJH, NEF, AF, MEP, JLS, EAO, SK, LEBF, MS, AWolk, NH, GLA, RNH, MJM, KDS, MB, WJB, WZ, EDY, JEM, YJL, HWZ, NF, XM, YW, SCZ, ZS, SNT, SKM, DJS, CMW, GB, CM, TS, ML, ASK, BFDrake, OC, GCT, FM, TT, YAK, EMJ, EMG, LMK, KTK, SAI, MCStern, AV, AGC, LFachal, BSR, SLK, HO, MRT, PPaulo, AB, SWatya, ALubwama, JTB, ENB, JLM, JAT, MKogevinas, TDS, GCV, LCA, CCT, CDH, PPilie, YY, RJB, JG, SSS, LM, PB, LB, RK, CSlavov, VM, RJL, HB, XC, BH, BS, EAK,

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## Competing interests

The authors declare no competing interests.

## The Biobank Japan Project

Yuji Yamanashi[239], Yoichi Furukawa[240], Takayuki Morisaki[241], Yoshinori Murakami[242], Kaori Muto[243], Akiko Nagai[243], Wataru Obara[244], Ken Yamaji[245], Kazuhisa Takahashi[246], Satoshi Asai[247,248], Yasuo Takahashi[248], Takao Suzuki[249], Nobuaki Sinozaki[249], Hiroki Yamaguchi[250], Shiro Minami[251], Shigeo Murayama[252], Kozo Yoshimori[253], Satoshi Nagayama[254], Daisuke Obata[255], Masahiko Higashiyama[256], Akihide Masumoto[257], Yukihiro Koretsune[258]

[239]Division of Genetics, The Institute of Medical Science, Tokyo, Japan, [240]Division of Clinical Genome Research, The Institute of Medical Science, Tokyo, Japan, [241]Division of Molecular Pathology IMSUT Hospital, Department of Internal Medicine Project Division of Genomic Medicine and Disease Prevention, The Institute of Medical Science, Tokyo, Japan, [242]Department of Cancer Biology, The Institute of Medical Science, Tokyo, Japan, [243]Department of Public Policy, The Institute of Medical Science, Tokyo, Japan, [244]Department of Urology, Iwate, Japan, [245]Department of Internal Medicine and Rheumatology, Tokyo, Japan, [246]Department of Respiratory Medicine, Tokyo, Japan, [247]Division of Pharmacology, Department of Biomedical Science, Tokyo, Japan,

[248]Division of Genomic Epidemiology and Clinical Trials, Clinical Trials Research Center, Tokyo, Japan, [249]Tokyo, Japan, [250]Departmentof Hematology, Tokyo, Japan, [251]Department of Bioregulation, Kawasaki, Japan, [252]Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan, [253]Fukujuji Hospital, Tokyo, Japan, [254]The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan, [255]Center for Clinical Research and Advanced Medicine, Shiga University of Medical Science, Shiga, Japan, [256]Department of General Thoracic Surgery, Osaka International Cancer Institute, Osaka, Japan, [257]Iizuka Hospital, Fukuoka, Japan, [258]National Hospital Organization Osaka National Hospital, Osaka, Japan

## Figure Legends

**Figure 1.** Manhattan plot of results from the multi-ancestry prostate cancer meta-analysis.
Multi-ancestry meta-analysis (156,319 cases and 788,443 controls) was performed using an inverse-variance-weighted fixed-effects model. Nominal statistical significance is shown as $-\log_{10}P$ (two-sided) of z statistics on the y axis. Purple and orange circles indicate previously known or novel risk variants, respectively, that were genome-wide significant in multi-ancestry or ancestry-specific meta-analyses. The plot is truncated at $-\log_{10}P=600$.

**Figure 2.** Comparison of the ancestry-specific results of the 451 risk variants for prostate cancer.
(a) Venn diagram of genome-wide significant variants ($P<5\times10^{-8}$) among European, African, Asian, and Hispanic populations. (b) Venn diagram of nominally significant variants ($P<0.05$) among European, African, Asian, and Hispanic populations. (c) Comparison of ancestry-specific odds ratios (ORs) between European and African, Asian, and Hispanic populations, respectively. The number of variants is denoted in the lower right corner. Genome-wide significant variants among African, Asian, or Hispanic populations are highlighted in orange. Two-sided Pearson correlation tests were performed. The Pearson's correlation coefficient between effect size and corresponding *P*-value are denoted in the upper left in each sub-panel. Only common variants across all populations (MAF>1%, n=370) were included in (a), (b), and (c).

**Figure 3.** Percentage of cases in the lowest and highest genetic risk score (GRS) quintiles based on $GRS_{100}$, $GRS_{181}$, $GRS_{269}$, and $GRS_{451}$ in the multi-ancestry sample.
GRS risk quintiles were categorized based on GRS distributions among controls. Quintile 1 (orange bar) refers to the lowest quintile (0-20%), and quintile 5 (yellow bar) refers to the highest quintile (80-100%).

**Figure 4**. The associations of GRS and prostate cancer risk in GWAS discovery and replication samples.
ORs and 95% Confidence Intervals (CIs) from logistic regression for one standard deviation (SD) increase in (a) $GRS_{100}$, $GRS_{181}$, $GRS_{269}$, and $GRS_{451}$ and total prostate cancer risk by ancestry in the GWAS discovery studies; (b) $GRS_{269}$ and $GRS_{451}$ and total

prostate cancer risk in the replication studies: Michigan Genomics Initiative (MGI), Mass General Brigham Biobank (MGB), Estonian Biobank (EstBB ), and Men of African Descent and Carcinoma of the Prostate (MADCaP); (c) $GRS_{451}$ and total prostate cancer risk by age; (d) $GRS_{451}$ and $GRS_{400}$ and prostate cancer aggressiveness among prostate cancer cases in the GWAS discovery studies. 'META' refers to the meta-analyzed results for all populations using the inverse-variance weighted method. Incremental percentage change of ORs were calculated for each comparison. The columns 'case' and 'control' show the case and control sample sizes, and the columns 'agg' and 'non-agg' show the aggressive and non-aggressive cases sample sizes, respectively.

**Figure 5.** Cumulative absolute risk by age.

Solid lines are the cumulative absolute risk for individuals in the top 16% GRS for African ancestry and top 20% for European ancestry. These GRS categories represent the percent of individuals in each population with at least a 2-fold increase in risk in comparison to the median GRS (as indicated in the inset distributions for African and European ancestries, respectively). Dashed horizontal lines indicate the lifetime absolute risk achieved at age 85 for the average (50% GRS) in African (11.6%) and European (7.8%) ancestry populations. Solid dots indicate the ages at which lifetime absolute risk levels are achieved for men of African ancestry in the top 16% GRS (age = 66 years) and men of European ancestry in the top 20% GRS (age = 69 years).

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## Online Methods

**Study subjects in the multi-ancestry GWAS.** The institutional review board at the University of Southern California approved the study protocol. The meta-analysis included 107,247 prostate cancer cases and 127,006 controls that were part of a previous multi-ancestry meta-analysis (**Supplementary Table 1**)[2]. The present study included an additional 49,072 cases and 661,437 controls from the UK Biobank, the FinnGen study, the Electronic Medical Records and Genomics (eMERGE) Network, the BioVU Biobank, the BioMe Biobank, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), the MD Anderson prostate cancer study (MD Anderson), the California and Uganda Prostate Cancer Study (CA UG), the VA Million Veteran Program (MVP), and the Maryland Prostate Cancer Case-Control Study (NCI-MD) (**Supplementary Table 1**). Each study includes adult males over the age of 21 years. All participants provided written informed consents, and study protocols were approved by the Institutional Review Board at each study site. In total, there were 122,188 cases and 604,640 controls of European ancestry, 19,391 cases and 61,608 controls of African ancestry, 10,809 cases and 95,790 controls of Asian ancestry, and 3,931 cases and 26,405 controls of Hispanic ancestry. The effective sample size for each population was calculated using the formula $N_{eff} = 4/(1/N_{cases} + 1/N_{controls})$.

**Genotyping and imputation in the multi-ancestry GWAS.** The details of study design, inclusion and exclusion criteria, genotyping, imputation and quality control procedures are provided in **Supplementary Tables 1 and 2**. Imputation in each study was performed using Minimac3/Minimac4[39], Impute2[40], Eagle2[41], or Beagle 4.1[42] under the 1000 Genome phase 3[43], the NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium freeze 5[44], Haplotype Reference Consortium (HRC), UK10K[45], or SISu v3 imputation[42] panels. For most studies, single nucleotide polymorphisms (SNPs) and small insertion/deletions (indels) with MAF≥0.1% and imputation quality scores ≥0.3 were included in the association analysis. A higher cutoff of imputation quality score was applied in FinnGen (>0.6) and BioMe (≥0.8).

**Statistical analysis for GWAS.** Genetic similarity was estimated with uncorrelated SNPs using principal component analysis in each study based. In total, 42,428,922 variants (SNPs and indels) were examined for association using logistic regression adjusting for age, sub-study (if applicable, see **Supplementary Table 1**) and up to 10 principal components. Per-allele ORs and standard errors from individual studies were combined

by a fixed-effects inverse-variance weighted meta-analysis using METAL in ancestry-specific analyses as well as across all four ancestry groups to obtain multi-ancestry estimates of effects. Heterogeneity of effect sizes across ancestries were examined by the statistic $I^2$ with corresponding tests of significance (**Supplementary Table 6**). The genomic inflation factors (λ) were calculated in each study/consortium and within each population (**Supplementary Table 3**). Each inflation factor was then rescaled to $\lambda_{1000}$, which represents the inflation factor for an equivalent study of 1,000 cases and 1,000 controls[46].

**Risk variants identification.** Genome-wide significant associations were defined as variants with $P<5x10^{-8}$ in the multi-ancestry meta-analysis. To identify independent index risk variants in the newly identified and previously known risk regions, we implemented a forward-selection conditional analysis approach using a multi-population Joint Analysis of Marginal summary statistic (mJAM). Within each region, the forward selection process started with a model containing the variants with the most significant multi-ancestry marginal *P* value, and additional variants were added if they were independent of the selected variants (LD $R^2<0.1$ in all four populations). Variants with a conditional multi-ancestry $P<5x10^{-8}$ were retained in the model. Imputation quality scores of all individual studies were checked for all selected risk variants (**Supplementary Table 5**).

Genome-wide significant variants were considered "novel" if they were not in LD with any previously known risk variants in any of the four populations and remained genome-wide significant after conditioning on nearby known risk variants. Previously known variants were 1) dropped if their marginal *P* values were below the genome-wide significance threshold, 2) replaced by a correlated new lead variant with a more significant conditional *P* value, or 3) not replaced.

**GRS construction.** We constructed a GRS from the summed risk allelic dosages weighted by the per-allele log-odds ratios in the marginal model for independent variants and in the conditional model for the variants in the same region. GRS was constructed for the 451 risk variants, and also for risk variant sets reported in previous prostate cancer GWAS meta-analyses: (1) N=269 variants reported in a multi-ancestry study (107,247 cases / 127,006 controls)[2], (2) N=181 variants reported in European (25,723 cases / 26,274 controls)[35], African (10,202 cases / 10,810 controls)[47] and Asian (3,000 cases /

4,394 controls)[6] ancestry-specific studies, respectively, and (3) N=100 variants reported in a multi-ancestry study (43,303 cases / 43,737 controls)[8].

**Discriminative improvement of GRS.** To visualize the improvement of predictive ability of prostate cancer GRS over time with the increasing number of risk variants included, we categorized the distributions of previous GRS ($GRS_{100}$, $GRS_{181}$, $GRS_{269}$) and the current GRS ($GRS_{451}$) into quintiles ([0-20%], (20-40%], (40-60%], (60-80%], and (80-100%]) based on the distribution of the score in controls for each study or consortium. We used Sankey diagrams to visualize the change in risk categorization from the previous GRS to the subsequent GRS among controls and cases, respectively.

To quantify the discriminative ability improvement by inclusion of additional risk variants, we calculated continuous-based NRI in our GWAS discovery sample[36]. For each study, we calculated NRI comparing a risk model with age only (adjusted for sub-studies and top 10 principal components) to risk models with additional inclusion of $GRS_{100}$, $GRS_{181}$, $GRS_{269}$, and $GRS_{451}$, respectively. Additionally, we calculated NRI comparing the $GRS_{451}$ model to the $GRS_{269}$ model to show the discriminative ability improvement of the current GRS relative to last GRS. The 95% CIs for NRI were estimated using 1,000 bootstrap replications.

**GRS association analysis.** The risk of prostate cancer was estimated for the per SD GRS change and for each percentile category of the GRS: [0-10%], (10-20%], (20-30%], (30-40%], (40-60%], (60-70%], (70-80%], (80-90%], and (90-100%]. Additional analysis was performed to obtain the risk of prostate cancer for the top 1% ((99-100%]). We reported the GRS associations using the median quintile (40-60%] category (**Supplementary Table 13**) as well as the bottom decile [0%-10%] category as the reference groups (**Supplementary Table 14**), respectively. The mean and SD, and the GRS categories were determined by the observed distribution among controls for each study or consortium. We applied the conditional multi-ancestry effect estimates from the overall meta-analysis to calculate GRS for individuals from studies mentioned above. In each study, logistic regression was performed to estimate the OR and 95%CI corresponding to per SD change of GRS or each GRS category, adjusted for age, sub-study (if applicable), and up to 10 principal components. Within each population, the associations of GRS with prostate

cancer risk were meta-analyzed across individual studies using a fixed-effect inverse-variance-weighted method.

**GRS association in replication and overall samples.** We validated the GRS performance in independent samples that were not part of the GWAS discovery, including the Michigan Genomics Initiative[48] (MGI; European: 3,244 cases, 10,537 controls; African: 189 cases, 450 controls), Mass General Brigham Biobank[49,50] (MGB; European: 1868 cases, 10,980 controls; African: 85 cases, 471 controls), Men of African Descent and Carcinoma of the Prostate[51] (MADCaP; African: 2,505 cases, 2,160 controls), and Estonian Biobank[52] (EstBB; European: 2,352 cases, 28,546 controls). Details of study population, genotyping and imputation were described in **Supplementary Tables 1 and 2**. $GRS_{451}$ and $GRS_{269}$ were constructed and weighted by the multi-ancestry conditional weights. ORs per SD and for each decile were estimated within study population using logistic regression adjusted for age, sub-study (if applicable), and up to 10 principal components.

**Genome-wide PRS.** We compared our $GRS_{451}$ to a recent genome-wide PRS approach PRS-CSx[53], an extension of the Bayesian PRS-CS approach[54] that integrates GWAS summary statistics from multiple ancestry groups to improve cross-population polygenic modeling. We previously found that PRS-CSx was more predictive of prostate cancer risk relative to several other genome-wide PRS approaches in both European and African ancestry men[38]. PRS-CSx was evaluated with the fully Bayesian approach to identify the optimal global shrinkage parameter phi, as recommended for large GWAS training data. PRS-CSx was trained on the population-specific (European, African, East Asian, and Hispanic populations) marginal GWAS summary statistics from the current investigation, using the meta=TRUE option to generate a multi-ancestry genome-wide PRS. Variants included were the 1.1 million HapMap3 panel variants[55]. Populations from the 1000 Genomes Project[51] were used for LD reference panels. The resulting genome-wide PRS was evaluated in independent studies of European ancestry men from MGI and African ancestry men from MADCaP. Performance metrics included ORs calculated for the continuous standardized genome-wide PRS, adjusting for age, sub-study (if applicable), and up to 10 principal components.

**GRS by Age and Disease Aggressiveness.** We investigated the association of GRS with prostate cancer risk stratified by age and its association with disease aggressiveness. In age-stratified analysis, cases and controls were both stratified into two age groups (age ≤55 vs. age >55 years). prostate cancer was defined as aggressive if one or more of the following criteria were met: tumor stage T3/T4, regional lymph node involvement, metastatic disease (M1), Gleason score ≥ 8, PSA level ≥ 20 ng/mL, or prostate cancer as the underlying cause of death. Non-aggressive prostate cancer was defined as prostate cancer without aggressive features and meeting one or more of the following criteria: Gleason score ≤ 7.0, PSA < 20 ng/mL, and stage ≤ T2. Logistic regressions were performed with prostate cancer status (non-aggressive vs. control, aggressive vs. control, or aggressive vs. non-aggressive) as the outcome and per SD GRS or GRS categories as the independent predictors, adjusting for age, sub-study (if applicable), and up to 10 principal components. Ancestry-specific GRS estimates were obtained via an inverse-variance weighted fixed effects meta-analysis performed within each population. Heterogeneity between stratum was assessed via a Q-statistic between effect estimates with corresponding tests of significance.

**Impact of PSA screening on prostate cancer GWAS.** We compared the 128 PSA variant reported in the latest PSA GWAS[57] to the 451 prostate cancer risk variants and found 50 overlapping variants (in high LD ($R^2$>0.8) or identical index variant; **supplementary Table 7**). Three of the variants (2 of which overlapped with the PSA variants) are near the KLK3 gene, which encodes the PSA protein and are very strongly associated with PSA level. For the 48 overlapping variants (removing KLK3), it is currently difficult to differentiate whether they are prostate cancer risk variants, PSA variants or both. To better understand the likelihood of these variants being identified as the result of altering PSA levels, leading to biopsy and a prostate cancer diagnosis, we examined their aggregate effect on disease aggressiveness in our GWAS discovery samples. Additionally, we removed the 48 potential PSA variants (and 3 KLK3 variants) from the prostate cancer GRS (with 400 variants) and examine the association with aggressive versus non-aggressive prostate cancer in the multi-ancestry sample.

To account for the multiple comparisons being made in our sub-group analyses described above (in total 20 independent tests), we applied Bonferroni correction to the significance level (0.05/20=0.0025).

**Age-specific absolute risk estimation.** Absolute risk for a given age for each GRS percentile and each population has been described previously[2,58-61]. The approach constrains the GRS-specific absolute risks for a given age to be equivalent to the age-specific incidence for the entire population while accounting for competing causes of death. For each ancestry group, absolute risks by age $t$ were calculated using age-specific prostate cancer incidence, $\mu(t)$, and age-specific mortality rates, $\mu_D(t)$, from the Surveillance, Epidemiology, and End Results (SEER) Program (2014-2018)[62,63].

**Variant annotation.** Lead variants were annotated for indicators of functionality according to a framework described previously[2], and incorporating additional datasets. Gene-based information was obtained using wANNOVAR[64]. Chromatin Immunoprecipitation Sequencing peaks were obtained from the Cistrome Data Browser[65] for the prostate cancer cell-lines LNCaP, PC3 and VCaP and prostate epithelium cell-line PrEC[66]. Peak data were obtained for open chromatin (DNase-Seq and ATAC-seq), histone modifications (H3K27Ac, H3K9Ac, H3K4me1, H3K4me2 and H3K4me3), and transcription factor binding. A list of datasets included is provided in **Supplementary Table 19**.

Data for significant variant-gene pairs for differential gene expression (eQTLs) in three prostate tissue cohorts (GTEx v8[67], normal prostate tissue, n=221; TCGA PRAD[68], prostate adenocarcinoma, n=359; MAYO[30], tumor-adjacent normal prostate tissue, n=471) were obtained as described previously[2]. All significantly associated genes at False Discovery Rate (FDR) ≤0.05 identified were reported for each lead variant.

Data for significant variant-gene pairs for differential gene splicing (sQTLs) were obtained for two prostate tissue cohorts. sQTLs for GTEx v8 normal prostate tissue (n=221) were downloaded from the GTEx portal. sQTLs for TCGA PRAD (n=485) were obtained from the CancerSplicingQTL database[69]. All genes significantly associated with alternative splicing in the respective datasets were reported for each lead variant.

**Functional enrichment permutations.** To quantify the extent to which the prostate cancer risk variants are enriched with regulatory activity compared to the genome-wide background, we performed a permutation test based on simulations. Briefly, we sought to sample 439 autosomal variants from the genomic background and compare the number

of functional annotations observed with those observed in the original 439 autosomal prostate cancer risk variants. We first estimated the deciles of MAF and LD scores among the 439 prostate cancer risk variants using the combined Human Genome Diversity Project (HGDP)[70] and 1000 Genomes Project[56] datasets as reference. For a given simulation, we sampled 439 variants from the genomic background, after stratifying by the number of variants observed in the MAF and LD deciles. For a given functional category $C$, let $C(S)$ denote the number of variants in set $S$ with annotation $C$. We computed a permutation *P* value as $p(C) = \frac{1}{1001} + \frac{1}{1001}\sum_S C(S) \geq C(R)$, where $R$ denotes the 439 prostate cancer risk variants. The additional 1/1001 term is the result of $R$ acting as an "identity" permutation of the data and to prevent permutation *P* values of 0. Similarly, we computed enrichment as $e(C) = \frac{C(R)}{\overline{C}(S)}$ where $\overline{C}(S) = \frac{1}{1000}\sum_S C(S)$ represents the average number of annotated variants in the genomic background. We performed this procedure using genomic annotations from prostate eQTL and sQTL in GTEx v8[67], tumor prostate eQTL in TCGA PRAD [68], and cis-regulatory elements (CRE) in prostate samples using EnTEx/ENCODE annotations[71].

**Fitting prediction models of gene expression in prostate tissues.** To perform a TWAS, we fitted predictive models using genotype and mRNA measurements from samples of normal prostate in GTEx v8 (n=221)[29] and histologically normal prostate in refZ (n=471)[30]. We performed quality control (QC) on genotype data and kept only biallelic SNPs with MAF ≥0.01, HWE *P* >5 x $e^{-5}$, imputation quality score>0.6, and were annotated in HapMap3. Using the FUSION pipeline, we estimated cis-h2g using QC'd genotypes within 1 Mb flanking the gene body (i.e., ±500 Kb transcription start and stop sites)[27]. For GTEx expression data, we adjusted expression models using eQTL covariates described in reference[29], which included 5 principal components, 30 PEER factors[70], and two binary indicators for sequencing protocol and platform. For expression data in refZ[30], we adjusted expression models for histologic characteristics, percent lymphocytic population, percent epithelium present, and 14 gene expression principal components, which were defined in refZ. We limited downstream model fitting to genes whose expression levels exhibited evidence of genetic control by testing for non-zero cis-heritability (*P*<0.01) using GCTA[73]. To build prediction models of expression, we fit penalized linear models using a modified version of the FUSION software which included SuSiE[74].

**TWAS and PWAS using predicted gene and protein expression levels.** To perform downstream TWAS, we used the FUSION software[27] to integrate our fitted prostate expression models together with the current multi-ancestry GWAS summary statistics. In addition to our fitted models of prostate expression, we also downloaded prediction models of gene expression in prostate adenocarcinoma samples from TCGA (n=468)[31]. To test the association between genetically predicted levels of protein expression in plasma with prostate cancer risk, we downloaded prediction models fitted using the INTERVAL study (n=3301)[32]. In total, we performed m=19,352 association tests (m_GTEx=5063, m_refZ=8632, m_TCGA=4664, m_INTERVAL=993). We used a per-reference panel Bonferroni adjustment to determine transcriptome- or proteome-wide significance (TWAS $P < 0.05$ / m_study). To quantify the extent to which novel risk regions identify from TWAS replicate in larger GWAS, we also performed TWAS and PWAS using a smaller, previously published meta-analyzed GWAS summary statistics of prostate cancer (N=234,253)[2]. A region exhibiting TWAS/PWAS significant signal was determined to be novel if it did fall within 250Kb of a lead GWAS variant.

## Data Availability

The full summary statistics resulting from this investigation are available in the GWAS Catalog (https://www.ebi.ac.uk/gwas/) under accession codes as follows: cross-ancestry (GCST90274713), European (GCST90274714), African (GCST90274715), Asian (GCST90274716), and Hispanic (GCST90274717). Genotype and covariate data used in this study are deposited in dbGaP under accession codes phs001391.v1.p1, phs000306.v4.p1, phs001120.v2.p2 phs001221.v1.p1, phs000812.v1.p1, and phs000838.v1.p1. The variants and weights for the $GRS_{269}$ and $GRS_{451}$ are available on the PGS Catalog under accession codes PGP000122 and PGP000488, respectively (https://www.pgscatalog.org/). Publicly available data described in this manuscript can be found from the following websites: 1000 Genomes Project (http://ftp.1000genomes.ebi.ac.uk/vol1/ftp/phase3/); Human Genome Diversity Project (https://www.internationalgenome.org/data-portal/data-collection/hgdp); SEER (https://seer.cancer.gov/); National Center for Health Statistics, CDC (https://www.cdc.gov/nchs/index.htm); Cistrome Data Browser (http://cistrome.org/db/); MAYO refZ (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000985.v1.p1); GTEx (https://gtexportal.org/home/datasets); TCGA (https://portal.gdc.cancer.gov); CancerSplicingQTL database (http://www.cancersplicingqtl-hust.com/); and EnTEx/ENCODE (http://entex.encodeproject.org/).

## Code Availability

Imputation was performed using IMPUTE2, MACH 1.0, Beagle 4.1, Beagle 5.1, EAGLE v2.4, Minimac3, and Minimac4. Association testing was performed using PLINK 1.07 and 2.0, SNPtest v2.5.2, SAIGE v.0.20, and R v3.6.3. Meta-analyses were conducted using METAL v2011-03-25 and fine-mapping with mJAM (https://github.com/USCbiostats/hJAM/. Genome-wide PRS was derived from PRS-CSx v1.0.0 (https://github.com/getian107/PRScsx). Variant annotation was performed with wANNOVAR (https://wannovar.wglab.org/, accessed 20 May, 2022) and R package rtracklayer v1.42.2. TWAS was performed with FUSION (https://github.com/gusevlab/fusion_twas, accessed 20 May, 2022; TWAS weights: GTExv8 and TCGA: http://gusevlab.org/projects/fusion/, MAYO RefZ: https://www.mancusolab.com/prostate-twas/, INTERVAL:

https://www.mancusolab.com/pwas/) and GCTA v1.94.0beta. Data visualization was performed using ggplot2 v3.4.2 and gwasforest v1.0.0 packages in R software (v3.6.3).

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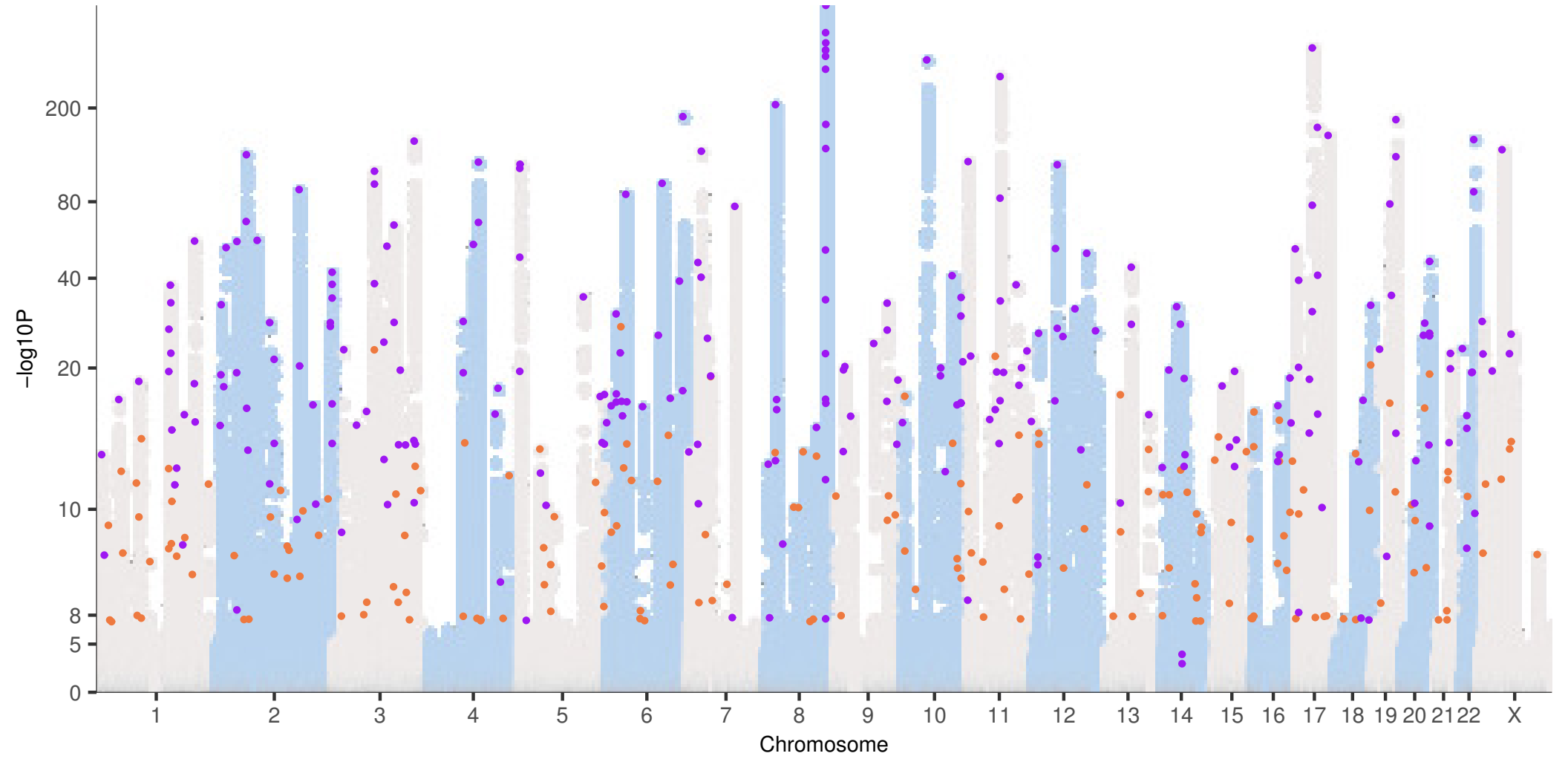
−log10P
200
80
40
20
10
8
5
0
1
2
3
4
5
6
7
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9
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11
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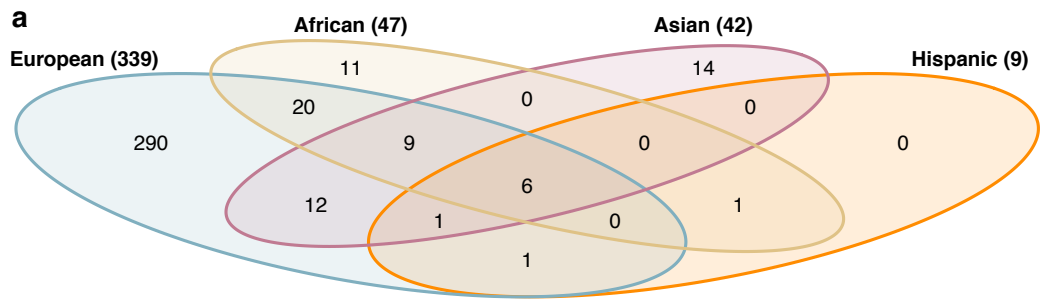
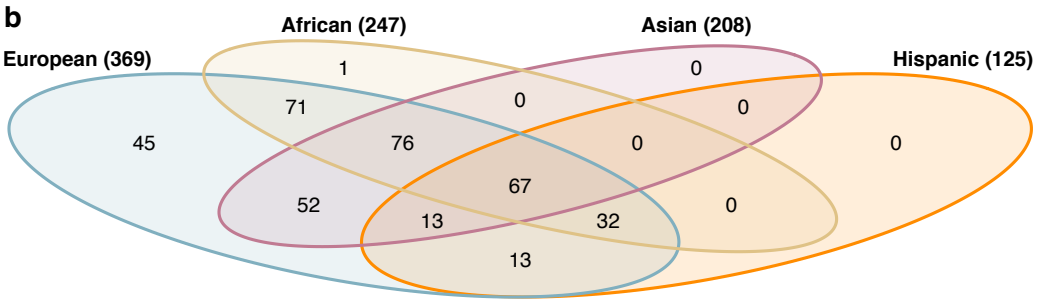
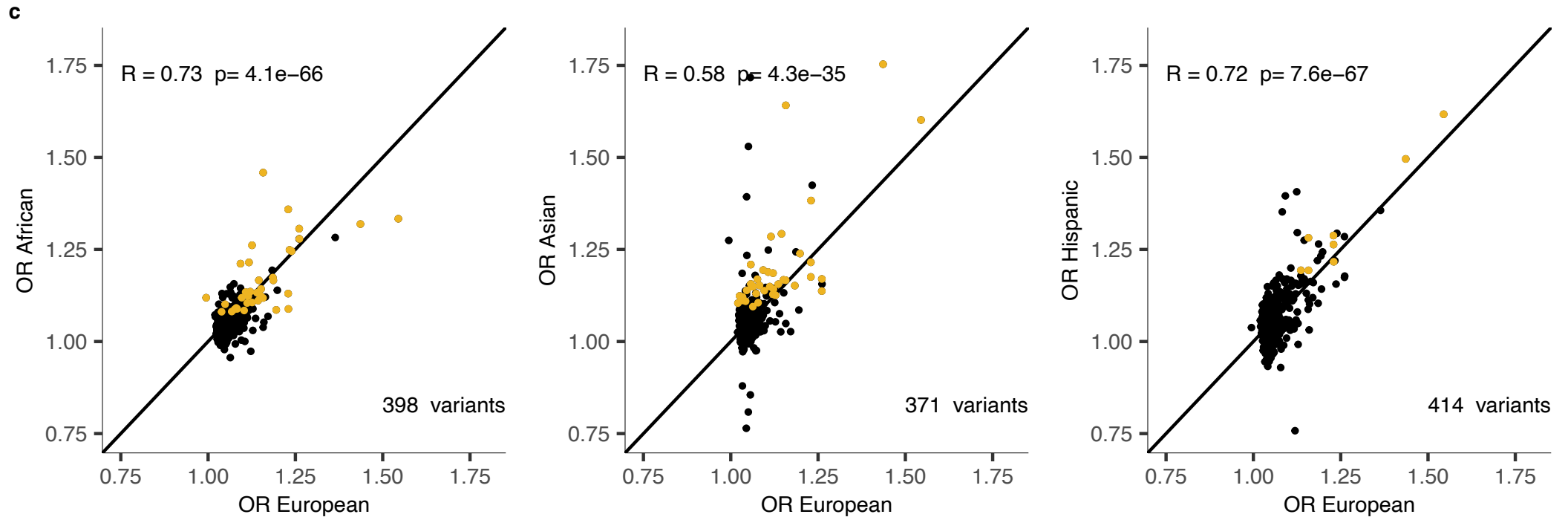
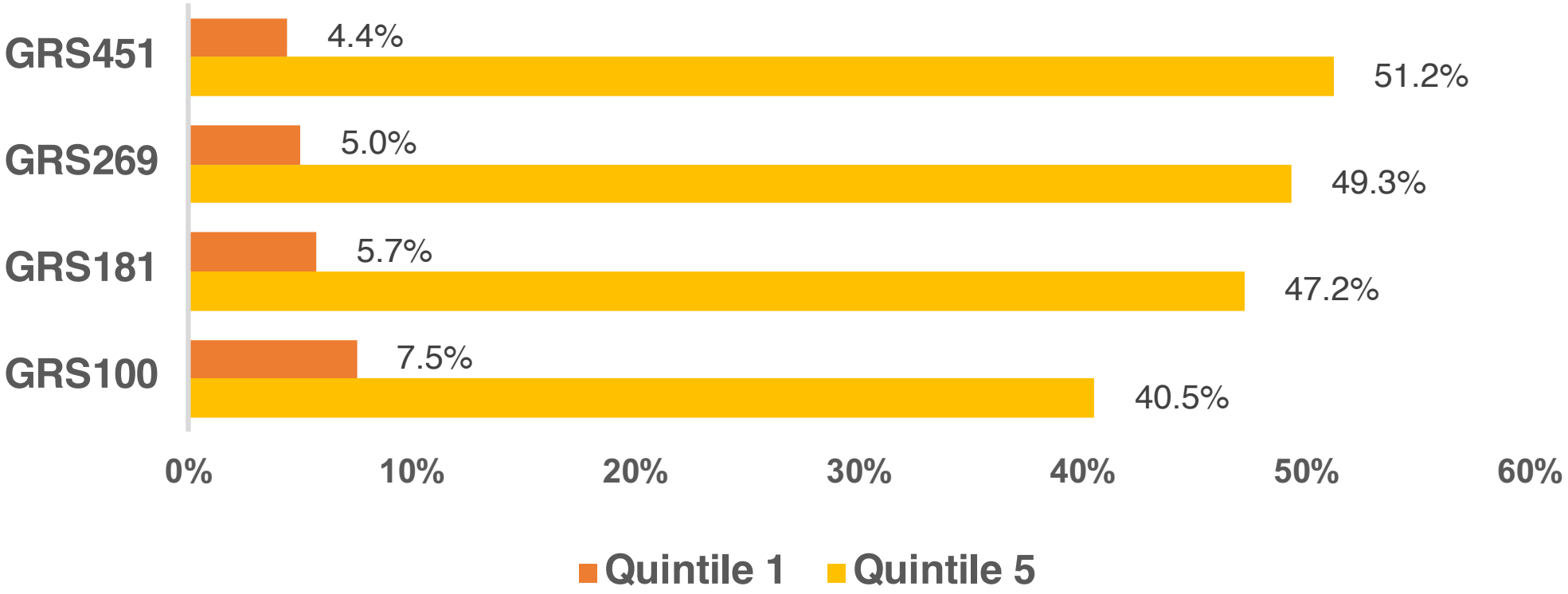
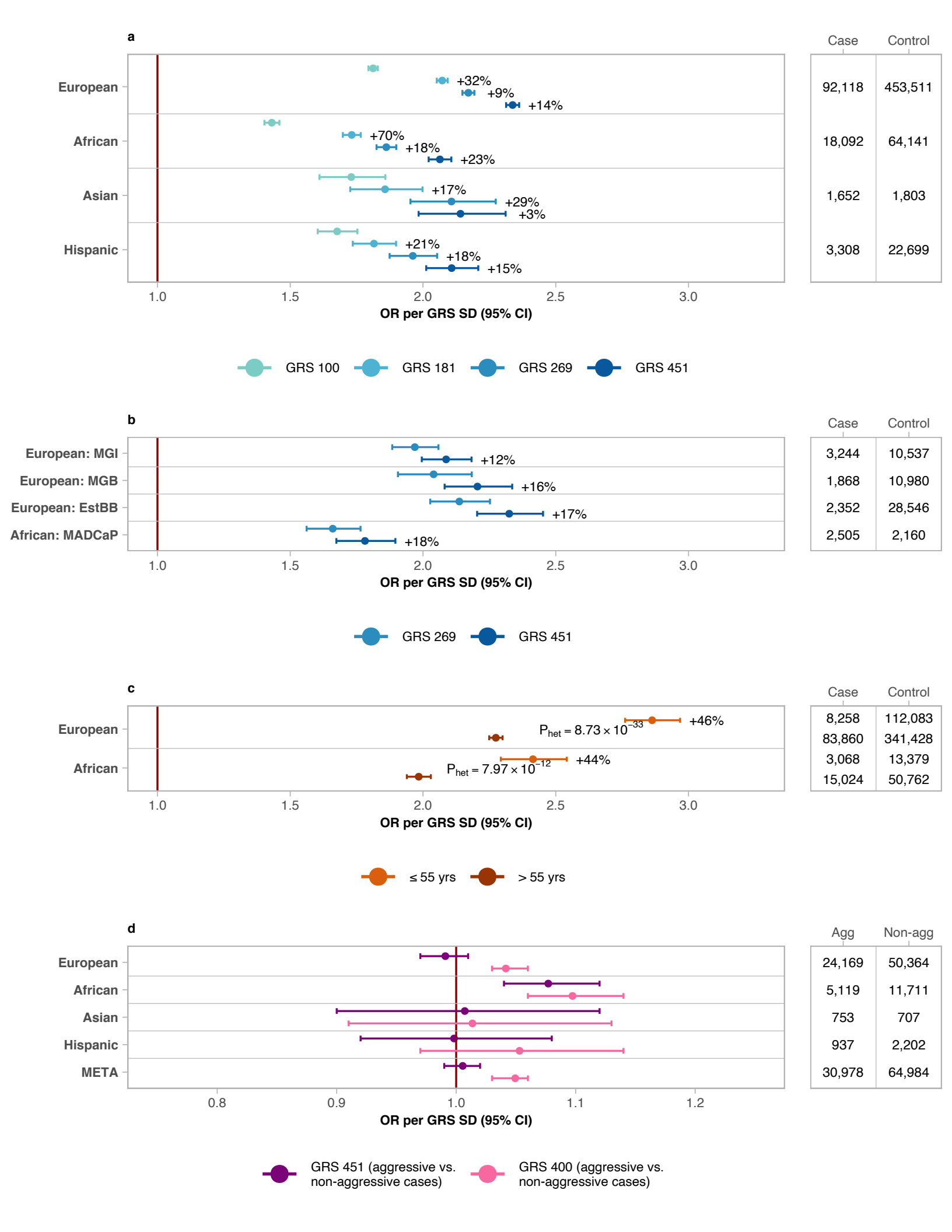
21
22
X
Chromosome

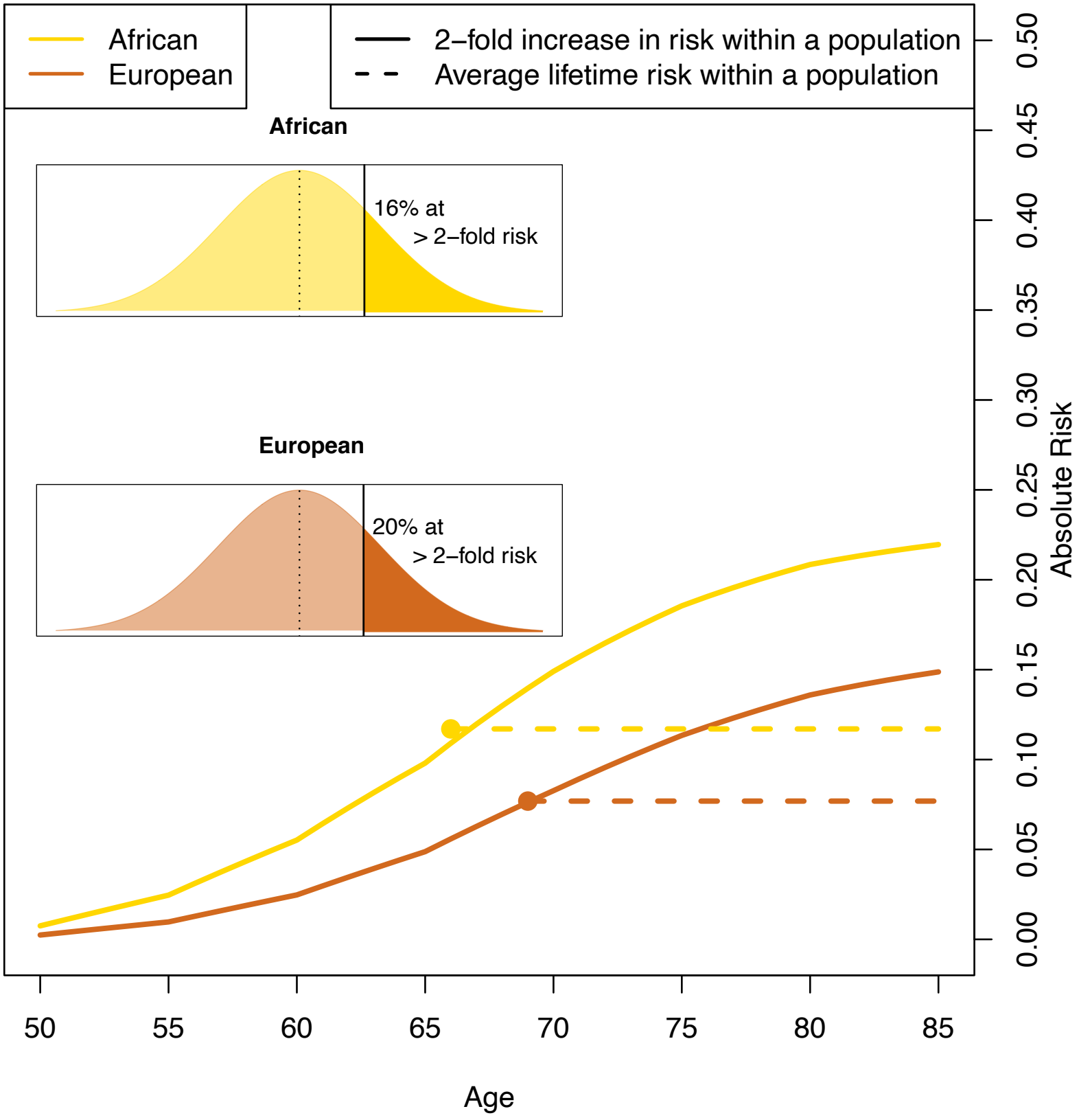

a
European (339)
African (47)
Asian (42)
Hispanic (9)
290
11
20
9
12
6
1
14
0
0
0
0
1
0
1
0

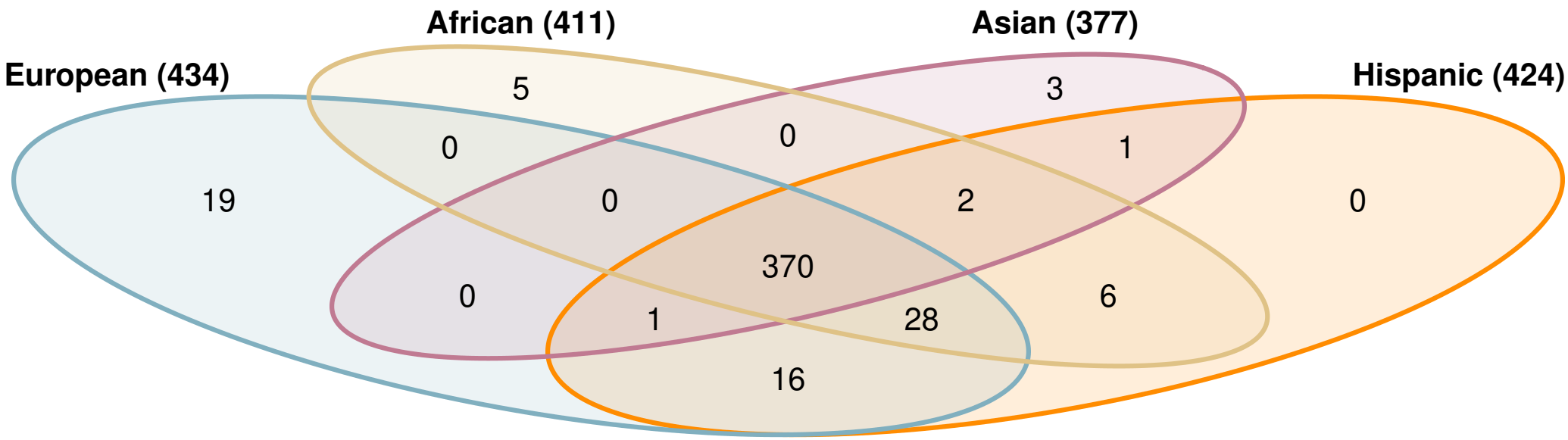

b
European (369)
African (247)
Asian (208)
Hispanic (125)
45
1
71
76
52
67
13
13
0
0
0
0
32
0

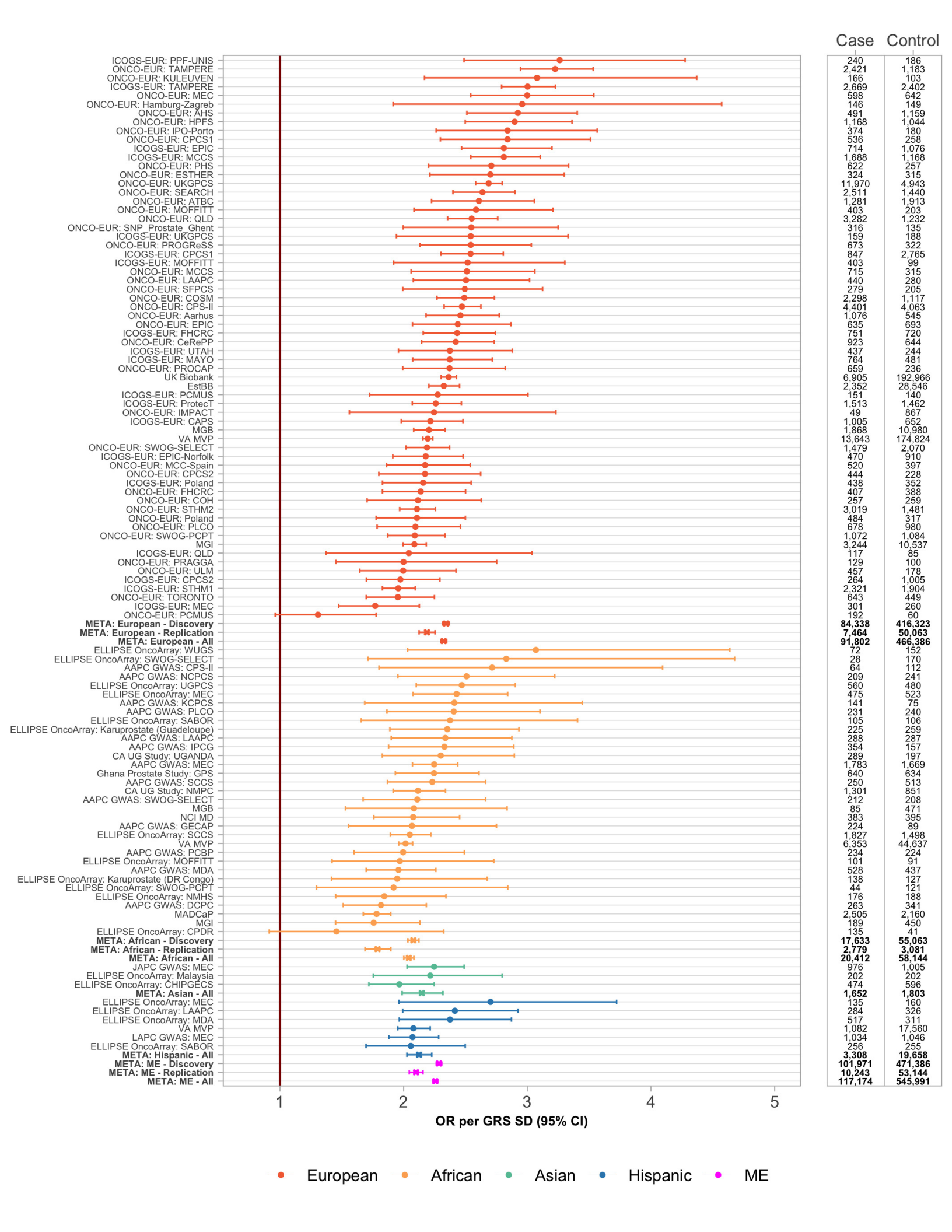

c
R = 0.73 p= 4.1e−66
398 variants
OR African
OR European
R = 0.58 p= 4.3e−35
371 variants
OR Asian
OR European
R = 0.72 p= 7.6e−67
414 variants
OR Hispanic
OR European
0.75
1.00
1.25
1.50
1.75


GRS451
4.4%
51.2%
GRS269
5.0%
49.3%
GRS181
5.7%
47.2%
GRS100
7.5%
40.5%
0%
10%
20%
30%
40%
50%
60%
Quintile 1
Quintile 5


a
European
African
Asian
Hispanic
+32%
+9%
+14%
+70%
+18%
+23%
+17%
+29%
+3%
+21%
+18%
+15%
1.0
1.5
2.0
2.5
3.0
OR per GRS SD (95% CI)
Case
Control
92,118
453,511
18,092
64,141
1,652
1,803
3,308
22,699
GRS 100
GRS 181
GRS 269
GRS 451
b
European: MGI
European: MGB
European: EstBB
African: MADCaP
+12%
+16%
+17%
+18%
1.0
1.5
2.0
2.5
3.0
OR per GRS SD (95% CI)
Case
Control
3,244
10,537
1,868
10,980
2,352
28,546
2,505
2,160
GRS 269
GRS 451
c
European
African
P_het = 8.73 × 10^-33
+46%
P_het = 7.97 × 10^-12
+44%
1.0
1.5
2.0
2.5
3.0
OR per GRS SD (95% CI)
Case
Control
8,258
112,083
83,860
341,428
3,068
13,379
15,024
50,762
≤ 55 yrs
> 55 yrs
d
European
African
Asian
Hispanic
META
0.8
0.9
1.0
1.1
1.2
OR per GRS SD (95% CI)
Agg
Non-agg
24,169
50,364
5,119
11,711
753
707
937
2,202
30,978
64,984
GRS 451 (aggressive vs. non-aggressive cases)
GRS 400 (aggressive vs. non-aggressive cases)


African
European
2–fold increase in risk within a population
Average lifetime risk within a population
African
16% at
> 2–fold risk
European
20% at
> 2–fold risk
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
0.50
Absolute Risk
50
55
60
65
70
75
80
85
Age


European (434)
African (411)
Asian (377)
Hispanic (424)
19
5
0
0
3
0
1
2
0
370
0
1
28
6
16


Case
Control
ICOGS-EUR: PPF-UNIS 240 186
ONCO-EUR: TAMPERE 2,421 1,183
ONCO-EUR: KULEUVEN 166 103
ICOGS-EUR: TAMPERE 2,669 2,402
ONCO-EUR: MEC 598 642
ONCO-EUR: Hamburg-Zagreb 146 149
ONCO-EUR: AHS 491 1,159
ONCO-EUR: HPFS 1,168 1,044
ONCO-EUR: IPO-Porto 374 180
ONCO-EUR: CPCS1 536 258
ICOGS-EUR: EPIC 714 1,076
ICOGS-EUR: MCCS 1,688 1,168
ONCO-EUR: PHS 622 257
ONCO-EUR: ESTHER 324 315
ONCO-EUR: UKGPCS 11,970 4,943
ONCO-EUR: SEARCH 2,511 1,440
ONCO-EUR: ATBC 1,281 1,913
ONCO-EUR: MOFFITT 403 203
ONCO-EUR: QLD 3,282 1,232
ONCO-EUR: SNP_Prostate_Ghent 316 135
ICOGS-EUR: UKGPCS 159 188
ONCO-EUR: PROGReSS 673 322
ICOGS-EUR: CPCS1 847 2,765
ICOGS-EUR: MOFFITT 403 99
ONCO-EUR: MCCS 715 315
ONCO-EUR: LAAPC 440 280
ONCO-EUR: SFPCS 279 205
ONCO-EUR: COSM 2,298 1,117
ONCO-EUR: CPS-II 4,401 4,063
ONCO-EUR: Aarhus 1,076 545
ONCO-EUR: EPIC 635 693
ICOGS-EUR: FHCRC 751 720
ONCO-EUR: CeRePP 923 644
ICOGS-EUR: UTAH 437 244
ICOGS-EUR: MAYO 764 481
ONCO-EUR: PROCAP 659 236
UK Biobank 6,905 192,966
EstBB 2,352 28,546
ICOGS-EUR: PCMUS 151 140
ICOGS-EUR: ProtecT 1,513 1,462
ONCO-EUR: IMPACT 49 867
ICOGS-EUR: CAPS 1,005 652
MGB 1,868 10,980
VA MVP 13,643 174,824
ONCO-EUR: SWOG-SELECT 1,479 2,070
ICOGS-EUR: EPIC-Norfolk 470 910
ONCO-EUR: MCC-Spain 520 397
ONCO-EUR: CPCS2 444 228
ICOGS-EUR: Poland 438 352
ONCO-EUR: FHCRC 407 388
ONCO-EUR: COH 257 259
ONCO-EUR: STHM2 3,019 1,481
ONCO-EUR: Poland 484 317
ONCO-EUR: PLCO 678 980
ONCO-EUR: SWOG-PCPT 1,072 1,084
MGI 3,244 10,537
ICOGS-EUR: QLD 117 85
ONCO-EUR: PRAGGA 129 100
ONCO-EUR: ULM 457 178
ICOGS-EUR: CPCS2 264 1,005
ICOGS-EUR: STHM1 2,321 1,904
ONCO-EUR: TORONTO 643 449
ICOGS-EUR: MEC 301 260
ONCO-EUR: PCMUS 192 60
META: European - Discovery 84,338 416,323
META: European - Replication 7,464 50,063
META: European - All 91,802 466,386
ELLIPSE OncoArray: WUGS 72 152
ELLIPSE OncoArray: SWOG-SELECT 28 170
AAPC GWAS: CPS-II 64 112
AAPC GWAS: NCPCS 209 241
ELLIPSE OncoArray: UGPCS 560 480
ELLIPSE OncoArray: MEC 475 523
AAPC GWAS: KCPCS 141 75
AAPC GWAS: PLCO 231 240
ELLIPSE OncoArray: SABOR 105 106
ELLIPSE OncoArray: Karuprostate (Guadeloupe) 225 259
AAPC GWAS: LAAPC 288 287
AAPC GWAS: IPCG 354 157
CA UG Study: UGANDA 289 197
AAPC GWAS: MEC 1,783 1,669
Ghana Prostate Study: GPS 640 634
AAPC GWAS: SCCS 250 513
CA UG Study: NMPC 1,301 851
AAPC GWAS: SWOG-SELECT 212 208
MGB 85 471
NCI MD 383 395
AAPC GWAS: GECAP 224 89
ELLIPSE OncoArray: SCCS 1,827 1,498
VA MVP 6,353 44,637
AAPC GWAS: PCBP 234 224
ELLIPSE OncoArray: MOFFITT 101 91
AAPC GWAS: MDA 528 437
ELLIPSE OncoArray: Karuprostate (DR Congo) 138 127
ELLIPSE OncoArray: SWOG-PCPT 44 121
ELLIPSE OncoArray: NMHS 176 188
AAPC GWAS: DCPC 263 341
MADCaP 2,505 2,160
MGI 189 450
ELLIPSE OncoArray: CPDR 135 41
META: African - Discovery 17,633 55,063
META: African - Replication 2,779 3,081
META: African - All 20,412 58,144
JAPC GWAS: MEC 976 1,005
ELLIPSE OncoArray: Malaysia 202 202
ELLIPSE OncoArray: CHIPGECS 474 596
META: Asian - All 1,652 1,803
ELLIPSE OncoArray: MEC 135 160
ELLIPSE OncoArray: LAAPC 284 326
ELLIPSE OncoArray: MDA 517 311
VA MVP 1,082 17,560
LAPC GWAS: MEC 1,034 1,046
ELLIPSE OncoArray: SABOR 256 255
META: Hispanic - All 3,308 19,658
META: ME - Discovery 101,971 471,386
META: ME - Replication 10,243 53,144
META: ME - All 117,174 545,991
1
2
3
4
5
OR per GRS SD (95% CI)
European
African
Asian
Hispanic
ME

**Supplementary Table 1.** Description and study design of the studies included in the meta-analysis and GRS replicatio

| Substudy Name | Substudy Abbreviation | Study/Consortium Name | Ancestry | No. of Cases in study | No. of Controls in study | No. of Cases in the analysis |
|---|---|---|---|---|---|---|
| **African Ancestry Studies** | | | | | | |
| Multiethnic Cohort (MEC) | MEC | AAPC GWAS | African | 1841 | 1758 | 1784 |
| Southern Community Cohort Study | SCCS | AAPC GWAS | African | 263 | 523 | 250 |
| The Prostate, Lung, Colorectal, and Ovarian Cancer | PLCO | AAPC GWAS | African | 286 | 269 | 231 |
| The Cancer Prevention Study II Nutrition Cohort | CPS-II | AAPC GWAS | African | 76 | 152 | 64 |
| Prostate Cancer Case-Control Studies at MD Anderson | MDA | AAPC GWAS | African | 543 | 474 | 528 |
| Identifying Prostate Cancer Genes | IPCG | AAPC GWAS | African | 368 | 172 | 354 |
| The Los Angeles Study of Aggressive Prostate Cancer | LAAPC | AAPC GWAS | African | 296 | 303 | 288 |
| Prostate Cancer Genetics Study | CaP Genes | AAPC GWAS | African | 75 | 85 | 71 |
| Case-Control Study of Prostate Cancer among African | DCPC | AAPC GWAS | African | 292 | 359 | 263 |
| King County (Washington) Prostate Cancer Studies | KCPCS | AAPC GWAS | African | 145 | 81 | 141 |
| The Gene-Environment Interaction in Prostate | GECAP | AAPC GWAS | African | 234 | 92 | 224 |
| North Carolina Prostate Cancer Study | NCPCS | AAPC GWAS | African | 216 | 249 | 209 |
| Selenium and Vitamin E Cancer Prevention Trial | SWOG-SELECT | AAPC GWAS | African | 223 | 224 | 212 |
| Prostate Cancer in a Black Population | PCBP | AAPC GWAS | African | 238 | 231 | 234 |
| Ghana Prostate Study | GPS | Ghana Prostate Study | African | 642 | 636 | 640 |
| Kaiser | ProHealth | ProHealth Kaiser GWAS | African | 610 | 1,665 | 601 |
| Vanderbilt Bio Vu | BioVu | ELLIPSE OncoArray | African | 213 | 0 | 204 |
| Center for Prostate Disease Research | CPDR | ELLIPSE OncoArray | African | 145 | 44 | 135 |
| EPIdemiology of Prostate CAncer | EPICAP | ELLIPSE OncoArray | African | 64 | 63 | 20 |

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|---|---|---|---|---|---|---|
| Karuprostate | Karuprostate | ELLIPSE OncoArray | African | 384 | 411 | 363 |
| Multiethnic Cohort Study | MEC | ELLIPSE OncoArray | African | 489 | 529 | 475 |
| Moffitt Prostate Cancer Study | MOFFITT | ELLIPSE OncoArray | African | 106 | 93 | 101 |
| Nashville Men's Health Study | NMHS | ELLIPSE OncoArray | African | 188 | 201 | 176 |
| Prostate Cancer Prevention Trial | SWOG-PCPT | ELLIPSE OncoArray | African | 44 | 129 | 44 |
| The North Carolina-Louisiana Prostate Cancer Project | PCaP | ELLIPSE OncoArray | African | 1022 | 0 | 967 |
| The Prostate Cancer and Environment Study | PROtEuS | ELLIPSE OncoArray | African | 72 | 58 | 70 |
| CerePP French Prostate Cancer Case-Control Study | ProGene | ELLIPSE OncoArray | African | 107 | 105 | 101 |
| Southern Community Cohort Study | SCCS | ELLIPSE OncoArray | African | 301 | 1557 | 291 |
| South Carolina Prostate Cancer Study | SCPCS | ELLIPSE OncoArray | African | 64 | 39 | 57 |
| Selenium and Vitamin E Cancer Prevention Trial | SWOG-SELECT | ELLIPSE OncoArray | African | 30 | 173 | 28 |
| San Francisco Prostate Cancer Study | SFPCS | ELLIPSE OncoArray | African | 86 | 37 | 81 |
| A Case Control Study in Uganda | UGPCS | ELLIPSE OncoArray | African | 571 | 485 | 560 |
| UK Prostate Cancer Study | UKGPCS | ELLIPSE OncoArray | African | 375 | 0 | 365 |
| San Antonio Biomarkers of Risk | SABOR | ELLIPSE OncoArray | African | 106 | 106 | 105 |
| Wake Forest Prostate Cancer Study | WFPCS | ELLIPSE OncoArray | African | 59 | 66 | 59 |
| Washington University Prostate Cancer Study | WUGS | ELLIPSE OncoArray | African | 75 | 153 | 72 |
| California and Uganda Prostate Cancer Study | CA UG Study | CA UG Study | African | 1,586 | 1,047 | 1586 |
| Vanderbilt BioVu | BioVu | BioVU | African | 302 | 799 | 302 |
| Charles Bronfman Institute of Personalized Medicine | IPM BioME | IPM BioME | African | 154 | 2498 | 154 |
| Electronic Medical Records and Genomics Network | eMERGE | eMERGE | African | 233 | 1258 | 233 |

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|---|---|---|---|---|---|---|
| NCI-Maryland prostate Cancer Case-Control Study | NCI-MD | NCI-MD | African | 489 | 486 | 383 |
| VA Million Veteran Program | VA MVP | VA MVP | African | 6,355 | 59,452 | 6353 |

**European Ancestry Studies**

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|---|---|---|---|---|---|---|
| Aarhus Prostate Cancer Study | Aarhus | ELLIPSE OncoArray | European | 1140 | 570 | 1076 |
| Agricultural Health Study | AHS | ELLIPSE OncoArray | European | 514 | 1314 | 471 |
| Alpha-Tocopherol Beta-Carotene | ATBC | ELLIPSE OncoArray | European | 1474 | 2205 | 1205 |
| Prostate Active Surveillance Study | Canary PASS | ELLIPSE OncoArray | European | 380 | 0 | 362 |
| CCI Prostate | CCI | ELLIPSE OncoArray | European | 285 | 0 | 266 |
| French Prostate Case Control Study | ProGene | ELLIPSE OncoArray | European | 1064 | 881 | 922 |
| City Of Hope | COH | ELLIPSE OncoArray | European | 263 | 269 | 257 |
| Cohort of Swedish Men | COSM | ELLIPSE OncoArray | European | 2406 | 1204 | 2049 |
| Copenhagen Prostate Cancer Study 1 & 2 | CPCS1 | ELLIPSE OncoArray | European | 552 | 269 | 532 |
| Copenhagen Prostate Cancer Study 1 & 2 | CPCS2 | ELLIPSE OncoArray | European | 461 | 238 | 439 |
| American Cancer Society (CPS-II) | CPS-II | ELLIPSE OncoArray | European | 4743 | 4508 | 4394 |
| European Prospective Investigation Into Cancer and Nutrition | EPIC | ELLIPSE OncoArray | European | 697 | 739 | 631 |
| Erasmus Medical Centre | ERSPC | ELLIPSE OncoArray | European | 75 | 75 | 71 |
| Fred Hutchinson Cancer Research Centre | FHCRC | ELLIPSE OncoArray | European | 434 | 421 | 403 |
| | Hamburg-Zagreb | ELLIPSE OncoArray | European | 154 | 154 | 146 |
| Health Professionals Follow-up Study | HPFS | ELLIPSE OncoArray | European | 1233 | 1095 | 1167 |
| Identification of Men with a genetic predisposition to | IMPACT | ELLIPSE OncoArray | European | 60 | 993 | 49 |
| Portuguese Oncology Institute, Porto | IPO-Porto | ELLIPSE OncoArray | European | 386 | 190 | 371 |
| Katholieke Universiteit Leuven | KULEUVEN | ELLIPSE OncoArray | European | 175 | 103 | 166 |

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|---|---|---|---|---|---|---|
| Los Angeles Study of Aggressive Prostate Cancer | LAAPC | ELLIPSE OncoArray | European | 789 | 621 | 436 |
| Multi Case Control Study-Spain | MCC-Spain | ELLIPSE OncoArray | European | 542 | 443 | 520 |
| Melbourne Collaborative Cohort Study | MCCS | ELLIPSE OncoArray | European | 780 | 334 | 398 |
| MD Anderson Cancer Center, active surveillance trial | MDACC_AS | ELLIPSE OncoArray | European | 633 | 0 | 501 |
| Multiethnic Cohort (MEC) | MEC | ELLIPSE OncoArray | European | 655 | 689 | 70 |
| Moffitt Prostate Cancer Study | MOFFITT | ELLIPSE OncoArray | European | 602 | 346 | 394 |
| Prostate Cancer study Medical University Sofia | PCMUS | ELLIPSE OncoArray | European | 195 | 90 | 192 |
| Physicians Health Study | PHS | ELLIPSE OncoArray | European | 664 | 286 | 621 |
| Prostate, Lung, Colorectal, and Ovarian Cancer | PLCO | ELLIPSE OncoArray | European | 1010 | 1275 | 677 |
| The Poland Group | Poland | ELLIPSE OncoArray | European | 510 | 345 | 483 |
| PRostate cAncer Genetics in Galicia | PRAGGA | ELLIPSE OncoArray | European | 133 | 104 | 129 |
| PROgression in Cancer of the Prostate | PROCAP | ELLIPSE OncoArray | European | 677 | 339 | 612 |
| Genetic prostate cancer risk stratification for | PROFILE | ELLIPSE OncoArray | European | 32 | 88 | 13 |
| Prostate cancer : Mechanisms of progression and | PROGReSS | ELLIPSE OncoArray | European | 696 | 349 | 673 |
| Prostate testing for cancer and Treatment | ProMPT | ELLIPSE OncoArray | European | 1002 | 12 | 775 |
| Prostate testing for cancer and Treatment | ProtecT | ELLIPSE OncoArray | European | 4 | 1448 | 4 |
| QLD = Retrospective Queensland Study & APCB = Australian | QLD & APCB | ELLIPSE OncoArray | European | 3489 | 1356 | 3250 |
| Radiogenomics: Assessment of Polymorphisms for | RAPPER | ELLIPSE OncoArray | European | 2350 | 0 | 2096 |
| Study of Epidemiology and Risk factors in Cancer Heredity | SEARCH | ELLIPSE OncoArray | European | 2932 | 1520 | 2408 |
| San Francisco Prostate Cancer Study | SFPCS | ELLIPSE OncoArray | European | 378 | 249 | 278 |
| Serum Proteomic analysis for biomarkers of Aggressive prostate | SNP_Prostate_Ghent | ELLIPSE OncoArray | European | 334 | 141 | 316 |
| Serum Proteomic analysis for biomarkers of Aggressive prostate | SPAG | ELLIPSE OncoArray | European | 47 | 192 | 40 |

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|---|---|---|---|---|---|---|
| Stockholm 2 | STHM2 | ELLIPSE OncoArray | European | 3148 | 1576 | 3011 |
| Prostate Cancer Prevention Trial | SWOG-PCPT | ELLIPSE OncoArray | European | 1211 | 1424 | 1070 |
| Selenium and Vitmain E Cancer Prevention Trial | SWOG-SELECT | ELLIPSE OncoArray | European | 1877 | 3295 | 1472 |
| Finnish Genetic Predisposition to Prostate Cancer Study | TAMPERE | ELLIPSE OncoArray | European | 2544 | 1226 | 2406 |
| | Toronto | ELLIPSE OncoArray | European | 821 | 599 | 668 |
| U.K. Genetic Prostate Cancer Study and The Prostate Cancer | UKGPCS | ELLIPSE OncoArray | European | 14,107 | 7,601 | 5,667 |
| Washington University Genetics Study | WUGS/WUPCS | ELLIPSE OncoArray | European | 930 | 153 | 668 |
| Cancer of the Prostate in Sweden | CAPS | PRACTICAL iCOGS | European | 1,197 | 677 | 408 |
| Stockholm 1 | STHM1 | PRACTICAL iCOGS | European | 2,056 | 2,330 | 2,006 |
| Copenhagen Prostate Cancer Study 1 | CPCS1 | PRACTICAL iCOGS | European | 892 | 3,039 | 1,113 |
| Copenhagen Prostate Cancer Study 2 | CPCS2 | PRACTICAL iCOGS | European | 349 | 1,065 | part of number above |
| European Prospective Investigation Into Cancer and Nutrition | EPIC | PRACTICAL iCOGS | European | 746 | 1,094 | 711 |
| European Prospective Investigation of Cancer - Norfolk | EPIC-Norfolk | PRACTICAL iCOGS | European | 500 | 941 | 484 |
| Epidemiological investigations of the chances of preventing, recognizing early and | ESTHER | PRACTICAL iCOGS | European | 330 | 334 | 313 |
| Fred Hutchinson Cancer Research Center | FHCRC | PRACTICAL iCOGS | European | 862 | 804 | 761 |
| Portuguese Oncology Institute, Porto | IPO-Porto | PRACTICAL iCOGS | European | 187 | 88 | 183 |
| Mayo Clinic Study | MAYO | PRACTICAL iCOGS | European | 780 | 496 | 767 |
| Melbourne Collaborative Cohort Study | MCCS | PRACTICAL iCOGS | European | 408 | 1,218 | 1,685 |
| Risk factors for prostate cancer | RFPCS | PRACTICAL iCOGS | European | 278 | | part of number abov |
| Early Onset Prostate Cancer Study | EOPCS | PRACTICAL iCOGS | European | 1127 | 13 | part of number above |
| Multiethnic Cohort Study | MEC | PRACTICAL iCOGS | European | 890 | 896 | 586 |
| The Moffitt Group | MOFFITT | PRACTICAL iCOGS | European | 449 | 117 | 414 |

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|---|---|---|---|---|---|---|
| Prostate Cancer study Medical University Sofia | PCMUS | PRACTICAL iCOGS | European | 152 | 145 | 151 |
| The Poland Group | Poland | PRACTICAL iCOGS | European | 453 | 473 | 438 |
| Prostate Project Foundation - Postgraduate Medical | PPF-UNIS | PRACTICAL iCOGS | European | 257 | 197 | 257 |
| Prostate cancer : Mechanisms of progression and | ProMPT | PRACTICAL iCOGS | European | 188 | 2 | 1,729 |
| Prostate testing for cancer and Treatment | ProtecT | PRACTICAL iCOGS | European | 1,628 | 1,499 | part of number above |
| Retrospective Queensland Study (QLD) and the Prostate | QLD | PRACTICAL iCOGS | European | 187 | 94 | 186 |
| Study of Epidemiology and Risk factors in Cancer Heredity | SEARCH | PRACTICAL iCOGS | European | 1,468 | 1,292 | 1,371 |
| Finnish Genetic Predisposition to Prostate Cancer Study | TAMPERE | PRACTICAL iCOGS | European | 2,837 | 2,770 | 2,754 |
| U.K. Genetic Prostate Cancer Study and The Prostate Cancer | UKGPCS | PRACTICAL iCOGS | European | 4,912 | 4,322 | 2,859 |
| Molecular Genetics of Prostate Cancer | ULM | PRACTICAL iCOGS | European | 609 | 508 | 603 |
| UTAH Study | UTAH | PRACTICAL iCOGS | European | 456 | 257 | 440 |
| UK-GWAS1 | UK1 | UK GWAS1 | European | 1,906 | 1,934 | 1,854 |
| UK-GWAS2 | UK2 | UK GWAS2 | European | 3,888 | 3,956 | 3,650 |
| UK-GWAS2-Melbourne | UK2 | UK GWAS2 | European | part of number above | part of number above | part of number above |
| Cancer of the Prostate in Sweden study 1 | CAPS | CAPS1 | European | 498 | 502 | 474 |
| Cancer of the Prostate in Sweden study 2 | CAPS | CAPS2 | European | 1,483 | 519 | 1,458 |
| ProstatE cancer Genetic Association Study of Uncommon | Pegasus | Pegasus | European | 4,622 | 2,954 | 4,600 |
| Multiethnic Cohort (MEC) | MEC | BPC3 | European | 244 | 259 | 244 |
| European Prospective Investigation into Cancer and Nutrition | EPIC | BPC3 | European | 431 | 426 | 431 |
| Physicians Health Study | PHS | BPC3 | European | 298 | 255 | 298 |
| Health Professionals Follow-up Study | HPFS | BPC3 | European | 214 | 204 | 214 |
| The Cancer Prevention Study II Nutrition Cohort | CPS-II | BPC3 | European | 636 | 622 | 636 |

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|---|---|---|---|---|---|---|
| Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) | ATBC | BPC3 | European | 245 | 1,245 | 245 |
| Kaiser | ProHealth | ProHealth Kaiser GWAS | European | 7,145 | 31,070 | 6,406 |
| UK Biobank | UK Biobank | UK Biobank | European | 8,765 | 193,322 | 8,046 |
| FinnGen Study, freeze 5 | FinnGen | FinnGen | European | 6,311 | 88,902 | 6,311 |
| Charles Bronfman Institute of Personalized Medicine BioMETM BioBank | IPM BioME | IPM BioME | European | 175 | 4,193 | 173 |
| Vanderbilt Bio Vu | BioVu | BioVu | European | 1,808 | 8,255 | 1,808 |
| Electronic Medical Records and Genomics Network | eMERGE | eMERGE | European | 3,204 | 11,954 | 3,204 |
| The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial | PLCO | PLCO | European | 1,755 | 31,546 | 1,755 |
| VA Million Veteran Program | VA MVP | VA MVP | European | 13,649 | 242,938 | 13,643 |
| Prostate Cancer Case-Control Studies at MD Anderson | MDA | OncoArray | European | 1,764 | 1,204 | 1,694 |
| **Latino Ancestry Studies** | | | | | | |
| Multiethnic Cohort (MEC) | MEC | LAPC GWAS | Latino | 1,079 | 1,083 | 1,034 |
| Multiethnic Cohort (MEC) | MEC | ELLIPSE OncoArray | Latino | 152 | 162 | 135 |
| The Los Angeles Study of Aggressive Prostate Cancer | LAAPC | ELLIPSE OncoArray | Latino | 320 | 331 | 284 |
| Prostate Cancer Case-Control Studies at MD Anderson | MDA | ELLIPSE OncoArray | Latino | 521 | 316 | 517 |
| San Antonio Biomarkers of Risk | SABOR | ELLIPSE OncoArray | Latino | 260 | 260 | 256 |
| Kaiser | ProHealth | ProHealth Kaiser GWAS | Latino | 491 | 3,147 | 488 |
| Charles Bronfman Institute of Personalized Medicine BioMETM BioBank | IPM BioME | IPM BioME | Latino | 135 | 3,606 | 135 |
| VA Million Veteran Program | VA MVP | VA MVP | Latino | 1,082 | 27,134 | 1,082 |
| **Asian Ancestry Studies** | | | | | | |
| Multiethnic Cohort (MEC) | MEC | JAPC GWAS | Asian | 1,104 | 1,109 | 976 |

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|---|---|---|---|---|---|---|
| Chinese Prostate Cancer Genetic and Environmental | CHIPGECS | ELLIPSE OncoArray | Asian | 533 | 666 | 474 |
| Prostate cancer study in Malaysia | Malaysia | ELLIPSE OncoArray | Asian | 210 | 210 | 202 |
| Biobank Japan | BBJ | Biobank Japan | Asian | 8,889 | 90,356 | 8,645 |
| Kaiser | ProHealth | ProHealth Kaiser GWAS | Asian | 290 | 2,943 | 288 |
| The Prostate, Lung, Colorectal, and Ovarian Cancer | PLCO | PLCO | Asian | 224 | 1,513 | 224 |

**GRS Replication Studies: European and African Ancestry Studies**

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|---|---|---|---|---|---|---|
| Mass General Brigham Biobank | MGB | MGB | European | 1,868 | 10,980 | 1,868 |
| Michigan Genomics Initiative | MGI | MGI | European | 3,244 | 10,537 | 3,244 |
| Estonian Biobank | EstBB | EstBB | European | 2,499 | 71,671 | 2,352 |
| Men of African Descent and Carcinoma of the | MADCaP | MADCaP | African | 223 | 228 | 223 |
| Men of African Descent and Carcinoma of the | MADCaP | MADCaP | African | 210 | 217 | 210 |
| Men of African Descent and Carcinoma of the | MADCaP | MADCaP | African | 372 | 337 | 372 |
| Men of African Descent and Carcinoma of the | MADCaP | MADCaP | African | 190 | 177 | 190 |
| Men of African Descent and Carcinoma of the | MADCaP | MADCaP | African | 162 | 161 | 162 |
| Men of African Descent and Carcinoma of the | MADCaP | MADCaP | African | 1,165 | 971 | 1,165 |
| Men of African Descent and Carcinoma of the | MADCaP | MADCaP | African | 183 | 132 | 183 |
| Mass General Brigham Biobank | MGB | MGB | African | 85 | 471 | 85 |
| Michigan Genomics Initiative | MGI | MGI | African | 189 | 450 | 189 |

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| No. of Controls in the analysis | Individual or Summary Level Data | Design, location | Source of cases | Source of controls |
|---|---|---|---|---|
| 1669 | Individual | Case-control in cohort, HI and CA, U.S. | MEC | MEC |
| 513 | Individual | Case-control in cohort, Southeastern U.S. | SCCS | SCCS |
| 240 | Individual | Case-control in screening trial, U.S. | PLCO | PLCO |
| 112 | Individual | Case-control in cohort, U.S. | CPS-II | CPS-II |
| 437 | Individual | Case-control, Houston, TX, U.S. | Houston Medical Center | Random-digit-dialing or hospital visitors |
| 157 | Individual | Case-control, Maryland, U.S. | Johns Hopkins Hospital and Sidney Kimmel Cancer Center | Men undergoing screening for prostate cancer at the same |
| 287 | Individual | Case-control, Los Angeles County, CA, U.S. | Los Angeles County Cancer Surveillance Program | Los Angeles County, neighborhood walk algorithm and the MEC |
| 85 | Individual | Case-control, Cleveland, OH, U.S. | Medical institutions in Cleveland, Ohio | Screened men at same medical institutions |
| 341 | Individual | Case-control, Washington, DC, U.S. | Howard University Hospital (HUH) | Men undergoing screening for prostate cancer at HUH |
| 75 | Individual | Case-control, King County, WA, U.S. | Seattle-Puget Sound SEER cancer registry | Random-digit-dialing |
| 89 | Individual | Case-control, Detroit, MI, U.S. | The Henry Ford Health System (HFHS) | HFHS population base |
| 241 | Individual | Case-control, NC, U.S. | North Carolina Central Cancer Registry | Friend referral, same county |
| 208 | Individual | Case-control in clinical trial, U.S. | Randomized clinical trial | Randomized clinical trial |
| 224 | Individual | Case-control, Barbados | All newly diagnosed cases in Barbados | Selected from a national database |
| 634 | Summary | Case-control, Greater Accra, Ghana | Patients from a local teaching hospital and cases identified from | Population-based, probability sample designed using the |
| 1,650 | Summary | Cohort, CA, US | African-American | RPGEH, CMHS |
| 0 | Individual | Opt-out clinical biobank linked to de-identified electronic health records, Nashville, TN, | Patients who had an outpatient visit at VUMC with a blood | N/a (no matching controls) |
| 41 | Individual | Retrospective cohort study; Greater Washington DC Metro Area, USA | Patients enrolled at Walter Reed National Military Medical Center | Patients enrolled at Walter Reed National Military Medical Center |
| 9 | Individual | Case-control, France | North African origins living in the France Metropolitan, Cancer | Population-based |

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|---|---|---|---|---|
| 386 | Individual | Population-based case-control in Guadeloupe and hospital-based case-control in DR Congo | Incident cases from Guadeloupe (Afro-Caribbean) and the DR Congo (African) | Free health screening program open to the general population (Guadeloupe); Men attending for prostate |
| 523 | Individual | Case-control in cohort, HI and CA, U.S. | MEC | MEC |
| 91 | Individual | Case-control at Moffitt Cancer Center | Moffitt Cancer Center | Non-cancer visitors |
| 188 | Individual | Case-control, Nashville, TN | Men seeking a prostate biopsy in all urology clinics in | Men without PC at biopsy from these urology clinics. |
| 121 | Individual | Case-control drawn from a randomized clinical trial; US and Canada | Randomized clinical trial | Randomized clinical trial |
| 0 | Individual | Population-based Case-only | North Carolina Central Cancer Registry for NC cases and LSUHSC | |
| 57 | Individual | Case-control, Montreal, Canada | New incident cases across Montreal hospitals | Electoral list, from same residential areas as cases |
| 85 | Individual | Case-control, France | North Africa, Africa or Caribbean origins, living in France | Controls were recruited as participating in a systematic health |
| 1498 | Individual | Case-control in cohort, Southeastern U.S. | SCCS | SCCS |
| 32 | Individual | Case-control, South Carolina, U.S. | South Carolina Central Cancer Registry | Health Care Financing Administration Medicare Beneficiary |
| 170 | Individual | Case-control in clinical trial, U.S. | Randomized clinical trial | Randomized clinical trial |
| 36 | Individual | Case-control in Bay Area, CA | Non-Hispanic African-American men ages 40-79 years diagnosed | Non-Hispanic African-American men ages 40-79 years without a |
| 480 | Individual | Case-control in Kampala, Uganda | Incident cases from Mulago Hospital | Patients in other clinics at Mulago |
| 0 | Individual | Cases from the UK | Cases identified through clinics at the Royal Marsden | |
| 106 | Individual | Case-control from SA, TX | Incident and Prevalent cases from SABOR | SABOR |
| 49 | Individual | Case-control, Winston-Salem, NC | Incident cases from Wake Forest Baptist Health Urology Clinic | Men with normal PSA/DRE from the same clinic |
| 152 | Individual | Case Control from St. Louis MO | Incident and Prevalent cases from Barnes Jewish Hospital | St. Louis MO |
| 1047 | Individual | Los Angeles, California and Kampala, Uganda | Cases from Los Angeles, CA through SEER registry and | Cancer-free controls were from the African American Eye Disease |
| 799 | Summary | Prospective cohort from Nashville, Tennessee | From Nashville, Tennessee | From Nashville, Tennessee |
| 2498 | Summary | Prospective longitudinal cohort from New York, NY | Mount Sinai Medical Center in the city of New York, NY | Mount Sinai Medical Center in the city of New York, NY |
| 1258 | Summary | Prospective cohort from 10 clinical sites in US | From 10 clnical sites in US | From 10 clnical sites in US |

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|---|---|---|---|---|
| 395 | Individual | Case-control from Baltimore, Maryland | Cases from two hospitals in Baltimore, Maryland | Controls from the Maryland Department of Motor Vehicles |
| 44,637 | Summary | Prospective cohort of veterans | From Veterans Affairs Central Cancer Registry | without any prostate cancer diagnostic codes, limited to |

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|---|---|---|---|---|
| 544 | Individual | Hospital-based, Retrospective, Observational, Aarhus, Denmark | Patients treated for prostate adenocarcinoma at | Age-matched males treated for myocardial infarction or |
| 1179 | Individual | Nested case-control study within prospective cohort, Maryland, USA | linkage to cancer registries in study states | matched controls from cohort |
| 1910 | Individual | Prospective, nested case-control, Maryland, USA | Finnish male smokers aged 50-69 years at baseline | Finnish male smokers aged 50-69 years at baseline |
| 0 | Individual | Prospective, Multi-site, Observational Active Surveillance Study, FHCRC | clinic based from Beth Israel Deaconness Medical Center, | |
| 0 | Individual | Case series, Hospital-based, Alberta, Canada | Cases identified through clinics at the Cross Cancer Institute | |
| 692 | Individual | Case-Control, Prospective, Observational, Hospital-based, Paris, France | Patients, treated in French departments of Urology, who had | Controls were recruited as participating in a systematic health |
| 259 | Individual | Hospital-based cases and controls from outside, Duarte, USA | Consented prostate cancer cases at City of Hope | Consented unaffected males that were part of other studies where |
| 1120 | Individual | Population-based cohort, Stockholm, Sweden | General population | General population |
| 256 | Individual | Case-control - Denmark, Copenhagen, Denmark | Hospital referrals | Copenhagen General Population Study |
| 227 | Individual | , Copenhagen, Denmark | Hospital referrals | Copenhagen General Population Study |
| 4061 | Individual | Nested case-control derived from a prospective cohort study, Atlanta, USA | Identified through self-report on follow-up questionnaires and | Cohort participants who were cancer-free at the time of diagnosis |
| 693 | Individual | Case-control - Germany, Greece, Italy, Netherlands, Spain, Sweden, UK, EU, Multi | Identified through record linkage with population-based | Cohort participants without a diagnosis of cancer. |
| 65 | Individual | Population-based randomised trial, Rotterdam, The Netherlands | Men with Pca from screening arm ERSPC Rotterdam | Men without Pca from screening arm ERSPC Rotterdam |
| 380 | Individual | Population-based, case-control, ages 35-74 years at diagnosis, King County, WA, | Identified through the Seattle-Puget Sound SEER cancer registry | Randomly selected, age-frequency matched residents |
| 149 | Individual | Hospital-based, Prospective, Hamburg, Germany | Prostate cancer cases seen at the Department of | Population-based (Croatia), healthy men, older than 50, with no |
| 1044 | Individual | Nested case-control, Harvard, USA | Participants of the HPFS cohort | Participants of the HPFS cohort |
| 866 | Individual | Observational, The Institute of Cancer Research, London, UK | Carriers and non carriers (with a known mutation in the family) | Carriers and non carriers (with a known mutation in the family) |
| 180 | Individual | Hospital-based, Porto, Portugal | Early onset and/or familial prostate cancer | Blood donors |
| 103 | Individual | Hospital-based, Prospective, Observational, Leuven, Belgium | Prostate cancer cases recruited at the University Hospital | Healthy males with no history of prostate cancer recruited at the |

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|---|---|---|---|---|
| 282 | Individual | Population-based, Case-control, California, USA | Los Angeles County Cancer Surveillance Program | Los Angeles County, neighborhood walk algorithm |
| 397 | Individual | Case-control, Barcelona, Spain | Identified through the urology departments of the participating | Population-based, frequency age and region matched, |
| 303 | Individual | Nested case-control, Melbourne, Victoria, Melbourne, Australia | Identified by linkage to the Victorian Cancer Registry | Cohort participants without a diagnosis of cancer |
| 0 | Individual | A prospective cohort study, Texas, USA | Men with clinically organ-confined prostate cancer | |
| 92 | Individual | Population-based, California & Hawaii, USA | MEC | MEC |
| 202 | Individual | Hospital-based, Florida, USA | clinic based from Moffitt Cancer Center | Moffitt Cancer Center affiliated Lifetime cancer screening |
| 89 | Individual | Case-control - Sofia, Bulgaria, Sofia, Bulgaria | Patients of Clinic of Urology, Alexandrovska | 72 patients with verified BPH and PSA<3,5; 78 healthy |
| 257 | Individual | Nested case-control, Harvard, USA | Participants of the PHS1 trial/cohort | Participants of the PHS1 trial/cohort |
| 980 | Individual | Nested case-control, Bethesda, USA | Men with a confirmed diagnosis of prostate cancer from the PLCO | Controls were men enrolled in the PLCO Cancer Screening Trial |
| 317 | Individual | Case-control, Szczecin, Poland | men with unselected prostate cancer, diagnosed in north- | cancer-free men from the same population, taken from the healthy |
| 100 | Individual | Case-control, Galicia, Spain | Population-based | Population-based |
| 236 | Individual | Population-based, Retrospective, Observational, Stockholm, Sweden | Cases were ascertained from the National Prostate | Controls were selected among men referred for PSA testing in |
| 21 | Individual | Hospital-based, Prospective, Observational, The Institute of Cancer Research, London, | Men with a family history of prostate cancer who are | Men with a family history of prostate cancer who are |
| 322 | Individual | Hospital-based, Prospective, Observational, Santiago de Compostela, Spain | Prostate cancer cases from the Hospital Clínico Universitario de | Cancer-free men from the same population |
| 12 | Individual | A study to collect samples and data from subjects with and without prostate cancer. | Subjects attending outpatient clincs in hospitals | Subjects attending outpatient clincs in hospitals |
| 1408 | Individual | Trial of treatment. Samples taken from subjects invited for PSA testing from the | Subjects who have a proven diagnosis of prostate cancer | Identified through invitation of subjects in the community. |
| 1241 | Individual | QLD = Case-control APCB = Hospital based, prospective study, QLD = | QLD = A longitudinal cohort study (Prostate Cancer Supportive | QLD = Controls comprised healthy male blood donors with |
| 0 | Individual | Multi-centre, hosptial based blood sample collection study in patients enrolled in clinical | Prostate cancer patients enrolled in radiotherapy trials: | |
| 223 | Individual | Case-control - East Anglia, UK, Cambridge, UK | Men < 70 years of age registered with prostate cancer at the | Men attending general practice in East Anglia with no known prostate |
| 205 | Individual | Population-based case-control study, Retrospective, Observational, California, | non-Hispanic white and African-American men ages 40-79 years | non-Hispanic white and African-American men ages 40-79 years |
| 135 | Individual | Hospital-based, Retrospective, Observational, Ghent, Belgium | Men treated with IMRT as primary or postoperative | Employees of the University hospital and members of social |
| 170 | Individual | Hospital-based, Retrospective, Observational, Manchester; Southampton, | Guernsey | Guernsey |

| | | | | |
|---|---|---|---|---|
| 1480 | Individual | Population-based, Retrospective, Observational, Stockholm, Sweden | Cases were selected among men referred for PSA testing in | Controls were selected among men referred for PSA testing in |
| 1024 | Individual | Case-control from a randomized clinical trial, Seattle, USA | Randomized clinical trial | Randomized clinical trial |
| 2122 | Individual | Case-cohort from a randomized clinical trial, Seattle, USA | Randomized clinical trial | Randomized clinical trial |
| 1176 | Individual | Case-control - Finland, Retrospective, Observational, Population-based, Tampere, | Identified through linkage to the Finnish Cancer Registry and | Cohort participants without a diagnosis of cancer |
| 455 | Individual | Prospective hospital-based biopsy cohort, Toronto, Canada | Positive biopsies in our database | No prior history of prostate cancer; negative biopsy (or |
| 927 | Individual | ICR, UK | Cases identified through clinics at the Royal Marsden | Ken Muir's control-2000 |
| 0 | Individual | Cases Series, USA, St. Louis, USA | Identified through clinics at Washington University in St. Louis | Men diagnosed and managed with prostate cancer in University |
| 271 | Individual | Case-control | Identified through Swedish Cancer Registry | Population controls without a diagnosis of cancer |
| 2,224 | Individual | Cohort | Identified through Swedish Cancer Registry | Cohort participants with negative prostate biopsy. |
| 3,780 | Individual | Case-control Denmark | Hospital referrals | Copenhagen General Population Study |
| part of number above | Individual | Case-control Denmark | Hospital referrals | Copenhagen General Population Study |
| 1079 | Individual | Nested case-control study, Germany, Greece, Italy, Netherlands, Spain, Sweden, | Identified through linkage through record linkage with population- | Cohort participants without a diagnosis of cancer |
| 917 | Individual | Nested case-control study | Identified through record linkage with population based | Cohort participants without a diagnosis of cancer |
| 318 | Individual | Case-control study, Germany | Prostate cancer cases in all hospitals in the state of Saarland, from 2001-2003 | Random sample of participants from routine health check-up in Saarland, in 2000- |
| 730 | Individual | Population-based, case-control, ages 35-74 years at diagnosis, King County, WA, USA | Identified through the Seattle-Puget Sound SEER cancer registry | Population-based, frequency age matched (5-year groups), ascertained |
| 66 | Individual | Patient series, Portugal | Patients treated with open radical prostatectomy at IPO- | Blood donors |
| 488 | Individual | | Hospital based cases | Geographically, population via Rochester |
| 1,183 | Individual | Nested case control, Melbourne, Victoria | Identified by linkage to the Victorian Cancer Registry | Cohort participants without a diagnosis of cancer |
| 'e | Individual | Population based case-control study, Victoria | Victorian Cancer Registry | Selected from the Victorian Electoral Roll |
| part of number above | Individual | Population based case-series of men diagnosed less than 60 yrs, plus brothers, Victoria | Victorian Cancer registry | Brothers of cases |
| 597 | Individual | Case-control in cohort, HI and CA, U.S. | MEC | MEC |
| 100 | Individual | Hospital based case-control | Clinic based from Moffitt Cancer Center | Moffitt Cancer Center affiliated Lifetime cancer screening |

| | | | | |
|---|---|---|---|---|
| 140 | Individual | Case-control, Sofia, Bulgaria | Patients of Clinic of Urology, Alexandrovska | 72 patients with verified BPH and PSA<3,5; 78 healthy |
| 359 | Individual | Case-control | Men with unselected prostate cancer, diagnosed in north- | Cancer-free men from the same population, taken from the healthy |
| 176 | Individual | Case-control | Men with newly diagnosed prostate cancer, presenting in | Cancer free men from the same population, know to have a low |
| 1,476 | Individual | A study to collect samples and data from subjects with and without prostate cancer | Subjects attending outpatient clinics in hospitals | Subjects attending outpatient clinics in hospitals |
| part of number above | Individual | Trial of treatment. Samples taken from subjects invited for PSA testing from the | Subjects who have a proven diagnosis of prostate cancer | Identified through invitation of subjects in the community. |
| 87 | Individual | Case-control, Queensland, Australia | Acquired through the Queensland node of the Australian Prostate | Healthy males with no personal history of prostate cancer |
| 1,244 | Individual | Case control, East Anglia, UK | Men < 70 years of age registered with prostate cancer at the | Men attending general practice in East Anglia with no known prostate |
| 2,413 | Individual | Case-control, Finland | Identified through linkage to the Finnish Cancer Registry and | Cohort participants without a diagnosis of cancer |
| 2,193 | Individual | ICR, UK | Cases identified through clinics at the Royal Marsden | Ken Muir's control-2000 |
| 354 | Individual | Case-control, Germany | Familial cases (n=292): identified through questionnaires | Age-matched controls (n=209): age-matched men without prostate |
| 245 | Individual | Pedigree Study, Utah USA | Identified in the Utah Cancer Registry | |
| 1,894 | Summary | Case-control UK | UKGPCS | ProtecT |
| 3,940 | Summary | Case-control UK | UKGPCS | ProtecT |
| part of number above | Summary | Case-control Australia | MCCS | RFPCS |
| 482 | Summary | Case-control Sweden | Identified through Swedish Cancer Registry | Population controls without a diagnosis of cancer |
| 512 | Summary | Case-control Sweden | Identified through Swedish Cancer Registry | Population controls without a diagnosis of cancer |
| 2,941 | Summary | Nested case-control in the Prostate, Lung, Colorectal, and Ovarian Cancer | Identified through screening and self-report with verification | Male cohort participants without a diagnosis of cancer |
| 259 | Summary | Case-control in cohort, HI and CA, U.S. | MEC | MEC |
| 416 | Summary | Nested case-control in cohort | EPIC | EPIC |
| 255 | Summary | Case-control in cohort, U.S. | PHS | PHS |
| 204 | Summary | Case-control in cohort, U.S. | HPFS | HPFS |
| 614 | Summary | Case-control in cohort, U.S. | CPS-II | CPS-II |

| | | | | |
|---|---|---|---|---|
| 1,245 | Summary | Nested case-control, Finland | Identified through linkage to the Finnish Cancer Registry | Cohort participants without a diagnosis of cancer |
| 30,866 | Summary | Cohort, CA, US | non-Hispanic white | RPGEH, CMHS |
| 191,825 | Individual | Case-control in cohort, UK. | UKBB | UKBB |
| 88,902 | Summary | Finnish biobank participants | FinnGen | FinnGen |
| 4,193 | Summary | Prospective longitudinal cohort from New York, NY | Mount Sinai Medical Center in the city of New York, NY | Mount Sinai Medical Center in the city of New York, NY |
| 8,255 | Summary | Prospective cohort from Nashville, Tennessee | From Nashville, Tennessee | From Nashville, Tennessee |
| 11,954 | Summary | Prospective cohort from 10 clinical sites in US | From 10 clnical sites in US | From 10 clnical sites in US |
| 31,546 | Summary | Nested case-control, Bethesda, USA | Men with a confirmed diagnosis of prostate cancer from PLCO and not included in | Controls were men enrolled in the PLCO Cancer Screening Trial without a diagnosis of |
| 174,824 | Summary | Prospective cohort of veterans | From Veterans Affairs Central Cancer Registry | MVP participants without any prostate cancer diagnostic |
| 1,169 | Summary | Case-control, Houston, TX, U.S. | MD Anderson | Age-matched cancer free controls from random-digit-dialing or |

| | | | | |
|---|---|---|---|---|
| 1,046 | Individual | Case-control in cohort, HI and CA, U.S. | MEC | MEC |
| 160 | Individual | Case-control in cohort, HI and CA, U.S. | MEC | MEC |
| 326 | Individual | Case-control, Los Angeles County, CA, U.S. | Los Angeles County Cancer Surveillance Program | Los Angeles County, neighborhood walk algorithm and the MEC |
| 311 | Individual | Case-control, Houston, TX, U.S. | Houston Medical Center | Random-digit-dialing or hospital visitors |
| 255 | Individual | Case-control from SA, TX | Incident and Prevalent cases from SABOR | SABOR |
| 3,141 | Summary | Cohort, CA, US | Latino | RPGEH, CMHS |
| 3,606 | Summary | Prospective longitudinal cohort from New York, NY | Mount Sinai Medical Center in the city of New York, NY | Mount Sinai Medical Center in the city of New York, NY |
| 17,560 | Summary | Prospective cohort of veterans | From Veterans Affairs Central Cancer | MVP participants without any prostate |

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|---|---|---|---|---|
| 1,005 | Individual | Case-control in cohort, HI and CA, U.S. | MEC | MEC |

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|---|---|---|---|---|
| 596 | Individual | Shanghai, China | Cases were hospital based with pathological diagnosis | cancer-free controls were recruited from the community or hospitals |
| 202 | Individual | Kuala Lumpur, Malaysia | Patients attended the outpatient urology or uro-onco clinic at | Population-based, age matched (5-year groups), ascertained |
| 89,536 | Summary | Case-control, Japan | Cohort participants with BBJ | Cohort participants with BBJ |
| 2,938 | Summary | Cohort, CA, US | Asian | RPGEH, CMHS |
| 1,513 | Summary | Nested case-control, Bethesda, USA | Men with a confirmed diagnosis of prostate cancer from the PLCO | Controls were men enrolled in the PLCO Cancer Screening Trial |

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|---|---|---|---|---|
| 10,980 | Individual | Case-control, Massachusetts, US | Incident or prevalent prostate cancer cases within the MGB hospital system | Prostate cancer-free controls within the MGB hospital system |
| 10,537 | Individual | Hospital based case-control, Michigan, USA | Cases were ICD code based (PheWAS code system, at least one | Controls were ICD code based (PheWAS code system) |
| 28,542 | Individual | Estonian Biobank, Tartu, Estonia | Estonian Biobank | Estonian Biobank |
| 228 | Individual | Men of African Descent and Carcinoma of the Prostate | Hôpital Général de Grand Yoff/Institut de Formation et de | Hôpital Général de Grand Yoff/Institut de Formation et de |
| 212 | Individual | Men of African Descent and Carcinoma of the Prostate | 37 Military Hospital, Accra, Ghana | 37 Military Hospital, Accra, Ghana |
| 330 | Individual | Men of African Descent and Carcinoma of the Prostate | Korle-Bu Teaching Hospital, Accra, Ghana | Korle-Bu Teaching Hospital, Accra, Ghana |
| 177 | Individual | Men of African Descent and Carcinoma of the Prostate | University College Hospital, Ibadan, Nigeria | University College Hospital, Ibadan, Nigeria |
| 153 | Individual | Men of African Descent and Carcinoma of the Prostate | University of Abuja Teaching Hospital, Abuja, Nigeria | University of Abuja Teaching Hospital, Abuja, Nigeria |
| 938 | Individual | Men of African Descent and Carcinoma of the Prostate | WITS Health Consortium/National Health Laboratory | WITS Health Consortium/National Health Laboratory |
| 122 | Individual | Men of African Descent and Carcinoma of the Prostate | Stellenbosch University, Cape Town, South Africa | Stellenbosch University, Cape Town, South Africa |
| 471 | Individual | Case-control, Massachusetts, US | Incident or prevalent prostate cancer cases within the MGB hospital system | Prostate cancer-free controls within the MGB hospital system |
| 450 | Individual | Hospital based case-control, Michigan, USA | Cases were ICD code bases (PheWAS code system, at least one | Controls were ICD code bases (PheWAS code system) |

| Study Reference |
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| SUN study = Michael A, Zylstra J, Pandha H. (2011) 'The sun study-a biobank of sequential blood samples from patients with prostate cancer'. WILEY- |
| ProMPT study-Molecular mechanisms and the development of novel treatment strategies in progressing prostate cancer-Northern(and Bristol) |
| The ProtecT trial: Evaluating the effectiveness of treatment for clinically localized Prostate Cancer (http://www.epi.bris.ac.uk/protect) |
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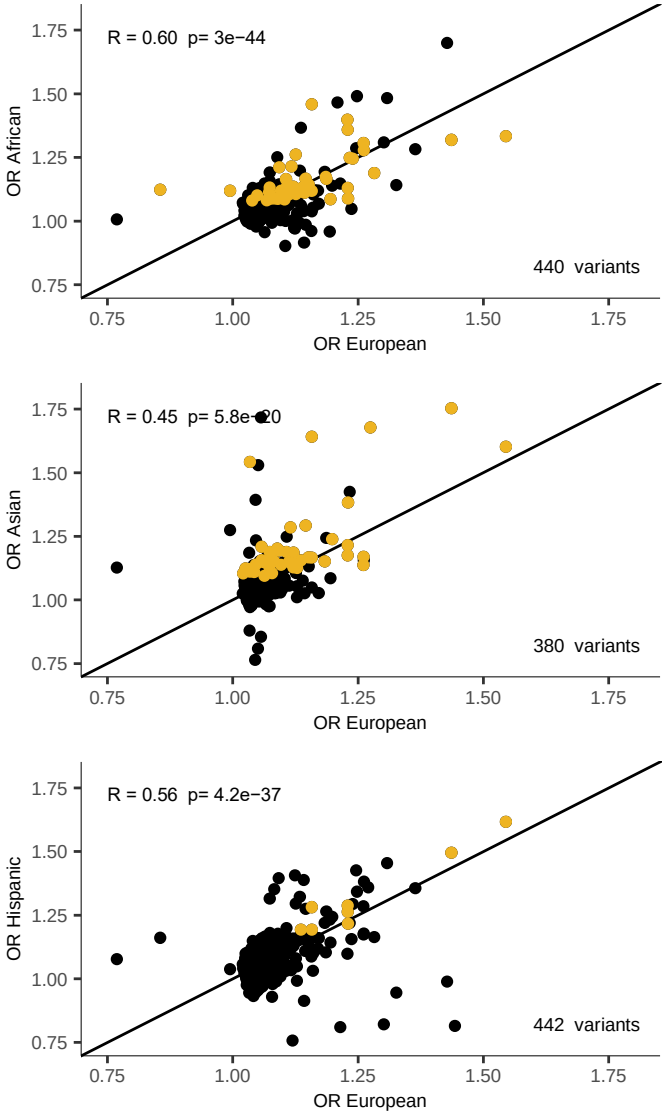
cluded to prevent sample overlap

asus or Oncoarray

## Supplementary Note

## Supplementary Figures




**Supplementary Figure 1.** Comparison of ancestry-specific ORs between European and African, Asian, and Hispanic populations, respectively. Variants present in both populations are compared; the number of variants is denoted in the lower right corner. Genome-wide significant variants among African, Asian, or Hispanic populations are highlighted in orange. The Pearson's correlation coefficient between effect sizes and corresponding p-value are denoted in the upper left in each sub-panel.

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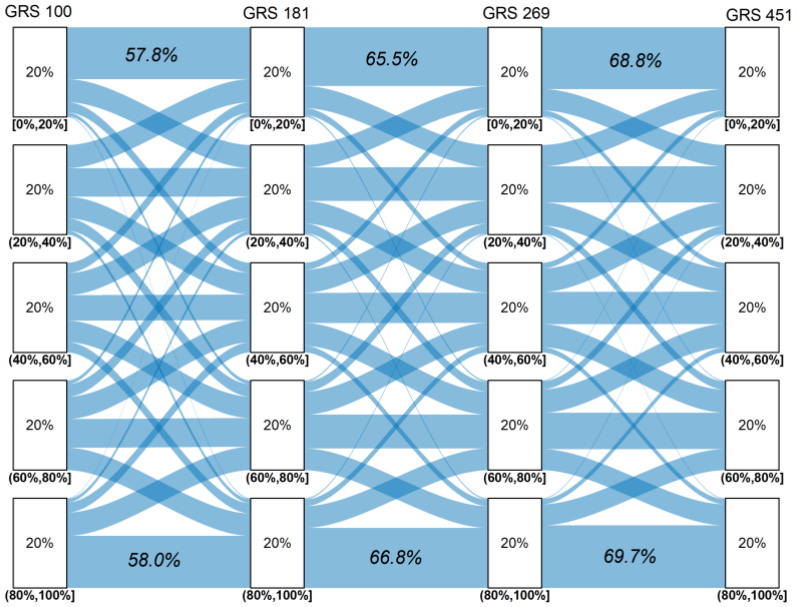


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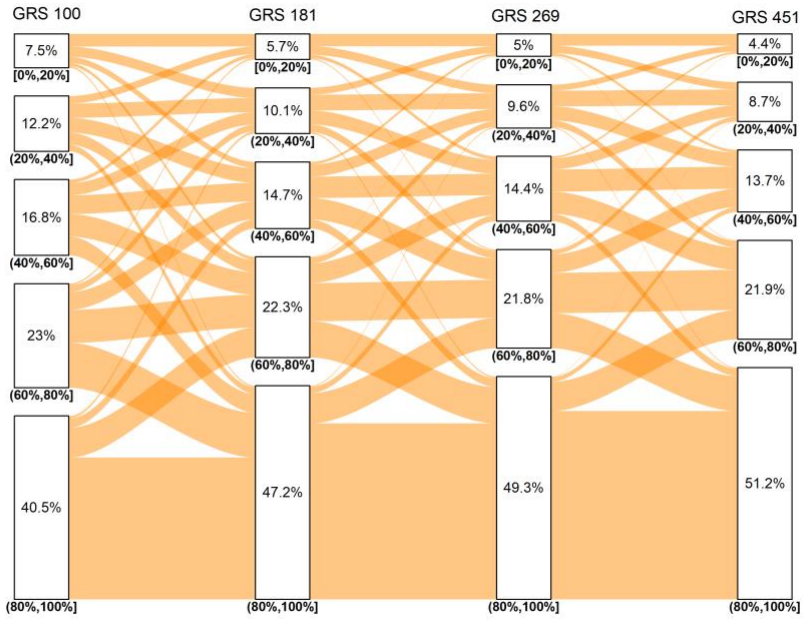
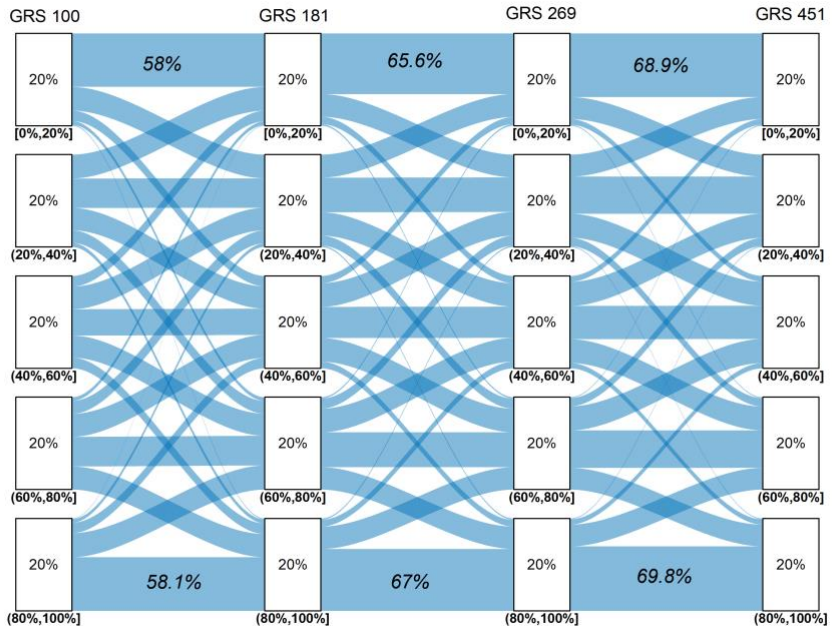



**Supplementary Figure 2.** Sankey diagram of GRS risk categorization based on $GRS_{100}$, $GRS_{181}$, $GRS_{269}$, and $GRS_{451}$ in the multi-ancestry sample. (a) GRS quantiles in all controls; (b) GRS quantiles in all cases. Percentage of individuals in each GRS quantile are labelled in corresponding boxes. Percentage of controls that remain in the lowest quintile [0%, 20%] and highest quintile (80%, 100%] from a previous to a more current GRS are indicated on corresponding flows in (a). In (b), the highest GRS quintile contains 51.2% of the cases.

(a)

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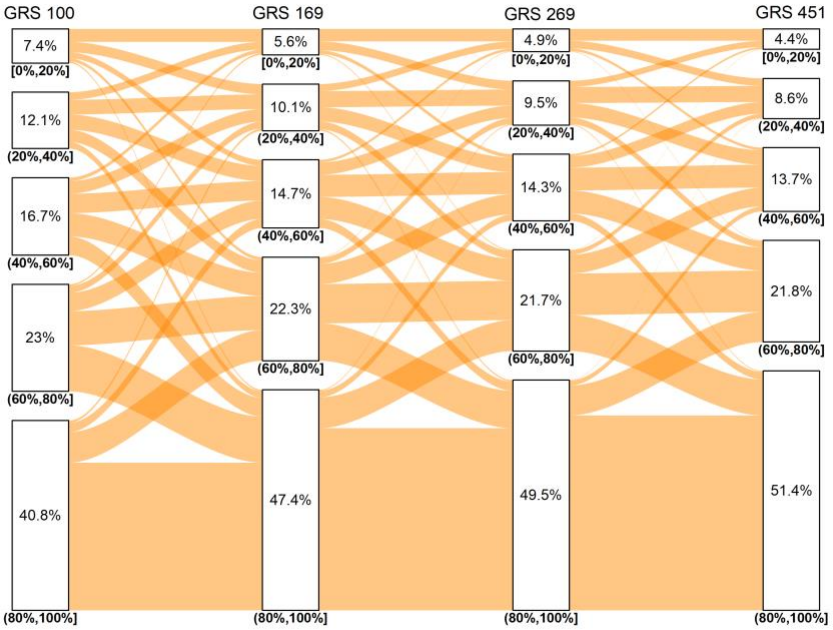
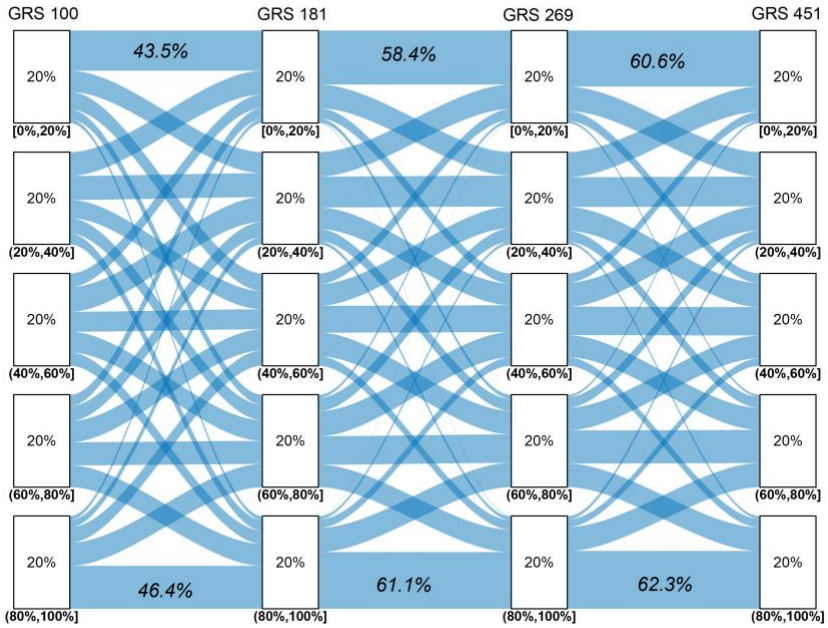



**Supplementary Figure 3.** Sankey diagram of GRS risk categorization based on $GRS_{100}$, $GRS_{181}$, $GRS_{269}$, and $GRS_{451}$ in the European ancestry sample. (a) GRS quantiles in all controls; (b) GRS quantiles in all cases.

(a)

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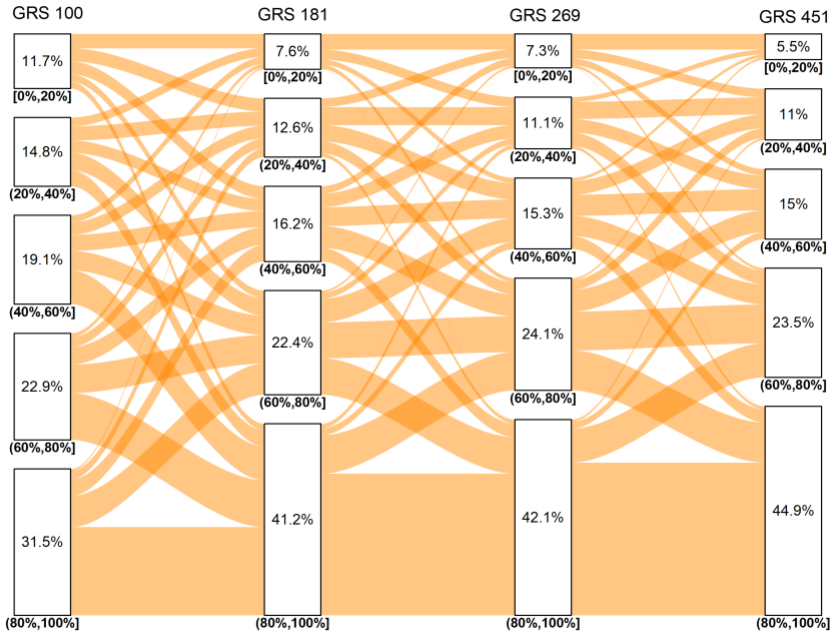


**Supplementary Figure 4.** Sankey diagram of GRS risk categorization based on $GRS_{100}$, $GRS_{181}$, $GRS_{269}$, and $GRS_{451}$ in the African ancestry sample. (a) GRS quantiles in all controls; (b) GRS quantiles in all cases.

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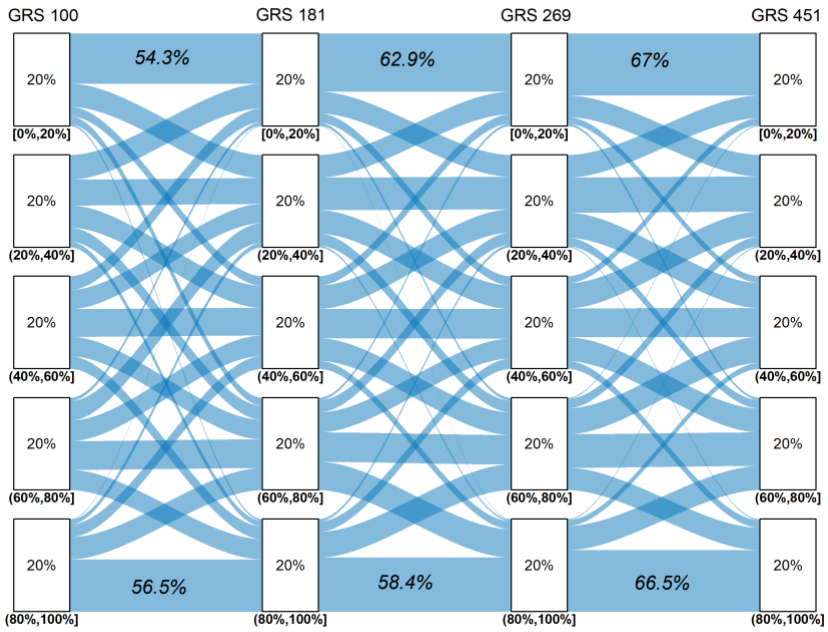


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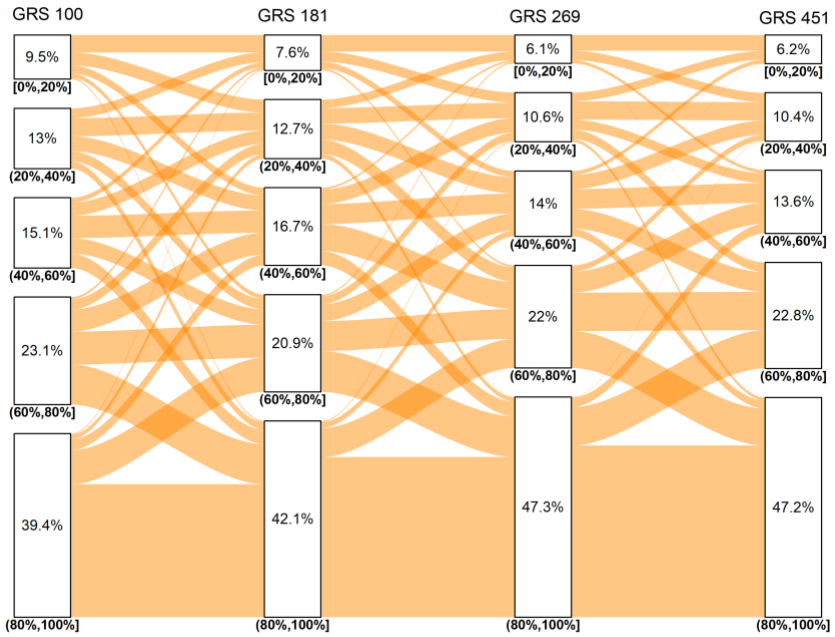
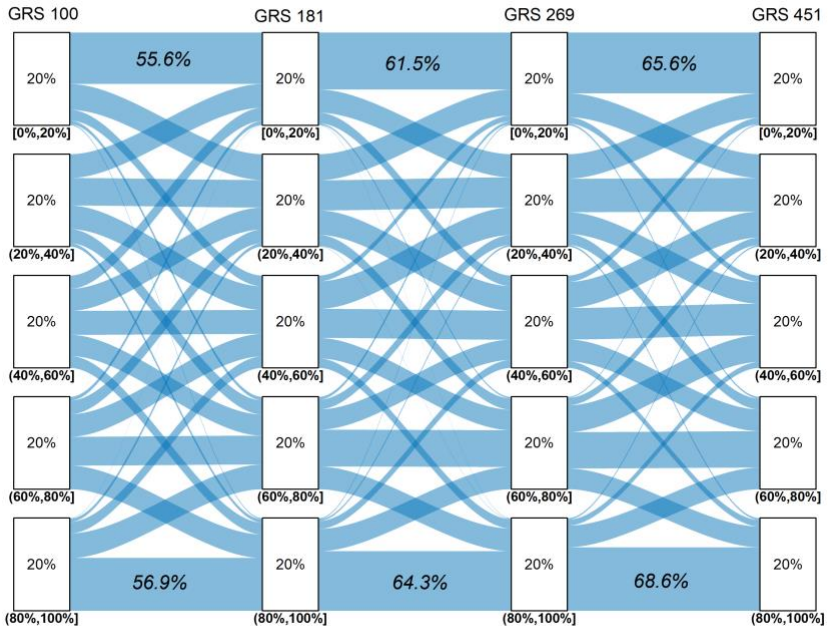



**Supplementary Figure 5.** Sankey diagram of GRS risk categorization based on $GRS_{100}$, $GRS_{181}$, $GRS_{269}$, and $GRS_{451}$ in the Asian ancestry sample. (a) GRS quantiles in all controls; (b) GRS quantiles in all cases.

(a)

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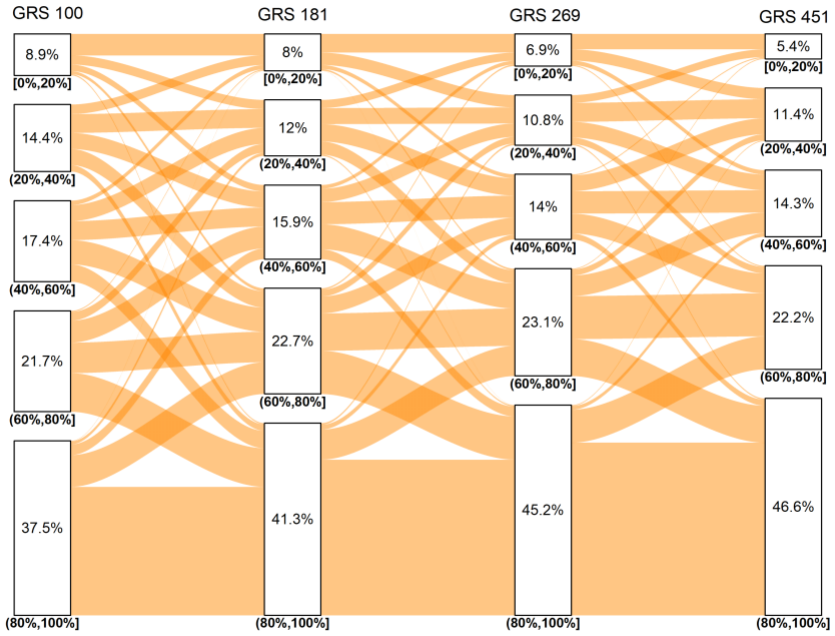
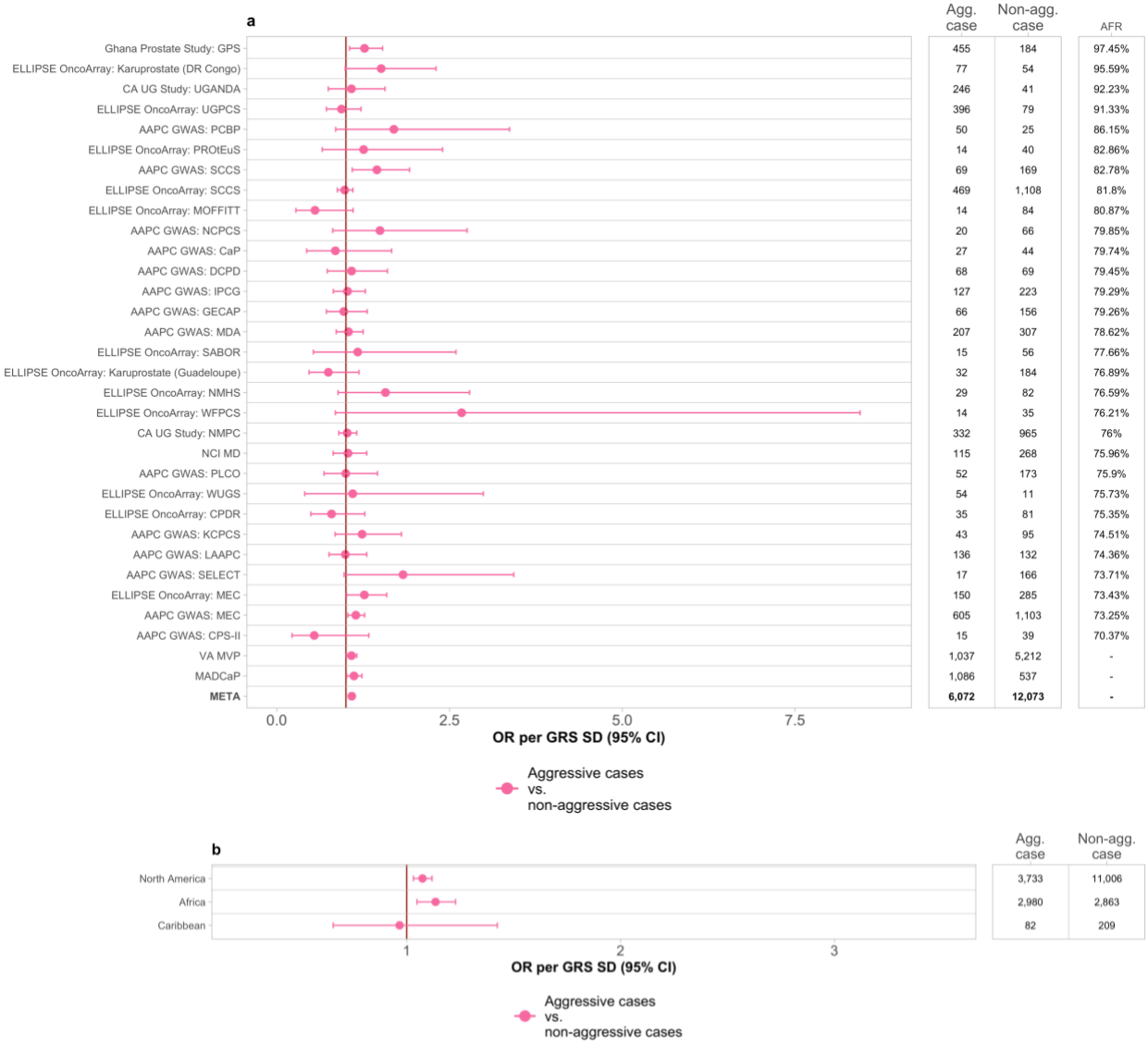



**Supplementary Figure 6.** Sankey diagram of GRS risk categorization based on $GRS_{100}$, $GRS_{181}$, $GRS_{269}$, and $GRS_{451}$ in the Hispanic sample. (a) GRS quantiles in all controls; (b) GRS quantiles in all cases.




**Supplementary Figure 7.** Associations of GRS451 with aggressive vs. non-aggressive prostate cancer (a) by sub-study in African ancestry, ranked by percentage of African ancestry in the controls in each study; (b) by continent in African ancestry.

**Acknowledgements**

CRUK and PRACTICAL consortium

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The Prostate Cancer Program of Cancer Council Victoria also acknowledge grant support from The National Health and Medical Research Council, Australia (126402, 209057, 251533, 396414, 450104, 504700, 504702, 504715, 623204, 940394, 614296,), VicHealth, Cancer Council Victoria, The Prostate Cancer Foundation of Australia, The Whitten Foundation, PricewaterhouseCoopers, and Tattersall's.

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Additional Collaborators can be found on the PRACTICAL website: http://practical.icr.ac.uk/.