ARTICLE

Analysis of Heritability and Shared Heritability Based on Genome-Wide Association Studies for 13 Cancer Types

Joshua N. Sampson, William A. Wheeler*, Meredith Yeager*, Orestis Panagiotou*, Zhaoming Wang*, Sonja I. Berndt*, Qing Lan*, Christian C. Abnet*, Laufey T. Amundadottir*, Jonine D. Figueroa*, Maria Teresa Landi*, Lisa Mirabello*, Sharon A. Savage*, Philip R. Taylor*, Immaculata De Vivo*, Katherine A. McGlynn*, Mark P. Purdue*, Preetha Rajaraman*, Hans-Olov Adami, Anders Ahlbom, Demetrius Albanes, Maria Fernanda Amary, She-Juan An, Ulrika Andersson, Gerald Andriole Jr., Irene L. Andrulis, Emanuele Angelucci, Stephen M. Ansell, Cecilia Arici, Bruce K. Armstrong, Alan A. Arslan, Melissa A. Austin, Dalsu Baris, Donald A. Barkauskas, Bryan A. Bassig, Nikolaus Becker, Yolanda Benavente, Simone Benhamou, Christine Berg, David Van Den Berg, Leslie Bernstein, Kimberly A. Bertrand, Brenda M. Birmann, Amanda Black, Heiner Boeing, Paolo Boffetta, Marie-Christine Boutron-Ruault, Paige M. Bracci, Louise Brinton, Angela R. Brooks-Wilson, H. Bas Bueno-de-Mesquita, Laurie Burdett, Julie Buring, Mary Ann Butler, Qiuyin Cai, Geraldine Cancel-Tassin, Federico Canzian, Alfredo Carrato, Tania Carreon, Angela Carta, John K. C. Chan, Ellen T. Chang, Gee-Chen Chang, I-Shou Chang, Jiang Chang, Jenny Chang-Claude, Chien-Jen Chen, Chih-Yi Chen, Chu Chen, Chung-Hsing Chen, Constance Chen, Hongyan Chen, Kexin Chen, Kuan-Yu Chen, Kun-Chieh Chen, Ying Chen, Ying-Hsiang Chen, Yi-Song Chen, Yuh-Min Chen, Li-Hsin Chien, María-Dolores Chirlaque, Jin Eun Choi, Yi Young Choi, Wong-Ho Chow, Charles C. Chung, Jacqueline Clavel, Françoise Clavel-Chapelon, Pierluigi Cocco, Joanne S. Colt, Eva Comperat, Lucia Conde,

Joseph M. Connors, David Conti, Victoria K. Cortessis, Michelle Cotterchio, Wendy Cozen, Simon Crouch, Marta Crous-Bou, Olivier Cussenot, Faith G. Davis, Ti Ding, W. Ryan Diver, Miren Dorronsoro, Laure Dossus, Eric J. Duell, Maria Grazia Ennas, Ralph L. Erickson, Maria Feychting, Adrienne M. Flanagan, Lenka Foretova, Joseph F. Fraumeni Jr., Neal D. Freedman, Laura E. Beane Freeman, Charles Fuchs, Manuela Gago-Dominguez, Steven Gallinger, Yu-Tang Gao, Susan M. Gapstur, Montserrat Garcia-Closas, Reina García-Closas, Randy D. Gascoyne, Julie Gastier-Foster, Mia M. Gaudet, J. Michael Gaziano, Carol Giffen, Graham G. Giles, Edward Giovannucci, Bengt Glimelius, Michael Goggins, Nalan Gokgoz, Alisa M. Goldstein, Richard Gorlick, Myron Gross, Robert Grubb III, Jian Gu, Peng Guan, Marc Gunter, Huan Guo, Thomas M. Habermann, Christopher A. Haiman, Dina Halai, Goran Hallmans, Manal Hassan, Claudia Hattinger, Qincheng He, Xingzhou He, Kathy Helzlsouer, Brian Henderson, Roger Henriksson, Henrik Hjalgrim, Judith Hoffman-Bolton, Chancellor Hohensee, Theodore R. Holford, Elizabeth A. Holly, Yun-Chul Hong, Robert N. Hoover, Pamela L. Horn-Ross, G. M. Monawar Hosain, H. Dean Hosgood III, Chin-Fu Hsiao, Nan Hu, Wei Hu, Zhibin Hu, Ming-Shyan Huang, Jose-Maria Huerta, Jen-Yu Hung, Amy Hutchinson, Peter D. Inskip, Rebecca D. Jackson, Eric J. Jacobs, Mazda Jenab, Hyo-Sung Jeon, Bu-Tian Ji, Guangfu Jin, Li Jin, Christoffer Johansen, Alison Johnson, Yoo Jin Jung, Rudolph Kaaks, Aruna Kamineni, Eleanor Kane, Chang Hyun Kang, Margaret R. Karagas, Rachel S. Kelly, Kay-Tee Khaw, Christopher Kim, Hee Nam Kim, Jin Hee Kim, Jun Suk Kim, Yeul Hong Kim, Young Tae Kim, Young-Chul Kim, Cari M. Kitahara, Alison P. Klein, Robert J. Klein, Manolis Kogevinas, Takashi Kohno, Laurence N. Kolonel, Charles Kooperberg, Anne Kricker, Vittorio Krogh, Hideo Kunitoh, Robert C. Kurtz, Sun-Seog Kweon, Andrea LaCroix, Charles Lawrence, Fernando Lecanda, Victor Ho Fun Lee, Donghui Li, Haixin Li, Jihua Li, Yao-Jen Li, Yuqing Li, Linda M. Liao, Mark Liebow, Tracy Lightfoot, Wei-Yen Lim, Chien-Chung Lin, Dongxin Lin, Sara Lindstrom, Martha S. Linet, Brian K. Link, Chenwei Liu, Jianjun Liu, Li Liu, Börje Ljungberg, Josep Lloreta, Simonetta Di Lollo, Daru Lu, Eiluv Lund, Nuria Malats, Satu Mannisto, Loic Le Marchand, Neyssa Marina, Giovanna Masala, Giuseppe Mastrangelo, Keitaro Matsuo, Marc Maynadie, James McKay, Roberta McKean-Cowdin, Mads Melbye, Beatrice S. Melin,

Dominique S. Michaud, Tetsuya Mitsudomi, Alain Monnereau, Rebecca Montalvan, Lee E. Moore, Lotte Maxild Mortensen, Alexandra Nieters, Kari E. North, Anne J. Novak, Ann L. Oberg, Kenneth Offit, In-Jae Oh, Sara H. Olson, Domenico Palli, William Pao, In Kyu Park, Jae Yong Park, Kyong Hwa Park, Ana Patiño-Garcia, Sofia Pavanello, Petra H. M. Peeters, Reury-Perng Perng, Ulrike Peters, Gloria M. Petersen, Piero Picci, Malcolm C. Pike, Stefano Porru, Jennifer Prescott, Ludmila Prokunina-Olsson, Biyun Qian, You-Lin Qiao, Marco Rais, Elio Riboli, Jacques Riby, Harvey A. Risch, Cosmeri Rizzato, Rebecca Rodabough, Eve Roman, Morgan Roupret, Avima M. Ruder, Silvia de Sanjose, Ghislaine Scelo, Alan Schned, Fredrick Schumacher, Kendra Schwartz, Molly Schwenn, Katia Scotlandi, Adeline Seow, Consol Serra, Massimo Serra, Howard D. Sesso, Veronica Wendy Setiawan, Gianluca Severi, Richard K. Severson, Tait D. Shanafelt, Hongbing Shen, Wei Shen, Min-Ho Shin, Kouya Shiraishi, Xiao-Ou Shu, Afshan Siddiq, Luis Sierrasesúmaga, Alan Dart Loon Sihoe, Christine F. Skibola, Alex Smith, Martyn T. Smith, Melissa C. Southey, John J. Spinelli, Anthony Staines, Meir Stampfer, Marianna C. Stern, Victoria L. Stevens, Rachael S. Stolzenberg-Solomon, Jian Su, Wu-Chou Su, Malin Sund, Jae Sook Sung, Sook Whan Sung, Wen Tan, Wei Tang, Adonina Tardón, David Thomas, Carrie A. Thompson, Lesley F. Tinker, Roberto Tirabosco, Anne Tjønneland, Ruth C. Travis, Dimitrios Trichopoulos, Fang-Yu Tsai, Ying-Huang Tsai, Margaret Tucker, Jenny Turner, Claire M. Vajdic, Roel C. H. Vermeulen, Danylo J. Villano, Paolo Vineis, Jarmo Virtamo, Kala Visvanathan, Jean Wactawski-Wende, Chaoyu Wang, Chih-Liang Wang, Jiu-Cun Wang, Junwen Wang, Fusheng Wei, Elisabete Weiderpass, George J. Weiner, Stephanie Weinstein, Nicolas Wentzensen, Emily White, Thomas E. Witzig, Brian M. Wolpin, Maria Pik Wong, Chen Wu, Guoping Wu, Junjie Wu, Tangchun Wu, Wei Wu, Xifeng Wu, Yi-Long Wu, Jay S. Wunder, Yong-Bing Xiang, Jun Xu, Ping Xu, Pan-Chyr Yang, Tsung-Ying Yang, Yuanqing Ye, Zhihua Yin, Jun Yokota, Ho-Il Yoon, Chong-Jen Yu, Herbert Yu, Kai Yu, Jian-Min Yuan, Andrew Zelenetz, Anne Zeleniuch-Jacquotte, Xu-Chao Zhang, Yawei Zhang, Xueying Zhao, Zhenhong Zhao, Hong Zheng, Tongzhang Zheng, Wei Zheng, Baosen Zhou, Meng Zhu, Mariagrazia Zucca, Simina M. Boca[†], James R. Cerhan[†], Giovanni M. Ferri[†], Patricia Hartge[†], Chao Agnes Hsiung[†], Corrado Magnani[†], Lucia Miligi[†], Lindsay M. Morton[†], Karin E. Smedby[†], Lauren R. Teras[†], Joseph Vijai[†], Sophia S. Wang[†], Paul Brennan[†],

Neil E. Caporaso†, David J. Hunter†, Peter Kraft†, Nathaniel Rothman†, Debra T. Silverman†, Susan L. Slager†, Stephen J. Chanock‡, Nilanjan Chatterjee‡

Affiliations of authors: Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD (JNS, OP, SIB, QL, CCA, LTA, JDF, MTL, LM, SAS, PRT, KAM, PR, DA, DB, BAB, AB, LBr, WHC, CCC, JSC, JFFJr, NDF, LEBF, MGC, AMG, RNH, NH, WH, PDI, BTJ, CK, CMK, LML, MSL, LEM, LPO, RSSS, WeiT, MT, CWa, SW, NW, KY, PH, LMM, NEC, NR, DTS, SJC, NC); Information Management Services, Silver Spring, MD (WAW, CG); Cancer Genomics Research Laboratory, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Gaithersburg, MD (MY, ZW, LBu, AH, CLi); Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (IDV, KAB, BMB, CoC, MCB, CF, EG, SL, JP, MSt, DJH); Department of Epidemiology, Harvard School of Public Health, Boston, MA (IDV, OA, KAB, CoC, MCB, CoC, MCB, EG, RSK, SL, JP, HDS, MSt, DTr, DJH, PK); Ontario Health Study, Toronto, Ontario, Canada (MPP); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (HOA, EWe); Unit of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (AA, MF); UCL Cancer Institute, London, UK (MFA, AMF, DH); Royal National Orthopaedic Hospital NHS Trust, Stanmore, Middlesex, UK (MFA, AMF, DH, RT); Guangdong Lung Cancer Institute, Guangdong Provincial Key Laboratory of Translational Medicine in Lung Cancer, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China (SJA, JS, YLW, XCZ); Department of Radiation Sciences, Oncology, Umea University, Umea, Sweden (UA, RH, BSM); Division of Urologic Surgery, Washington University School of Medicine, Saint Louis, MO (GAJr, RGIII); Litwin Centre for Cancer Genetics, University of Toronto, Ontario, Canada (ILA, NG, JSW); Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada (ILA, SG, NG, JSW); Hematology Unit, Ospedale Oncologico di Riferimento Regionale A. Businco, Cagliari, Italy (EA); Department of Medicine, Mayo Clinic, Rochester, MN (SMA, TMH, ML, AJN, TDS, CAT, TEW); Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy (CA, AnC, SPo); Sydney School of Public Health, The University of Sydney, Sydney, New South Wales, Australia (BKA, AKr); Department of Obstetrics and Gynecology, New York University School of Medicine, New York, NY (AAA); Department of Environmental Medicine, New York University School of Medicine, New York, NY (AAA, AZJ); Department of Population Health, New York University School of Medicine, New York, NY (AAA, AZJ); Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY (AAA, AZJ); Department of Epidemiology, University of Washington, Seattle, WA (MAA, EWh); Department of Preventive Medicine, USC Keck School of Medicine, University of Southern California, Los Angeles, CA (DAB, DVDB, DC, VKC, WC, BH, RMC, FS, VWS, MCS); Department of Environmental Health Sciences, Yale School of Public Health, New Haven, CT (BAB, YZ, TZ); Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Baden-Württemberg, Germany (NB, JCC, RK); Unit of Infections and Cancer (UNIC), Cancer Epidemiology Research Programme, Institut Catala d'Oncologia, IDIBELL, Barcelona, Spain (YB, SdS); Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain (YB, MDC, MD, JoL, SdS, ATa); Institut national de la sante et de la recherche medicale, U946, Foundation Jean Dausset Centre d'Etude du Polymorphisme Humain (CEPH), Paris, France (SB); Centre National de la Receherche Scientifique, UMR8200, Institut Gustave-Roussy, Villejuif, France (SB); Early Detection Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD (CB); Norris Comprehensive Cancer Center, USC Keck School of Medicine, University of Southern California, Los Angeles, CA (DVDB, DC, VKC, CAH, MCS); Department of Cancer Etiology, Beckman Research Institute of City of Hope, Duarte, CA (LBe, SSW); Department of Epidemiology, German Institute for Human Nutrition, Potsdam, Germany (HB); The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY (PBo); Inserm, Centre for research in Epidemiology and Population Health (CESP), U1018, Nutrition, Hormones and Women's Health team, F-94805, Villejuif, France (MCBR, FCC, LD); Université Paris Sud, UMRS 1018, F-94805, Villejuif, France (MCBR, JCl, FCC, LD, AM); Institut Gustave Roussy, F-94805, Villejuif, France (MCBR, FCC, LD); Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA (PMB, EAH); Genome Sciences Centre, BC Cancer Agency, Vancouver, British Columbia, Canada (ARBW); Department of Biomedical Physiology and Kinesiology, Simon Fraser University, Burnaby, British Columbia, Canada (ARBW); National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands (HBBdM); Department of Gastroenterology and Hepatology, University Medical Centre Utrecht, Utrecht, the Netherlands (HBBdM); Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (JB, JMG, HDS); Division of Aging, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MD (JB, JMG, HDS); Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Cincinnati, OH (MAB, TC, AMR); Department of Medicine, Vanderbilt University Medical Center, Nashville, TN (QC, XOS, WZ); Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN (QC, XOS, WZ); Centre de Recherche sur les Pathologies Prostatiques, Paris, France (GCT, EC, OC, MRo); UPMC Univ Paris 06, GRC n°5, ONCOTYPE-URO, Paris, France (GCT, EC, OC, MRo); Genomic Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany (FC, CR); Ramon y Cajal University Hospital, Madrid, Spain (AlC); Department of Pathology, Queen Elizabeth Hospital, Hong Kong, China (JKCC); Division of Epidemiology, Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA (ETC); Center for Epidemiology and Computational Biology, Health Sciences, Exponent, Inc., Menlo Park, CA (ETC); Department of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan (GCC); Department of Internal Medicine, Division of Chest Medicine, Taichung Veterans General Hospital, Taichung, Taiwan (GCC, KCC, TYY); National Institute of Cancer Research, National Health Research Institutes, Zhunan, Taiwan (ISH, CHC, FYT); Department of Etiology and Carcinogenesis, Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (JCh, DLin, WenT, CWu); Genomic Research Center, Taipei, Taiwan (CJC, YJL); Institute of Medicine, Division of Thoracic Surgery, Department of Surgery, Chung Shan Medical University, Chung Shan Medical University Hospital, Taichung, Taiwan (CYC); Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA (ChC, CHo); Department of Nutrition, Harvard School of Public Health, Boston, MA (ChC, EG, MSt, DJH); Ministry of Education Key Laboratory of Contemporary Anthropology, School of Life Sciences, Fudan University, Shanghai, China (HC, LJ, DLu, JCW, JWu, XZ, ZZ); Department of Epidemiology and Biostatistics, Key Laboratory of Cancer Prevention and Therapy, National Clinical Research Center of Cancer, Medical University Cancer Institute and Hospital, Tianjin, China (KC, HL, HZ); Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan (KYC, CJY); Saw Swee Hock School of Public Health, National University of Singapore, Republic of Singapore (YC, WYL, ASe); Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan (YHC, YSC, LHC, CFH, CAH); Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan (YMC, RPP); Taipei Cancer Center, Taipei Medical University, Taipei, Taiwan (YMC); Department of Epidemiology, Murcia Regional Health Authority, IMIB-Arrixaca, Murcia, Spain (MDC, JMH); Cancer Research Center, Kyungpook National University Medical Center, Daegu, Republic of Korea (JEC, YYC); Environmental epidemiology of Cancer Group, Inserm, Centre for research in Epidemiology and Population Health (CESP), U1018, Villejuif Cedex, France (JC, AM); Department of Public Health, Clinical and Molecular Medicine, University of Cagliari, Monserrato, Cagliari, Italy (PC, MRa); Department of Urology, Pitié-Salpétrière, Assistance-Publique Hôpitaux de Paris (APHP), Paris, France (EC, MRo); Department of Pathology, Pitié-Salpétrière, Assistance-Publique Hôpitaux de Paris (APHP), Paris, France (EC); Department of Epidemiology, School of Public Health and Comprehensive Cancer Center, Birmingham, AL (LC, JR, CFS); Division of Environmental Health Sciences, University of California Berkeley School of Public Health, Berkeley, CA (LC, JR, CFS, MTS); Center for Lymphoid Cancer, BC Cancer Agency, Vancouver, British Columbia, Canada (JMC, RDG); Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada (JMC); Department of Obstetrics and Gynecology, University of Southern California, Los Angeles, CA (VKC); Cancer Care Ontario, Toronto, Ontario, Canada (MC); Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada (MC); Department of Health Sciences, University of York, York, UK (SC, EK, TL, ER, ASm); Department of Urology, Tenon, Assistance-Publique Hôpitaux de Paris (APHP), Paris, France (OC); School of Public Health, University of Alberta, Edmonton, Alberta, Canada (FGD); Shanxi Cancer Hospital, Taiyuan, Shanxi, China (TD); Epidemiology Research Program, American Cancer Society, Atlanta, GA (WRD, SMG, MMG, EJJ, VLS, CT); Health Department, BioDonostia Research Institute, Basque Region, Spain (MD); Unit of Nutrition, Environment and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO), Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain (EJD); Department of Biomedical Science, University of Cagliari, Monserrato, Cagliari, Italy (MGE, MZ); Walter Reed Army Institute of Research, Silver Spring, MD (RLE); Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute and MF MU, Brno, Czech Republic (LF); Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA (CF, BMW); Genomic Medicine Group, Galician Foundation of Genomic Medicine, Servicio Galego de Saude (SERGAS), Instituto de Investigación Sanitaria de Santiago (IDIS), Santiago de Compostela, Spain (MGD); Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China (YTG); Division of Genetics and Epidemiology, Institute of Cancer Research, London, UK (MGC); Unidad de Investigación, Hospital Universitario de Canarias, La Laguna, Spain (RGC); Department of Pathology, University of British Columbia, Vancouver, British Columbia, Canada (RDG); Nationwide Children's Hospital, Columbus, OH (JGF); Department of Pathology and Pediatrics, The Ohio State University, Columbus, OH (JGF); Massachusetts Veteran's Epidemiology, Research and Information Center, Geriatric Research Education and Clinical Center, Veterans Affairs Boston Healthcare System, Boston, MA (JMG); Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, Victoria, Australia (GGG, GSe); Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Carlton, Victoria, Australia (GGG, GSe); Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden (BG); Department of Radiology, Oncology and Radiation Science, Uppsala University, Uppsala, Sweden (BG); Department of Oncology, Sidney Kimmel Cancer Center and Johns Hopkins University, Baltimore, MD (MGo); Department of Pathology, Sidney Kimmel Cancer Center and Johns Hopkins University, Baltimore, MD (MGo); Department of Medicine, Sidney Kimmel Cancer Center and Johns Hopkins University, Baltimore, MD (MGo); Albert

Einstein College of Medicine, The Children's Hospital at Montefiore, Bronx, NY (RG); Laboratory of Medicine and Pathology, University of Minnesota, Minneapolis, MN (MGr); Department of Epidemiology, M.D. Anderson Cancer Center, Houston, TX (JG, XW, YY); Department of Epidemiology, School of Public Health, China Medical University, Shenyang, China (PG, QH, WW, ZY, BZ); Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK (MGu, PHMP); Institute of Occupational Medicine and Ministry of Education Key Lab for Environment and Health, School of Public Health, Huazhong University of Science and Technology, Wuhan, China (HG, TW); Department of Public Health and Clinical Medicine, Nutritional Research, Umea University, Umea, Sweden (GH); Department of Gastrointestinal Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX (MH, DLi); Laboratory of Experimental Oncology, Orthopaedic Rizzoli Institute, Bologna, Italy (CHa, PP, KS, MSe); Chinese Center for Disease Control and Prevention, Beijing, China (XH); Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (KH, JHB, APK, KV); Department of Epidemiology Research, Division of Health Surveillance and Research, Statens Serum Institut, Copenhagen, Denmark (HH, MM); Department of Biostatistics, Yale School of Public Health, New Haven, CT (TRH); Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea (YCH); Cancer Prevention Institute of California, Fremont, CA (PLHR); New Hampshire State Cancer Registry, Concord, NH (GMMH); Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY (HDHIII); Taiwan Lung Cancer Tissue/Specimen Information Resource Center, National Health Research Institutes, Zhunan, Taiwan (CFH); Jiangsu Collaborative Innovation Center For Cancer Personalized Medicine, Nanjing Medical University, Nanjing, China (ZH, GJ, HS, WS, MZ); Jiangsu Key Laboratory of Cancer Biomarkers, Prevention and Treatment, Cancer Center, School of Public Health, Nanjing Medical University, Nanjing, China (ZH, GJ, HS, WS, MZ); Department of Internal Medicine, Kaohsiung Medical University Hospital, School of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan (MSH, JYH); Division of Endocrinology, Diabetes and Metabolism, The Ohio State University, Columbus, OH (RDJ); International Agency for Research on Cancer (IARC), Lyon, France (MJ, JM, GSc, PBr); Molecular Diagnostics and Imaging Center, Kyungpook National University, Daegu, Republic of Korea (HSJ); Unit of Survivorship, The Danish Cancer Society Research Center, Copenhagen, Denmark (CJ); Vermont Cancer Registry, Burlington, VT (AJ); Department of Thoracic and Cardiovascular Surgery, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea (YJJ, CHK, YTK, IKP); Group Health Research Institute, Seattle, WA (AKa); Geisel School of Medicine, Dartmouth College, Hanover, NH (MRK, ASc); MRC-PHE Centre for Environment and Health, School of Public Health, Imperial College London, London, UK (RSK, PV); School of Clinical Medicine, University of Cambridge, UK (KTK); Center for Creative Biomedical Scientists, Chonnam National University, Gwangju, Republic of Korea (HNK); Department of Environmental Health, Graduate School of Public Health, Seoul National University, Seoul, Republic of Korea (JHK); Department of Internal Medicine, Division of Medical Oncology, College of Medicine, Korea University Guro Hospital, Seoul, Republic of Korea (JSK); Department of Internal Medicine, Division of Oncology/Hematology, College of Medicine, Korea University Anam Hospital, Seoul, Republic of Korea (YHK, KHP); Lung and Esophageal Cancer Clinic, Chonnam National University Hwasun Hospital, Hwasun-eup, Republic of Korea (YCK, IJO); Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Republic of Korea (YCK, IJO); Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD (APK); Icahn Institute for Genomics and Multiscale Biology, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY (RJK); Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain (MK); Municipal Institute of Medical Research, (IMIM - Hospital del Mar), Barcelona, Spain (MK); National School of Public Health, Athens, Greece (MK); Division of Genome Biology, National Cancer Center Research Institute, Tokyo, Japan (TK, KS); The Cancer Research Center of Hawaii, Honolulu, HI (LNK); Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy (VK); Department of Medical Oncology, Japanese Red Cross Medical Center, Tokyo, Japan (HK); Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY (RCK, KO, DJV, AZ, JVo); Jeonnam Regional Cancer Center, Chonnam National University Hwasun Hospital, Hwasun-eup, Republic of Korea (SSK); Department of Preventive Medicine, Chonnam National University Medical School, Gwangju, Republic of Korea (SSK, MHS); Westat, Rockville, MD (CLa, RM); Department Of Pediatrics, University Clinic of Navarra, Universidad de Navarra, Pamplona, Spain (FL, APG, LS); Department of Clinical Oncology, The University of Hong Kong, Hong Kong, China (VHFL); Qujing Center for Diseases Control and Prevention, Sanjiangdadao, Qujing, China (JihL); Cancer Prevention Institute of California, Fremont, CA (YL); Department of Internal Medicine, National Cheng Kung University Medical College and Hospital, National Cheng Kung University, Tainan, Taiwan (CCL); Department of Internal Medicine, Carver College of Medicine, The University of Iowa, Iowa City, IA (PKL, GJW); Human Genetics, Genome Institute of Singapore, Singapore, Republic of Singapore (JiaL); Cancer Center, Union Hospital, Huazhong University of Science and Technology, Wuhan, China (LL); Department of Surgical and Perioperative Sciences, Urology and Andrology, Umea University, Umea, Sweden (BL); Department of Surgery and Translational Medicine, Section of Anatomo-Pathology, University of Florence, Florence, Italy (DSL); Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway (EL, EWe); Genetic and Molecular Epidemiology Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain (NM); Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland (SM, JaV); Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI (LLM, HY); Lucile Packard Children's Hospital, Stanford University, Palo Alto, CA (NM); Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute (ISPO), Florence, Italy (GioM, DP); Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy (GiuM, SPa); Division of Molecular Medicine, Aichi Cancer Research Institute, Nagoya, Japan (KM); EA 4184, Registre des Hémopathies Malignes de Côte d'Or, University of Burgundy and Dijon University Hospital, Dijon, France (MMa); Department of Medicine, Stanford University School of Medicine, Stanford, CA (MMe); Division of Biology and Medicine, Department of Epidemiology, Brown University, Providence, RI (DSM); School of Public Health, Imperial College London, London, UK (DSM, ER, ASi); Division of Thoracic Surgery, Kinki University School of Medicine, Sayama, Japan (TM); Registre des hémopathies malignes de la Gironde, Institut Bergonié, Bordeaux Cedex, France (AM); Section for Epidemiology, Aarhus University, Denmark (LMM); Department of Cardiology, Aalborg University Hospital, Denmark (LMM); Center for Chronic Immunodeficiency, University Medical Center Freiburg, Freiburg, Baden-Württemberg, Germany (AN); Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC (KEN); Carolina Center for Genome Sciences, University of North Carolina at Chapel Hill, Chapel Hill, NC (KEN); Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, MN (ALO); Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY (SHO, MCP); Division of Hematology and Oncology, Vanderbilt University Medical Center, Nashville, TN (WP); Lung Cancer Center, Kyungpook National University Medical Center, Daegu, Republic of Korea (JYP); 194Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands (PHMP, RCHV); Department of Primary Care and Public Health, School of Public Health, Imperial College London, London, UK (PHMP); Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, MN (GMP); Genomics Research Center, Academia Sinica, Taipei, Taiwan (BQ); Department of Epidemiology, Cancer Institute and Hospital, Chinese Academy of Medical Sciences, Beijing, China (YLQ); Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT (HAR); Department of Family Medicine and Public Health Sciences, Wayne State University, Detroit, MI (KS, RKS); Population Studies and Disparities Research Program, Karmanos Cancer Institute, Detroit, MI (KS); Maine Cancer Registry, Augusta, ME (MSc); Departament de Ciències Experimentals i de la Salut, Universitat Pompeu Fabra, Barcelona, Spain (CS); Human Genetics Foundation, Turin, Italy (GSe, PV); Department of Surgery, Division of Cardiothoracic Surgery, Queen Mary Hospital, Hong Kong, China (ADLS); Department of Pathology, University of Melbourne, Parkville, Victoria, Australia (MCS); Cancer Control Research, BC Cancer Agency, Vancouver, British Columbia, Canada (JJS); School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada (JJS); School of Nursing and Human Sciences, Dublin City University, Dublin, Ireland (ASt); National Cheng Kung University Medical College and Hospital, Tainan, Taiwan (WCS); Department of Surgical and Perioperative Sciences, Surgery, Umea University, Umea, Sweden (MSu); Cancer Research Institute, Korea University, Seoul, Republic of Korea (JSS); Department of Thoracic and Cardiovascular Surgery, Seoul St Mary's Hospital, Seoul, Republic of Korea (SWS); Instituto Universitario de Oncología, Universidad de Oviedo, Oviedo, Spain (ATa); The Kinghorn Cancer Centre, Garvan Institute of Medical Research, Darlinghurst, New South Wales, Australia (DTh); Danish Cancer Society Research Center, Copenhagen, Denmark (ATj); Cancer Epidemiology Unit, University of Oxford, Oxford, United Kingdom (RCT); Bureau of Epidemiologic Research, Academy of Athens, Athens, Greece (DTr); Hellenic Health Foundation, Athens, Greece (DTr); Department of Respiratory Thearpy, Chang Gung Memorial Hospital, Chiayi, Taiwan (YHT); Australian School of Advanced Medicine, Macquarie University, Sydney, New South Wales, Australia (JT); Department of Histopathology, Douglass Hanly Moir Pathology, Macquarie Park, New South Wales, Australia (JT); Prince of Wales Clinical School, University of New South Wales, Sydney, New South Wales, Australia (CMV); Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands (RCHV); Department of Social and Preventive Medicine, University at Buffalo, State University of New York, Buffalo, NY (JWW); Department of Pulmonary and Critical Care, Chang Gung Memorial Hospital, Taoyuan, Taiwan (CLW); State Key Laboratory of Genetic Engineering, School of Life Sciences, Fudan University, Shanghai, China (JCW); Centre for Genomic Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China (JWa); Department of Biochemistry, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China (JWa); China National Environmental Monitoring Center, Beijing, China (FW, GW); Cancer Registry of Norway, Oslo, Norway (EWe); Department of Genetic Epidemiology, Folkhalsan Research Center, Helsinki, Finland (EWe); Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (BMW); Department of Pathology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China (MPW); State Key Laboratory of Molecular Oncology, Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (CWu); Shanghai Cancer Institute, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China (YBX); School of Public Health, The University of Hong Kong, Hong Kong (JX); Department of Oncology, Wuhan Iron and Steel Corporation Staff Worker Hospital, Wuhan, China (PX); Department of Internal Medicine, National Taiwan University College of Medicine, Taipei, Taiwan (PCY); Institute of Predictive and Personalized Medicine of Cancer (IMPPC), Barcelona, Spain (JY);

Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea (HIY); University of Pittsburgh Cancer Institute, Pittsburgh, PA (JMY); Innovation Center for Biomedical Informatics, Georgetown University Medical Center, Washington, DC (JMB); Department of Oncology, Georgetown University Medical Center, Washington, DC (JMB); Department of Health Sciences Research, Mayo Clinic, Rochester, MN (JRC, SLS); Interdisciplinary Department of Medicine, University of Bari, Bari, Italy (GMF); CPO-Piemonte and Unit of Medical Statistics and Epidemiology, Department Translational Medicine, University of Piemonte Orientale, Novara, Italy (CM); Environmental and Occupational Epidemiology Unit, Cancer Prevention and Research Institute (ISPO), Florence, Italy (LM); Department of Medicine, Solna, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden (KES); Broad Institute of Harvard and MIT, Cambridge, MA (DJH); Department of Biostatistics, Harvard School of Public Health, Boston, MA (PK).

*Authors contributed equally to this work.
†Authors contributed equally to this work.
‡Authors contributed equally to this work.

Correspondence to: Joshua Sampson, PhD, Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, 7E594 Rockville, MD 20815 (e-mail: joshua.sampson@nih.gov) and Nilanjan Chatterjee, PhD, Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, 7E594 Rockville, MD 20815 (e-mail: nilanjan.chatterjee@nih.gov).

Abstract

Background: Studies of related individuals have consistently demonstrated notable familial aggregation of cancer. We aim to estimate the heritability and genetic correlation attributable to the additive effects of common single-nucleotide polymorphisms (SNPs) for cancer at 13 anatomical sites.

Methods: Between 2007 and 2014, the US National Cancer Institute has generated data from genome-wide association studies (GWAS) for 49 492 cancer case patients and 34 131 control patients. We apply novel mixed model methodology (GCTA) to this GWAS data to estimate the heritability of individual cancers, as well as the proportion of heritability attributable to cigarette smoking in smoking-related cancers, and the genetic correlation between pairs of cancers.

Results: GWAS heritability was statistically significant at nearly all sites, with the estimates of array-based heritability, h_l^2, on the liability threshold (LT) scale ranging from 0.05 to 0.38. Estimating the combined heritability of multiple smoking characteristics, we calculate that at least 24% (95% confidence interval [CI] = 14% to 37%) and 7% (95% CI = 4% to 11%) of the heritability for lung and bladder cancer, respectively, can be attributed to genetic determinants of smoking. Most pairs of cancers studied did not show evidence of strong genetic correlation. We found only four pairs of cancers with marginally statistically significant correlations, specifically kidney and testes ($\rho = 0.73$, SE = 0.28), diffuse large B-cell lymphoma (DLBCL) and pediatric osteosarcoma ($\rho = 0.53$, SE = 0.21), DLBCL and chronic lymphocytic leukemia (CLL) ($\rho = 0.51$, SE = 0.18), and bladder and lung ($\rho = 0.35$, SE = 0.14). Correlation analysis also indicates that the genetic architecture of lung cancer differs between a smoking population of European ancestry and a nonsmoking Asian population, allowing for the possibility that the genetic etiology for the same disease can vary by population and environmental exposures.

Conclusion: Our results provide important insights into the genetic architecture of cancers and suggest new avenues for investigation.

Studies of related individuals have consistently demonstrated that there is notable familial aggregation of cancer. The three largest studies, based on the Swedish Family-Cancer Database (1–3), the Utah Population and Cancer Registry Database (4,5), and the Icelandic Cancer Registry (6), have shown familial aggregation for cancer at nearly every anatomical site. For common cancers such as prostate, breast, and lung, the familial relative risk (FRR), defined as the increase in risk associated with each affected first-degree relative of an individual, is generally estimated to be below or around 2.0. In contrast, for some rare cancers occurring early in life, such as those of testes and bone, estimates of FRR can exceed 5. Although shared environmental factors contribute to this aggregation, studies of twins (7,8) and extended family members (6,9,10) have clearly identified a substantial genetic contribution, commonly known as heritability.

Genome-wide association studies (GWAS) have provided an opportunity to study the contribution of common single-nucleotide polymorphisms (SNPs) to the heritability of complex traits, including cancers. In addition to identifying specific susceptibility SNPs, novel mixed-effect modeling methods (11–13) can utilize GWAS data to quantify the additive heritability attributable to all common susceptibility SNPs captured by genotyping arrays, regardless of whether those SNPs individually have reached the stringent level of genome-wide statistical significance. Understanding the total contribution of common SNPs

will be instrumental for evaluating the potential clinical applications of genetics in risk stratification and for guiding future genetic studies of cancer(14,15).

Evidence also suggests that there is overlap between cancers with respect to their genetic architectures. Previous family studies have observed familial co-aggregation of cancers among certain sites (5,6), including pairs of cancers at neighboring sites, such as the colon and rectum, as well as for more distant and seemingly unrelated sites such as the cervix and esophagus (6). GWAS have also directly identified shared regions such as 8q24.1 and 5p15.33 (*TERT-CLPTM1L*) containing SNPs affecting cancer at multiple sites, while earlier studies have identified major genes such as *TP53* (16) and *BRCA* (17) containing highly penetrant rare variants affecting multiple cancers. Sites with overlapping genetic architectures may be studied together to understand shared biology and to increase power to detect susceptibility loci.

In this study, we performed an analysis of heritability and shared heritability for cancer at 13 different sites using data from case/control GWAS of more than 80 000 individuals carried out or reported to the US National Cancer Institute. We expand upon recent GWAS estimates of heritability (13) by nearly doubling the number of cases evaluated, exploring six new cancer (sub)types, and considering populations of non-European ancestry. We use detailed information on multiple

smoking characteristics to assess the proportion of heritability in smoking-related cancers that can be attributed to the genetic determinants of cigarette smoking. Furthermore, we use genetic correlation analysis to assess shared heritability across cancer sites and for lung cancer across two distinct ethnic populations to assess the evidence of gene-environment interactions for this complex malignancy. These analyses provide insights into the contribution of common SNPs to cancer heritability, coheritability and their relationships to a major environmental risk-factor, smoking.

Methods

Study Populations

The study includes 49 492 cancer case patients and 34 131 control patients who participated in large case/control GWAS that were genotyped at or reported to the National Cancer Institute's (NCI's) Cancer Genomics Research Laboratory (CGR) between 2007 and 2014. GWAS were conducted in individuals of European ancestry unless otherwise stated. Details about the GWAS can be found in the Supplementary Methods (available online). Studies were approved by the local institutional review boards, and all participants provided written informed consent.

Estimation of Heritability and Genetic Correlation

We estimated heritability, h_l^2, and genetic correlation using mixed model methodology (GCTA) software (11,12), adjusting for sex, substudy, and the top 20 eigenvectors, and after following the stringent quality control procedures described in the Supplementary Methods (available online). Genetic correlation was considered statistically significant if the two-sided test statistic provided a P value below .01. To estimate heritability attributable to undiscovered loci, we identified SNPs (Supplementary Table 1, available online) from the National Human Genome Research Institute (NHGRI) catalog or from recent publications (18–20) that were associated with a given cancer ($P < 5\times10^{-8}$) and removed all SNPs within 250 KB of those loci prior to calculation of the genetic relation matrix. A description of the GCTA methodology, determining FRR, and sensitivity analyses are provided in the Supplementary Methods (available online).

Shared SNP Analysis

Among the 375 SNPs associated with at least one of the studied cancers in the NHGRI catalog or a recent publication, we considered only the 318 SNPs that were outside regions surrounding TERT (1280000 +/- 500 kb on chromosome 5) and 8q24 (128000000 +/- 500 kb on chromosome 8), both already known to have pleiotripic effects on multiple cancers, and that were either genotyped or could be imputed accurately in at least one GWAS. Among those SNPs, we evaluated their associations with all other cancers and reported their associations if the corresponding two-sided P value was below .001.

Next, we created a polygenic risk score for each cancer. Let "T" denote a specific cancer site, R_{iT} be an individual's risk of cancer "T", Ω_T be the subset of the 318 SNPs associated with cancer "T", and G_{ij} be the number of minor alleles for individual i at SNP j in Ω_T. Then the polygenic risk score, Z_{Ti}, for individual i was defined as $Z_{Ti} = \sum_{j \in \Omega_T} \hat{\beta}_{Tj} G_{ij}$, where $\hat{\beta}_{Tj}$ was estimated from fitting the model

$$logit(R_{iT}) \propto \sum_{j \in \Omega_T} \beta_{Tj} G_{ij}$$

using our GWAS. We then tested for an association between the polygenic risk score of the primary cancer and the risk of each of the other cancers and considered the test to be statistically significant if the two-sided P value was below .05.

Estimation of the Heritability of Smoking and Its Contribution to Cancer Heritability

To estimate the proportion of cancer heritability that can be explained by genetic determinants of smoking, we first defined a smoking-related risk score variable (S_T) that weights three smoking-related risk factors, namely smoking status, intensity, and duration according to their strength of association with a particular cancer (Supplementary Methods, available online). Variability of S_T, a mathematical construct which we denote by $Var(S_T)$, explains the variation of cancer risk because of smoking in a population on the log-risk scale. The component of $Var(S_T)$ attributable to genetics can be estimated as $V_{GS} = h_{TS}^2 Var(S_T)$, where h_{TS}^2 is the heritability of S_T and $Var(S_T)$ is the total variability of S_T in the underlying population, which we approximate by the 10 530 control patients with relevant smoking variables. The proportion, P, of cancer heritability attributable to smoking is then estimated as $P = V_{GS} / V_G$, where $V_G = 2log(FRR)$ transforms our estimate of cancer heritability to the variability in risk on the log-risk scale (21).

Results

The estimates of array-based heritability, h_l^2, on the liability threshold (LT) scale ranged from 0.05 to 0.38 across the 13 cancer sites (Table 1), with esophageal cancer ($h_l^2 = 0.38$, 95% confidence interval [CI] = 0.17 to 0.59, Asian population), prostate cancer ($h_l^2 = 0.38$, 95% CI = 0.24 to 0.51), and testicular cancer ($h_l^2 = 0.30$, 95% CI = 0.08 to 0.51) displaying the strongest heritable components. After removing known susceptibility loci (Supplementary Table 1, available online), the adjusted estimates of heritability remained similar (Table 1) for most of the cancer sites, indicating that the majority of the common underlying susceptibility loci remain to be discovered. Known loci constituted the largest proportion of heritability for cancers of the testes (33%) and prostate (25%).

We transformed our measures of the genetic contribution to cancer from heritability on the liability threshold scale to familial relative risk (FRR) for direct comparison with registry-based family studies (Table 2). For most cancers, the FRR explained by GWAS SNPs was between 1.28 and 1.63. The estimates of FRR were highest for testicular cancer (FRR = 3.09, 95% CI = 1.41 to 6.05), osteosarcoma (2.90, 95% CI = 1.73 to 4.70) and CLL (2.28, 95% CI = 1.86 to 2.77). The GWAS estimates of excess risk (FRR-1) in the studies of European ancestry were in the range of 15% to 53% of the average estimates based on the Icelandic, Swedish, and Utah registry data, with the exception of DLBCL (4.5%). For lung cancer in an Asian population, our observed FRR of 1.31 (95 % CI = 1.16 to 1.46) (Table 2) can be compared with an estimate of 2.44 (95 % CI = 1.79 to 3.32) from a Taiwanese family study (22).

Smoking is heritable and is a strong risk factor for both lung and bladder cancers. We estimated the heritability of the lung cancer smoking-related risk score to be 0.15 (95% CI = 0.10 to 0.20) and the heritability of the bladder cancer smoking-related risk score to be 0.16 (95% CI = 0.09 to 0.22) (Table 3; Supplementary Tables 3–4 and Supplementary Figures 1–2, available online).

Table 1. GWAS estimates of cancer heritability on the liability scale*

Cancer	h_l^2 (95% CI)	h_r^2 (95% CI)
Bladder	0.123 (0.086 to 0.160)	0.112 (0.075 to 0.148)
Breast (ER-)	0.096 (0 to 0.199)	0.079 (0 to 0.181)
Endometrium	0.178 (0.085 to 0.270)	0.177 (0.085 to 0.270)
Esophagus†	0.381 (0.174 to 0.588)	0.370 (0.164 to 0.577)
Glioma	0.046 (0 to 0.116)	0.036 (0 to 0.106)
Kidney	0.147 (0.023 to 0.270)	0.136 (0.012 to 0.259)
Lung		
Asian†,‡	0.121 (0.064 to 0.177)	0.102 (0.046 to 0.159)
European	0.206 (0.142 to 0.271)	0.189 (0.125 to 0.253)
Lymphoma		
CLL	0.220 (0.162 to 0.278)	0.164 (0.105 to 0.222)
DLBCL	0.092 (0.038 to 0.145)	0.088 (0.035 to 0.142)
Osteosarcoma	0.159 (0.079 to 0.239)	0.158 (0.078 to 0.238)
Pancreas	0.098 (0.037 to 0.160)	0.084 (0.023 to 0.145)
Prostate		
Overall	0.378 (0.244 to 0.513)	0.285 (0.151 to 0.419)
Nonadvanced stage	0.351 (0.211 to 0.491)	0.259 (0.120 to 0.399)
Advanced stage	0.232 (0.157 to 0.307)	0.193 (0.119 to 0.268)
Stomach† (noncardia)	0.253 (0 to 0.522)	0.243 (0 to 0.512)
Testes	0.299 (0.084 to 0.513)	0.199 (0 to 0.415)

* h_l^2 (95% confidence interval [CI]) is the estimated heritability on the liability scale (95% CI) using all qualifying single-nucleotide polymorphisms (SNPs), while h_r^2 is the heritability after removing SNPs within 250 kb of a previous genome-wide association study hit. CI = confidence interval; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; ER = estrogen receptor; GWAS = genome-wide association study.
† Asian population.
‡ Nonsmoking women.

Based on a comparison with our estimates for the total heritability of cancer (Table 3), we estimated that 23.6% (95% CI = 14.2% to 37.4%) and 7.1% (95% CI = 4.3% to 11.3%) of the heritability for lung and bladder cancer, respectively, can be attributed to the genetic determinants of the three smoking characteristics. When restricting the analysis to ever-smokers, the heritability of the smoking-related risk scores remained similar (Table 3) and we estimated that 22.0% (95% CI = 7.8% to 43.0%) and 3.0% (95% CI = 1.2% to 5.9%) of the total heritability, respectively, was attributable to that of smoking behavior for lung and bladder cancers. Although limited by the number of never-smokers, we also noted lower estimates of heritability in this subgroup (Supplementary Table 5, available online).

The estimated genetic correlations between most pairs of cancer sites were modest and statistically nonsignificant (Figure 1; Supplementary Table 6, available online). Among the 91 compared pairs, all combinations of the 12 solid tumors, CLL, and DLBCL, the median (mean) correlation was 0.031 (0.055) and, in tests for statistical significance, only 12% and 22% of these 91 P values were below .1 and .2, providing little evidence of the enrichment that would be expected to occur with many strongly correlated pairs. The four pairs with the strongest correlations ($P < .01$) were kidney and testes ($\rho = 0.73$, SE = 0.28), DLBCL and osteosarcoma ($\rho = 0.53$, SE = 0.21), DLBCL and CLL ($\rho = 0.51$, SE = 0.18), and bladder and lung ($\rho = 0.35$, SE = 0.14). The two types, CLL and osteosarcoma, that were individually correlated with DLBCL showed minimal correlation ($\rho = 0.19$, SE = 0.15) with each other. For prostate cancer, the best-fitting estimate of the genetic correlation between aggressive and nonaggressive disease was at the upper boundary ($\rho = 1$, SE = 0.25), indicating a

Table 2. Estimates of first-degree familial relative risk from familial registries and GWAS*

	Sweden			Iceland†	Utah†	GWAS
	All 1ˢᵗ-degree relationships	Parent/child	Sibling			
Cancer	FRR (95% CI)	FRR (95% CI)	FRR (95% CI)	FRR (90% CI)	FRR (95% CI)	FRR (95% CI)
Bladder	1.69 (1.33 to 2.14)	1.53 (1.16 to 1.99)	3.30 (1.70 to 5.78)	1.68 (1.39 to 2.05)	1.8 (1.4 to 2.3)	1.37 (1.25 to 1.50)
Breast (ER-)	–	–	–	–	–	1.28 (0.98 to 1.63)
Endometrium	3.02 (2.33 to 3.92)	2.85 (2.08 to 3.82)	3.97 (1.97 to 7.13)	1.86 (1.31 to 2.62)	1.4 (1.1 to 1.8)	1.56 (1.25 to 1.92)
Esophagus	–	2.14 (0.77 to 4.70)	–	2.09 (1.30 to 3.31)	1.3 (0.2 to 10.0)	1.63‡ (1.27 to 2.05)
Glioma	1.67 (1.43 to 1.94)	–	3.31 (2.08 to 5.02)	1.41 (0.74 to 2.40)	2.3 (0.99 to 4.5)	1.19 (0.91 to 1.54)
Kidney	1.78 (1.33 to 2.39)	1.52 (1.06 to 2.11)	4.52 (2.15 to 8.35)	2.30 (1.89 to 2.80)	2.1 (1.3 to 3.5)	1.54 (1.07 to 2.13)
Lung						
European	1.70 (1.42 to 2.05)	1.64 (1.34 to 2.00)	2.61 (1.29 to 4.68)	2.00 (1.83 to 2.16)	2.4 (1.9 to 3.0)	1.42 (1.28 to 1.57)
Asian	–	–	–	–	–	1.31‡,§ (1.16 to 1.46)
Lymphoma						
CLL	8.5 (6.1 to 11.7)	–	–	–	6.1 (4.75 to 7.65)	2.28 (1.86 to 2.77)
DLBCL	9.8 (3.1 to 31.0)	–	–	–	–	1.40 (1.15 to 1.68)
Osteosarcoma	–	–	–	–	–	2.90 (1.73 to 4.70)
Pancreas	–	1.68 (1.16 to 2.35)	–	2.33 (1.83 to 2.96)	2.1 (1.3 to 3.2)	1.35 (1.12 to 1.62)
Prostate	2.75 (2.32 to 3.25)	2.71 (2.26 to 3.22)	4.91 (1.28 to 12.7)	1.89 (1.75 to 2.01)	2.1 (1.9 to 2.2)	1.51 (1.32 to 1.72)
Stomach	1.99 (1.47 to 2.71)	1.72 (1.19 to 2.40)	8.82 (3.50 to 18.3)	1.90 (1.74 to 2.05)	2.0 (1.1 to 3.7)	1.94‡ (0.95 to 3.49)
Testes	7.07 (5.34 to 9.37)	4.31 (2.05 to 7.95)	8.50 (6.01 to 11.7)	3.52 (1.18 to 7.37)	1.8 (0.4 to 8.6)	3.09 (1.41 to 6.05)

* Comparison of first-degree familial relative risk (95% CI) measured by our genome-wide association study (last column) with estimates of familial relative risk from the three largest family studies. Prior estimates are from (1, 6, 10), except for CLL (31), DLBCL (32), glioma (sibling) (33), pancreas (34), and esophagus (3). CI = confidence interval; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; ER = estrogen receptor; FRR = family relative risk; GWAS = genome-wide association study.
† All first-degree relationships.
‡ Asian population.
§ Nonsmoking women.

Table 3. Estimates of the contribution of smoking to cancer heritability*

Cancer	All subjects			Former/current smokers		
	V_{GS}: smoking (95% CI)	V_G: cancer (95% CI)	Ratio, % (95% CI)	V_{GS}: smoking (95% CI)	V_G: cancer (95% CI)	Ratio, % (95% CI)
Bladder	0.045 (0.029 to 0.061)	0.62 (0.44 to 0.81)	7.1 (4.3 to 11.3)	0.020 (0.0073 to 0.032)	0.66 (0.41 to 0.88)	3.0 (1.2% to 5.9)
Lung	0.166 (0.098 to 0.23)	0.70 (0.50 to 0.90)	23.6 (14.2 to 37.4)	0.11 (0.043 to 0.167)	0.47 (0.27 to 0.67)	22.0 (7.8% to 43.0)

* The ratio, V_{GS}:smoking/V_G:cancer, estimates the proportion of the genetic variability of cancer that can be attributed to the genetic determinants of smoking, where V_{GS}:smoking and V_G:cancer are the genetic variances of the smoking-related risk score and cancer, respectively. CI = confidence interval.
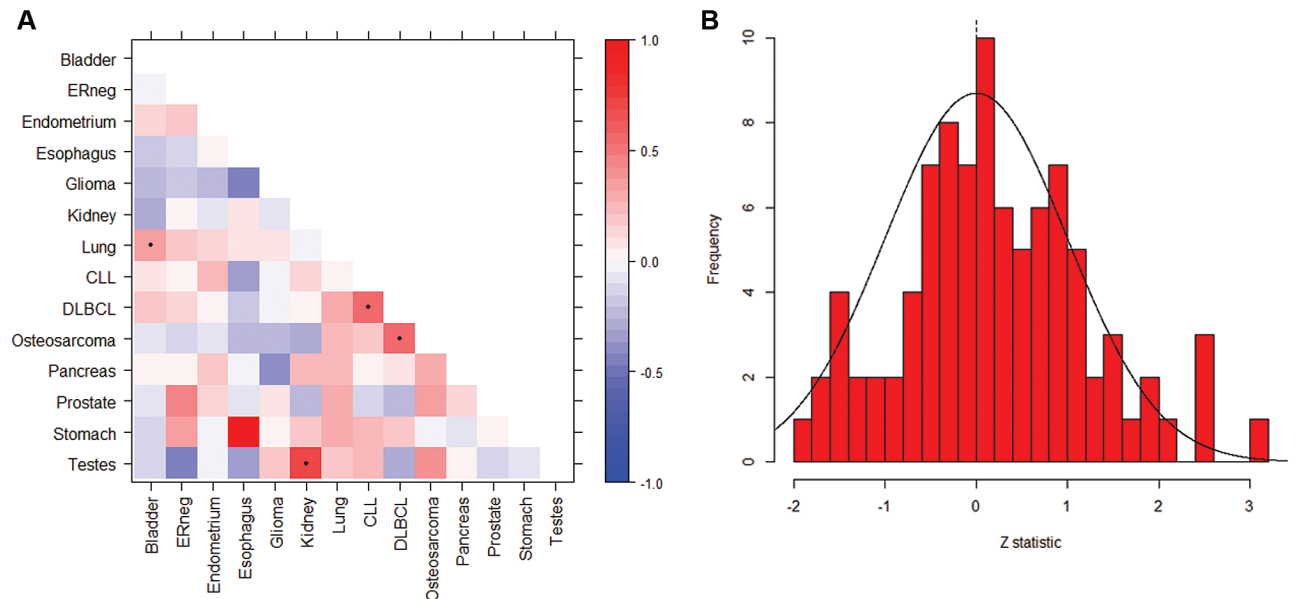

Figure 1. Genetic correlation of cancer pairs. **A)** The genetic correlation between cancer sites. **Dots** indicate *P* < .01. **B)** Distribution of the corresponding Z-statistics from testing the null hypotheses of no genetic correlations. **Black curve** illustrates the expected distribution under the null hypothesis of no genetic correlation. CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma.

shared genetic architecture between the two clinical subtypes of this malignancy. For lung cancer, on the other hand, we estimated the genetic correlation across two distinct racial/ethnic groups and found the correlation between nonsmoking Asian women and individuals of European ancestry to be only modest and statistically nonsignificant (ρ = 0.10, SE = 0.15), suggesting distinct genetic etiologies for the same malignancy in two distinct populations with different ethnic background and exposure history.

As a second means to assess genetic overlap, we tested whether the 318 SNPs previously associated with one of the 13 cancers at GWAS levels of statistical significance ($P < 5 \times 10^{-8}$), but outside the known pleiotropic regions of 5p15.33 and 8q24, were associated with other cancers (Supplementary Tables 7–8, available online). Among the 318 SNPs, 25 were associated with a second cancer at *P* values of less than .001 (Supplementary Tables 7–8, available online). We further calculated a polygenic risk score for each cancer (Methods) with at least ten associated SNPs among the 318 previously discovered. We found individuals with a high risk score for lung cancer were at an increased risk of bladder cancer (RR of bladder cancer comparing 90th vs 10th percentile = 1.07, 95% CI = 1.05 to 1.10) and individuals with a high risk score for CLL were at an increased risk of DLBCL (RR = 1.12, 95% CI = 1.07 to 1.16) (Supplementary Table 9–12, available online). After adjusting for status, intensity, and duration of smoking, the strength of association between the lung

cancer score and bladder cancer was reduced but remained statistically significant (RR = 1.05, 95% CI = 1.02 to 1.08).

We estimated heritability separately for men and women (Supplementary Tables 13–14, available online). Although we observed differences by sex, none reached statistical significance. When studies were divided by sex, the genetic correlation between cancer in men and women exceeded 0.9 in nearly all scenarios, with the 95% confidence interval always including 1. Moreover, we also estimated heritability under multiple additional analytical settings (Supplementary Table 15, available online) and found the results from these sensitivity analyses to be qualitatively similar. Sensitivity analyses further suggested that population stratification was adequately handled by adjusting for principal components (Supplementary Table 16, available online).

Discussion

Our analysis confirms that common SNPs meaningfully contribute to risk across the spectrum of cancers and account for different fractions of estimated heritability. The estimates of array-based heritability on the liability threshold scale spanned a wide range, from 5% (glioma) to 38% (prostate, esophageal cancer), and the majority of the observed heritability for most cancers is likely attributable to genetic variants that are not located in previously identified susceptibility regions. The corresponding estimates of familial relative risk were between 1.19 (glioma)

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and 2.90 (osteosarcoma). The estimated FRRs of the most common adult cancers were restricted to a narrow range of 1.4 to 1.6, which are lower than those previously observed in family-based studies (1,5,6). A number of additional factors are likely to contribute to familial aggregation, including rare genetic variants (23–25), nonadditive effects, and shared environment.

Expanding GWAS, either through new genotyping or meta-analyses, should continue to yield new susceptibility loci. The pace of expected discovery, measured by the number of additional associations for given study sizes, will likely continue to be faster for those cancers with the highest FRRs. For stomach cancer (Asian population), osteosarcoma, testes, and CLL, all with FRRs over 2, we predict that more loci may be identified for studies of comparable size (15). Consistent with this prediction, comparatively smaller GWAS of these highly heritable cancers have historically yielded more associations.

Genetic variants can influence cancer risk, either indirectly through associations with nicotine dependence and smoking behavior, or directly through other mechanisms (26). We estimate that the genetic determinants of smoking behavior accounted for at least 24% (95% CI = 14% to 37%) and 7% (4% to 11%) of the total heritability of lung and bladder cancers, respectively, in our study populations. These percentages likely underestimate the true influence of smoking genetics by not accounting for other, unmeasured, smoking characteristics, and may be slightly biased by systematic differences in the distribution of smoking characteristics between the general population and our GWAS control sample selected according to experimental design (Supplementary Table 17, available online). Our result is consistent with the largest meta-analysis (27) of case-control studies in which the excess relative risk (FRR = 1.82, 95% CI = 1.64 to 2.05) for lung cancer was reduced by 36% when focused on nonsmokers (FRR = 1.52, 95% CI = 1.11 to 2.06).

Our analysis of coheritability indicated that, in general, most pairs of cancers studied here are unlikely to have strong genetic correlations. Although our study had low power to detect modest but possibly important correlations between specific pairs of cancers (28), the distribution of test statistics over all pairs of cancers deviated little from the null (Figure 1), suggesting that at most a small fraction have modest or high (eg, $\rho > 0.3$) correlations (Supplementary Tables 18–19, available online). Four pairs of sites that show notable correlation in our study are bladder and lung, testes and kidney, DLBCL and CLL, and DLBCL and osteosarcoma. Pleiotropic analyses of polygenic risk scores offered additional evidence for overlapping genetic architectures between bladder and lung cancer and between DLBCL and CLL. While no family study has been of sufficient size to explore the connection between DLBCL and CLL or DLBCL and osteosarcoma, the Icelandic registry study (6) found that the relative risks for testicular cancer were elevated in relatives of kidney cancer case patients, as indicated by our results.

Analysis of the genetic correlation for the same cancer site but across distinct subtypes and populations can provide important insights. For instance, the strong genetic correlation between aggressive and nonaggressive prostate cancer indicates that common SNPs are unlikely to offer a diagnostic means to distinguish these two subtypes of cancer with different prognoses. On the other hand, there was an absence of correlation for lung cancer between studies in nonsmoking Asian females and a Caucasian population where case patients were primarily smokers. This result is consistent with the observation that distinct sets of susceptibility SNPs have emerged in these two populations (29,30). In general, low correlation across populations can be caused by different causal SNPs, differences in effect sizes or allele frequencies of shared causal SNPs, and differences in linkage disequilibrium (LD). Simulations (results not shown) based on empirical genotype data suggest that the observed low correlation ($\rho = 0.10$, SE = 0.15) is unlikely to be explained by general differences in the allele frequency and LD pattern between these two populations. However, substantial confounding may arise if disease-causing loci are particularly selected to have strong differences with respect to be these factors.

Our study has some limitations. While total sample size was large, the number of cases for certain cancer sites, especially when stratified by subtypes, could be limited, resulting in large confidence intervals for estimates of heritability. Such uncertainty, together with various sources of bias and variability of the prior estimates of FRR from registry-based studies, make it more difficult to assess the proportion of observed FRR that can be attributed to common SNPs. Because of the limited sample size, our analysis also lacked power to detect modest genetic correlations among specific cancer types/subtypes. This lack of precision may partially explain the more extensive familial co-aggregation observed in a study based on the Icelandic Cancer Registry (6). However, the discrepancy also can be attributed to different cancers pathologies, environmental differences across populations, and, most importantly, other sources of shared heritability. Another limitation is that principal components may not perfectly adjust for ancestry and therefore shared environments or behaviors among individuals with similar ancestry may inflate our estimates of heritability. However, tests for such inflation found little evidence to support this concern.

For some cancer sites, the individuals used in the previous study (13) of GWAS heritability overlap with a subset the individuals used here, and therefore the two studies do not offer independent assessments of heritability. For kidney cancer, our population overlaps considerably with that studied by Lu and colleagues (13), who estimated its heritability to be 0.18. For other cancers, including bladder, lung, pancreas, and prostate, the prior study populations are primarily subsets of our own populations, including the 25% to 50% of individuals from the earliest GWAS. Prior estimates for these four cancers were respectively 0.01, 0.10, 0.18, and 0.81, and show substantive differences from our updated estimates (Table 1). This analysis of more than 80 000 individuals provides important perspectives on the heritability of cancer across anatomical sites. We affirm that there is a large heritable component to most cancers, but the majority of cancer heritability cannot be attributed to known susceptibility loci. We further demonstrate that marker SNPs are not omnipresent across cancers, in that there does not appear to be strong genetic correlations between most pairs of cancer sites. Among smoking-related cancers, we showed that the genetic determinants of smoking make a statistically significant contribution to the heritability of lung and bladder cancer. Overall, as GWAS expand in size and design, a comprehensive analysis should continue to focus on cancers individually, look across groups of cancers identified as being genetically similar, and account for important environmental risk factors.

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References

1. Czene K, Lichtenstein P, Hemminki K. Environmental and heritable causes of cancer among 9.6 million individuals in the Swedish family-cancer database. *Int J Cancer*. 2002;99(2):260–266.
2. Hemminki K, Li X. Familial risk in testicular cancer as a clue to a heritable and environmental aetiology. *Br J Cancer*. 2004;90(9):1765–1770.
3. Ji J, Hemminki K. Familial risk for esophageal cancer: an updated epidemiologic study from Sweden. *Clin Gastroenterol Hepatol*. 2006;4(7):840–845.
4. Goldgar DE, Easton DF, Cannon-Albright LA, et al. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst*. 1994;86(21):1600–1608.
5. Kerber RA, O'Brien E. A cohort study of cancer risk in relation to family histories of cancer in the Utah population database. *Cancer*. 2005;103(9):1906–1915.
6. Amundadottir LT, Thorvaldsson S, Gudbjartsson DF, et al. Cancer as a complex phenotype: pattern of cancer distribution within and beyond the nuclear family. *PLoS Med*. 2004;1(3):e65.
7. Ahlbom A, Lichtenstein P, Malmström H, et al. Cancer in twins: genetic and nongenetic familial risk factors. *J Natl Cancer Inst*. 1997;89(4):287–293.
8. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med*. 2000;343(2):78–85.
9. Zaitlen N, Kraft P, Patterson N, et al. Using Extended Genealogy to Estimate Components of Heritability for 23 Quantitative and Dichotomous Traits. *PLoS Genet*. 2013;9(5):e1003520.
10. Cannon-Albright LA, Thomas A, Goldgar DE, et al. Familiality of cancer in Utah. *Cancer Res*. 1994;54(9):2378–2385.
11. Lee SH, Wray NR, Goddard ME, et al. Estimating missing heritability for disease from genome-wide association studies. *Am J Hum Genet*. 2011;88(3):294–305.
12. Yang J, Benyamin B, McEvoy BP, et al. Common SNPs explain a large proportion of the heritability for human height. *Nat Genet*. 2010;42(7):565–569.
13. Lu Y, Ek WE, Whiteman D, et al. Most common 'sporadic' cancers have a significant germline genetic component. *Hum Mol Genet*. 2014;23(22):6112–6118.
14. Chatterjee N, Wheeler B, Sampson J, et al. Projecting the performance of risk prediction based on polygenic analyses of genome-wide association studies. *Nat Genet*. 2013;45(4):400–405, 405e1–405e3.
15. Park JH, Wacholder S, Gail MH, et al. Estimation of effect size distribution from genome-wide association studies and implications for future discoveries. *Nat Genet*. 2010;42(7):570–575.
16. Petitjean A, Achatz MI, Borresen-Dale AL, et al. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. *Oncogene*. 2007;26(15):2157–2165.
17. Friedenson B. BRCA1 and BRCA2 pathways and the risk of cancers other than breast or ovarian. *Medscape Gen Med*. 2005;7(2):60.
18. Al Olama AA, Kote-Jarai Z, Berndt SI, et al. A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. *Nat Genet*. 2014;46(10):1103–1109.
19. Cerhan JR, Berndt SI, Vijai J, et al. Genome-wide association study identifies multiple susceptibility loci for diffuse large B cell lymphoma. *Nat Genet*. 2014;46(11):1233–1238.
20. Wolpin BM, Rizzato C, Kraft P, et al. Genome-wide association study identifies multiple susceptibility loci for pancreatic cancer. *Nat Genet*. 2014;46(9):994–1000.
21. Pharoah PDP, Antoniou A, Bobrow M, et al. Polygenic susceptibility to breast cancer and implications for prevention. *Nat Genet*. 2002;31(1):33–36.
22. Lo YL, Hsiao CF, Chang GC, et al. Risk factors for primary lung cancer among never smokers by gender in a matched case-control study. *Cancer Causes Control*. 2013;24(3):567–576.
23. Jones S, Hruban RH, Kamiyama M, et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. *Science*. 2009;324(5924):217.
24. Meindl A, Hellebrand H, Wiek C, et al. Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene. *Nat Genet*. 2010;42(5):410–414.
25. Wang Y, McKay JD, Rafnar T, et al. Rare variants of large effect in BRCA2 and CHEK2 affect risk of lung cancer. *Nat Genet*. 2014;46(7):736–741.
26. Subramanian J, Govindan R. Molecular genetics of lung cancer in people who have never smoked. *Lancet Oncol*. 2008;9(7):676–682.
27. Matakidou A, Eisen T, Houlston RS. Systematic review of the relationship between family history and lung cancer risk. *Br J Cancer*. 2005;93(7):825–833.
28. Visscher PM, Hemani G, Vinkhuyzen AAE, et al. Statistical Power to Detect Genetic (Co)Variance of Complex Traits Using SNP Data in Unrelated Samples. *Plos Genet*. 2014;10(4):10(4):e1004269.
29. Lan Q, Hsiung CA, Matsuo K, et al. Genome-wide association analysis identifies new lung cancer susceptibility loci in never-smoking women in Asia. *Nat Genet*. 2012;44(12):1330–1335.
30. Landi MT, Chatterjee N, Yu K, et al. A genome-wide association study of lung cancer identifies a region of chromosome 5p15 associated with risk for adenocarcinoma. *Am J Hum Genet*. 2009;85(5):679–691.
31. Goldin LR, Bjorkholm M, Kristinsson SY, et al. Elevated risk of chronic lymphocytic leukemia and other indolent non-Hodgkin's lymphomas among relatives of patients with chronic lymphocytic leukemia. *Haematologica*. 2009;94(5):647–653.
32. Goldin LR, Bjorkholm M, Kristinsson SY, et al. Highly increased familial risks for specific lymphoma subtypes. *Br J Haematol*. 2009;146(1):91–94.
33. Scheurer ME, Etzel CJ, Liu M, et al. Familial aggregation of glioma: a pooled analysis. *Am J Epidemiol*. 2010;172(10):1099–1107.
34. Hemminki K, Li X. Familial and second primary pancreatic cancers: a nationwide epidemiologic study from Sweden. *Int J Cancer*. 2003;103(4):525–530.