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Genome-wide association study identifies 25 known breast cancer susceptibility loci as risk factors for triple negative breast cancer

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Complete List of Authors:	Purrington, Kristen; Mayo Clinic, Department of Health Sciences Research Konstanta, Irene; National Centre for Scientific Research "Demokritos", Molecular Diagnostics Laboratory INRASTES Slager, Susan; College of Medicine, Mayo Clinic, Health Sciences Research Eccles, Diana; University of Southampton, Faculty of Medicine Yannoukakos, Drakoulis; National Centre for Scientific Research "Demokritos", Molecular Diagnostics Laboratory INRASTES Fasching, Peter; University Breast Center Franconia, University Hospital Erlangen; Friedrich-Alexander University Erlangen-Nuremberg, Department of Gynecology and Obstetrics; University of California at Los Angeles, David Geffen School of Medicine, Department of Medicine, Division Hematology/Oncology Miron, Penelope; Dana Farber Cancer Institute, Cancer Biology Carpenter, Jane; University of Sydney at the Westmead Millennium Institute, Australian Breast Cancer Tissue Bank Chang-Claude, Jenny; German Cancer Research Center, Division of Clinical Epidemiology Martin, Nicholas G Montgomery, Grant; 4Queensland Institute of Medical Research, 4Queensland Institute of Medical Research Kristensen, Vessela; Oslo University Hospital, Department of Genetics Anton-Culver, Hoda; University of California, Epidemiology Div. Goodfellow, Paul; Washington University School of Medicine, Barnes-Jewish Hospital, Siteman Cancer Center Tapper, William; University of Southampton, Faculty of Medicine Rafiq, Sajjad; University of Southampton, Faculty of Medicine Gerty, Susan; University of Southampton, Faculty of Medicine Durcan, Lorraine; University of Southampton, Faculty of Medicine Konstantopoulou, Irene; National Centre for Scientific Research "Demokritos", Molecular Diagnostics Laboratory INRASTES Fostira, Florentia; National Centre for Scientific Research "Demokritos", Molecular Diagnostics Laboratory INRASTES Vratimos, Athanassios; National Centre for Scientific Research "Demokritos", Molecular Diagnostics Laboratory INRASTES Apostolou, Paraskevi; National Centre for Scientific Research "Demokritos", Molecular Diagnostics Laboratory INRASTES

Kotoula, Vassiliki; Aristotle University of Thessaloniki School of Medicine, "Laboratory of Molecular Oncology, Hellenic Foundation for Cancer Research and Department of Pathology "
Lakis, Sotiris; Aristotle University of Thessaloniki School of Medicine, "Laboratory of Molecular Oncology, Hellenic Foundation for Cancer Research and Department of Pathology "
DIMOPOULOS, MELETIOS; ATHENS UNIVERSITY, CLINICAL THERAPEUTICS
Skarlos, Dimosthenis; "Metropolitan" Hospital, Second Department of Medical Oncology
Pectasides, Dimitrios; University of Athens School of Medicine, Oncology Section, Second Department of Internal Medicine, "Hippokration" Hospital
Fountzilas, George; Aristotle University of Thessaloniki School of Medicine, Department of Medical Oncology, "Papageorgiou" Hospital
Beckmann, Matthias; University Breast Center Franconia, University Hospital Erlangen; Friedrich-Alexander University Erlangen-Nuremberg, Department of Gynecology and Obstetrics
Hein, Alexander; University Breast Center Franconia, University Hospital Erlangen; Friedrich-Alexander University Erlangen-Nuremberg, Department of Gynecology and Obstetrics
Ruebner, Matthias; University Breast Center Franconia, University Hospital Erlangen; Friedrich-Alexander University Erlangen-Nuremberg, Department of Gynecology and Obstetrics
Ekici, Arif; University Hospital Erlangen; Friedrich-Alexander University Erlangen-Nuremberg, Institute of Human Genetics
Hartmann, Arndt; University Hospital Erlangen; Friedrich-Alexander University Erlangen-Nuremberg, Institute of Pathology
Schulz-Wendtland, Ruediger; University Hospital Erlangen; Friedrich-Alexander University Erlangen-Nuremberg, Institute of Diagnostic Radiology
Renner, Stefan; University Breast Center Franconia, University Hospital Erlangen; Friedrich-Alexander University Erlangen-Nuremberg, Department of Gynecology and Obstetrics
Ranni, Wolfgang; University Hospital Ulm, Department of Gynecology and Obstetrics
Rack, Brigitte; University Hospital Ludwig Maximilians University, Campus Innenstadt, Department of Gynecology and Obstetrics
Scholz, Christoph; University Hospital Ulm, Department of Gynecology and Obstetrics
Neugebauer, Julia; University Hospital Ludwig Maximilians University, Campus Innenstadt, Department of Gynecology and Obstetrics
Andergassen, Ulrich; University Hospital Ludwig Maximilians University, Campus Innenstadt, Department of Gynecology and Obstetrics
Lux, Michael; University Breast Center Franconia, University Hospital Erlangen; Friedrich-Alexander University Erlangen-Nuremberg, Department of Gynecology and Obstetrics
Haeberle, Lothar; University Breast Center Franconia, University Hospital Erlangen; Friedrich-Alexander University Erlangen-Nuremberg, Department of Gynecology and Obstetrics
Clarke, Christine; Sydney Medical School Westmead, University of Sydney at the Westmead Millennium Institute, Westmead Institute for Cancer Research
Pathmanathan, Nirmala; Westmead Hospital, Westmead Breast Cancer Institute
Rudolph, Anja; German Cancer Research Center, Division of Cancer Epidemiology
Flesch-Janys, Dieter; University Clinic Hamburg-Eppendorf, Institute for Medical Biometrics and Epidemiology
Nickels, Stefan; German Cancer Research Center, Division of Cancer Epidemiology
Olson, Janet; Mayo Clinic, Health Sciences Research
Ingle, James; Mayo Clinic, Department of Oncology

Cafourek, Vicki; Mayo Clinic, Health Sciences Research
Olswold, Curtis; Mayo Clinic, Health Sciences Research
Slettedahl, Seth; Mayo Clinic, Health Sciences Research
Eckel-Passow, Jeanette; Mayo Clinic, Health Sciences Research
Anderson, S.; Mayo Clinic, Department of Health Sciences Research
Visscher, Daniel; Mayo Clinic, Department of Laboratory Medicine and Pathology
Sicotte, Hugues; Mayo Clinic, Department of Health Sciences Research
Prodduturi, Naresh; Mayo Clinic, Department of Health Sciences Research
Weiderpass, Elisabete; University of Tromsø, Department of Community Medicine
Bernstein, Leslie; City of Hope Comprehensive Cancer Center, Beckman Research Institute
Ziogas, Argyrios; University of California–Irvine, Department of Epidemiology
Ivanovich, Jennifer; Washington University School of Medicine,, Barnes-Jewish Hospital and Siteman Cancer Center
Giles, Graham
Baglietto, Laura; The Cancer Council Victoria, Cancer Epidemiology Centre
Southey, Melissa; The University of Melbourne, Department of Pathology
Kosma, Veli-Matti; University of Eastern Finland, School of Medicine, Institute of Clinical Medicine, Pathology and Forensic Medicine; Biocenter Kuopio, Cancer Center of Eastern Finland, University of Eastern Finland, Kuopio, Finland and Imaging Center, Department of Clinical Pathology, Kuopio University Hospital, Kuopio, Finland
Fischer, Hans-Peter; Medical Faculty of the University of Bonn, Institute of Pathology
Cai, Qiuyin; Vanderbilt University Medical Center, Medicine
Shu, Xiao Ou; Vanderbilt University, Center for Health Services Research, Vanderbilt Ingram Cancer Center
Daly, Mary; Fox Chase Cancer Center, Department of Clinical Genetics
Weaver, JoEllen; University of Pennslyvania School of Medicine, PennMed Biobank
Ross, Eric; Fox Chase Cancer Center, Department of Biostatistics and Bioinformatics
Sharma, Priyanka; University of Kansas Medical Center, Department of Oncology/Hematology
Klemp, Jennifer; University of Kansas Medical Center, Department of Oncology/Hematology
Torres, Diana; German Cancer Research Center (DKFZ), Molecular Genetics of Breast Cancer
Rüdiger, Thomas; Städtisches Klinikum Karlsruhe, Institute of Pathology
Wölfing, Heidrun; Städtisches Klinikum Karlsruhe, Institute of Pathology
Ulmer, Hans-Ulrich; Frauenklinik der Stadtklinik Baden-Baden, University of Jena
Försti, Asta; German Cancer Research Center (DKFZ), Division of Molecular Genetic Epidemiology
Khoury, Thaer; Roswell Park Cancer Institute, Department of Pathology
Kumar, Shicha; Roswell Park Cancer Institute, Department of Surgical Oncology
Pilarski, Robert; Comprehensive Cancer Center, The Ohio State University, Division of Human Genetics, Department of Internal Medicine
Shapiro, Charles; Comprehensive Cancer Center, The Ohio State University, Division of Medical Oncology, Department of Internal Medicine
Greco, Dario; University of Helsinki and Helsinki University Central Hospital, Department of Obstetrics and Gynecology
Heikkilä, Päivi; Helsinki University Central Hospital, Department of Pathology
Aittomäki, Kristiina; Helsinki University Central Hospital, Department of Clinical Genetics
Blomqvist, Carl; Helsinki University Central Hospital, Department of

	Oncology Irwanto, Astrid; Genome Institute of Singapore, Human Genetics Division Liu, Jianjun; Genome Institute of Singapore, Human Genetics Division Pankratz, Vernon; Mayo Clinic, Biostatistics Wang, Xianshu; Mayo Clinic, Experimental Pathology Severi, Gianluca; The Cancer Council of Victoria, Cancer Epidemiology Centre Mannermaa, Arto; University of Eastern Finland, School of Medicine, Institute of Clinical Medicine, Pathology and Forensic Medicine; Biocenter Kuopio, Cancer Center of Eastern Finland, University of Eastern Finland, Kuopio, Finland and Imaging Center, Department of Clinical Pathology, Kuopio University Hospital, Kuopio, Finland Easton, Douglas; University of Cambridge, Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, Department of Oncology Hall, Per; University of Tuebingen, Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology Ambrosone, Christine; Roswell Park Cancer Institute, Dept.of Epidemiology Toland, Amanda; The Ohio State University, Molecular Virology, Immunology and Medical Genetics Nevanlinna, Heli; Helsinki University Central Hospital, Obstetrics and gynecology Vachon, Celine; Mayo Clinic, Department of Health Sciences Research Couch, Fergus; Mayo Clinic, Pathology
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Genome-wide association study identifies 25 known breast cancer susceptibility loci as risk factors for triple negative breast cancer

Short title: GWAS and known breast cancer risk loci in TN breast cancer

Kristen S. Purrington[1], Susan Slager[1], Diana Eccles[2], Drakoulis Yannoukakos[3], Peter A. Fasching[5,4], Penelope Miron[6], Jane Carpenter[7], Jenny Chang-Claude[8], Nicholas G. Martin[9], Grant W Montgomery[9], Vessela Kristensen[10,11], Hoda Anton-Culver[12], Paul Goodfellow[13], William J. Tapper[2], Sajjad Rafiq[2], Susan M. Gerty[2], Lorraine Durcan[2], Irene Konstantopoulou[3], Florentia Fostira[3], Athanassios Vratimos[3], Paraskevi Apostolou[3], Irene Konstanta[3], Vassiliki Kotoula[14], Sotiris Lakis[15], Meletios A. Dimopoulos[16], Dimosthenis Skarlos[17], Dimitrios Pectasides[18], George Fountzilas[19], Matthias W. Beckmann[5], Alexander Hein[5], Matthias Ruebner[5], Arif B. Ekici[20], Arndt Hartmann[21], Ruediger Schulz-Wendtland[22], Stefan P. Renner[5], Wolfgang Janni[23], Brigitte Rack[24], Christoph Scholz[23], Julia Neugebauer[24], Ulrich Andergassen[24], Michael P. Lux[5], Lothar Haeberle[5], Christine Clarke[25], Nirmala Pathmanathan[26], Anja Rudolph[8], Dieter Flesch-Janys[27], Stefan Nickels[8], Janet E. Olson[1], James N. Ingle[28], Curtis Olswold[1], Seth Slettedahl[1], Jeanette E. Eckel-Passow[1], S. Keith Anderson[1], Daniel W. Visscher[29], Vicky Cafourek[1], Hugues Sicotte[1], Naresh Prodduturi[1], Elisabete Weiderpass[30,31,32], Leslie Bernstein[33], Argyrios Ziogas[12], Jennifer Ivanovich[13], Graham G. Giles[34], Laura Baglietto[34], Melissa Southey[35], Veli-Matti Kosma[36], Hans-Peter Fischer[37], The GENICA Network[38,j2,40,41,42,43], Malcom W.R. Reed[44], Simon S. Cross[45], Sandra Deming-Halverson[46], Martha Shrubsole[46], Qiuyin Cai[46], Xiao-Ou Shu[46], Mary Daly[47], JoEllen Weaver[48], Eric Ross[49], Jennifer Klemp[50,51], Priyanka Sharma[50], Diana Torres[43], Thomas Rüdiger[52], Heidrun Wölfing[52], Hans-Ulrich Ulmer[53], Asta Försti[55,54], Thaer Khoury[56], Shicha Kumar[57], Robert Pilarski[58], Charles L. Shapiro[59], Dario Greco[60], Päivi Heikkilä[61], Kristiina Aittomäki[61], Carl Blomqvist[61], Astrid Irwanto[62], Jianjun Liu[62], V. Shane Pankratz[1], Xianshu Wang[29], Gianluca Severi[34], Arto Mannermaa[36], Douglas Easton[65], Per Hall[66], Hiltrud Brauch[38], Angela Cox[44], Wei Zheng[46], Andrew K. Godwin[67], Ute Hamann[43], Christine Ambrosone[68], Amanda Ewart Toland[69], Heli Nevanlinna[60], Celine M. Vachon[1], Fergus J. Couch[1,29*]

1 Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA
2 Faculty of Medicine, University of Southampton, Southampton, UK
3 Molecular Diagnostics Laboratory INRASTES, National Centre for Scientific Research "Demokritos", Athens, Greece
4 Department of Medicine, Division Hematology/Oncology, University of California at Los Angeles, David Geffen School of Medicine, Los Angeles, CA, USA
5 Department of Gynecology and Obstetrics, University Breast Center Franconia, University Hospital Erlangen; Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany
6 Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, MA, USA
7 Australian Breast Cancer Tissue Bank, University of Sydney at the Westmead Millennium Institute, Westmead, New South Wales, Australia
8 Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

9 QIMR GWAS Collective, Queensland Institute of Medical Research, Brisbane, Queensland, Australia
10 Department of Genetics, Institute for Cancer Research, Oslo University Hospital, Radiumhospitalet, Oslo, Norway
11 Faculty of Medicine (Faculty Division Ahus), Universitetet i Oslo, Oslo, Norway
12 Department of Epidemiology, University of California–Irvine, Irvine, CA, USA
13 Washington University School of Medicine, Barnes-Jewish Hospital and Siteman Cancer Center, St. Louis, MO, USA
14 Laboratory of Molecular Oncology, Hellenic Foundation for Cancer Research and Department of Pathology, Aristotle University of Thessaloniki School of Medicine, Thessaloniki, Greece
15 Laboratory of Molecular Oncology, Hellenic Foundation for Cancer Research, Aristotle University of Thessaloniki School of Medicine, Thessaloniki, Greece
16 Department of Clinical Therapeutics, "Alexandra" Hospital, University of Athens School of Medicine, Athens, Greece
17 Second Department of Medical Oncology , "Metropolitan" Hospital, Athens, Greece
18 Oncology Section, Second Department of Internal Medicine, "Hippokration" Hospital, University of Athens School of Medicine, Athens, Greece
19 Department of Medical Oncology, "Papageorgiou" Hospital, Aristotle University of Thessaloniki School of Medicine, Thessaloniki, Greece
20 Institute of Human Genetics, University Hospital Erlangen; Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany
21 Institute of Pathology, University Hospital Erlangen; Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany
22 Institute of Diagnostic Radiology, University Hospital Erlangen; Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany
23 Department of Gynecology and Obstetrics, University Hospital Ulm, Ulm, Germany
24 Department of Gynecology and Obstetrics, University Hospital Ludwig Maximilians University, Campus Innenstadt, Munich, Germany
25 Westmead Institute for Cancer Research, Sydney Medical School Westmead, University of Sydney at the Westmead Millennium Institute, Westmead, New South Wales, Australia
26 Westmead Breast Cancer Institute, Westmead Hospital, Westmead, New South Wales, Australia
27 Institute for Medical Biometrics and Epidemiology, University Clinic Hamburg-Eppendorf, Hamburg, Germany
28 Department of Oncology, Mayo Clinic, Rochester, MN, USA
29 Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA
30 Department of Community Medicine, University of Tromsø, Tromsø, Norway
31 Folkhälsan Research Cancer Centre, Helsinki, Finland
32 Cancer Registry of Norway, Oslo, Norway
33 Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute, City of Hope, Duarte, USA
34 Cancer Epidemiology Centre, The Cancer Council Victoria, Melbourne, Victoria, Australia

35 Department of Pathology, The University of Melbourne, Melbourne, Victoria, Australia
36 School of Medicine, Institute of Clinical Medicine, Pathology and Forensic Medicine; Biocenter Kuopio, Cancer Center of Eastern Finland, University of Eastern Finland, Kuopio, Finland and Imaging Center, Department of Clinical Pathology, Kuopio University Hospital, Kuopio, Finland, University of Eastern Finland, Kuopio, Finland
37 Department of Pathology, Medical Faculty University Bonn, Bonn, Germany
38 Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart and University of Tuebingen, Germany
39 Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany
40 Institute for Occupational Medicine and Maritime Medicine, University Medical Center Hamburg-Eppendorf, Germany
41 Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, Germany
42 Institute of Pathology, Medical Faculty of the University of Bonn, Bonn, Germany
43 Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany
44 Department of Oncology, Cancer Research UK/Yorkshire Cancer Research Sheffield Cancer Research Centre, University of Sheffield, Sheffield, UK
45 Department of Neuroscience, University of Sheffield, Sheffield, UK
46 Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Division of Epidemiology, Vanderbilt University School of Medicine, Nashville, TN, USA
47 Department of Clinical Genetics, Fox Chase Cancer Center, Philadelphia, PA, USA
48 PennMed Biobank, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
49 Department of Biostatistics and Bioinformatics, Fox Chase Cancer Center, Philadelphia, PA, USA
50 Department of Oncology/Hematology, University of Kansas Medical Center, Kansas City, KS, USA
51 Institute of Human Genetics, Pontificia University Javeriana, Bogota, Colombia
52 Institute of Pathology, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany
53 Frauenklinik der Stadtklinik Baden-Baden, Baden-Baden, Germany, , Baden-Baden, Germany
54 Center for Primary Health Care Research, University of Lund, Malmö, Sweden
55 Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany
56 Department of Pathology, Roswell Park Cancer Institute, Buffalo, NY, USA
57 Department of Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY, USA
58 Division of Human Genetics, Department of Internal Medicine, Comprehensive Cancer Center, The Ohio State University, Columbus, OH, USA
59 Division of Medical Oncology, Department of Internal Medicine, Comprehensive Cancer Center, The Ohio State University , Columbus, OH, USA
60 Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland

61 Department of Pathology, Helsinki University Central Hospital, Helsinki, Finland
62 Department of Clinical Genetics, Helsinki University Central Hospital, Helsinki, Finland
63 Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland
64 Human Genetics Division, Genome Institute of Singapore, Singapore
65 Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, Department of Oncology, University of Cambridge, Cambridge, UK
66 Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
67 Department of Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City, KS, USA
68 Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY, USA
69 Division of Human Cancer Genetics, Departments of Internal Medicine and Molecular Virology, Immunology and Medical Genetics, Comprehensive Cancer Center, The Ohio State University, Columbus, OH, USA

***To whom correspondence should be addressed**: Fergus J. Couch, Stabile 2-42, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Tel: (507) 284-3623; Fax: (507) 538-1937; Email: couch.fergus@mayo.edu

Abstract

Triple negative (TN) breast cancer is an aggressive subtype of breast cancer associated with a unique set of epidemiologic and genetic risk factors. We conducted a two-stage genome-wide association study (GWAS) of TN breast cancer (stage 1: 1,529 TN cases, 3,399 controls; stage 2: 2,148 cases, 1,309 controls) to identify loci that influence TN breast cancer risk. Variants in the 19p13.1 and *PTHLH* loci showed genome-wide significant associations ($p<5x10^{-8}$) in stage 1 and 2 combined. Results also suggested a substantial enrichment of significantly associated variants among the SNPs analyzed in stage 2. Variants from 25 of 74 known breast cancer susceptibility loci were also associated with risk of TN breast cancer ($p<0.05$). Associations with TN breast cancer were confirmed for ten loci (*LGR6*, *MDM4*, *CASP8*, 2q35, 2p24.1, *TERT*-rs10069690, *ESR1*, *TOX3*, 19p13.1, *RALY*), and we identified associations with TN breast cancer for 15 additional breast cancer loci ($p<0.05$: *PEX14*, 2q24.1, 2q31.1, *ADAM29*, *EBF1*, *TCF7L2*, 11q13.1, 11q24.3, 12p13.1, *PTHLH*, *NTN4*, 12q24, *BRCA2*, *RAD51L1*-rs2588809, *MKL1*). Further, two SNPs independent of previously reported signals in *ESR1* (rs12525163 Odds Ratio (OR)=1.15, $p=4.9x10^{-4}$) and 19p13.1 (rs1864112 OR=0.84, $p=1.8x10^{-9}$) were associated with TN breast cancer. A polygenic risk score (PRS) for TN breast cancer based on known breast cancer risk variants showed a 4-fold difference in risk between the highest and lowest PRS quintiles (OR=4.03, 95% CI 3.46-4.70, $p=4.8x10^{-69}$). This translates to an absolute risk for TN breast cancer ranging from 0.8% to 3.4%, suggesting that genetic variation may be used for TN breast cancer risk prediction.

Summary

In a genome-wide scan, we show that 30 variants in 25 genomic regions are associated with risk of triple negative breast cancer. Women carrying many of the risk variants may have four-fold increased risk relative to women with few variants.

Introduction

Triple negative (TN) breast cancer is a distinct histopathological subtype of breast cancer that accounts for approximately 15% of all invasive breast cancers (1,2). This disease subtype is defined by low or no expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2). In addition, TN tumors tend to be of higher histologic grade, more proliferative, and have medullary and metaplastic features (1,3). Women with TN tumors are more likely to be *BRCA1* mutation carriers, young or premenopausal, and African American or Hispanic ethnicity, and experience higher rates of disease recurrence and progression, especially within the first three years following treatment, compared to other breast cancer subtypes (4). TN breast cancer is also associated with low socioeconomic status, an earlier age at menarche, higher body mass index (BMI) during premenopausal years, higher parity, and lower lifetime duration of breast feeding (1,5).

In addition to these epidemiologic factors, several common genetic variants have been established as risk factors for TN breast cancer (6). Among these, 19p13.1 (7), *TERT*-rs10069690 (8), and *MDM4* (9) are specific to TN breast cancer, such that these loci are not associated with risk of ER-positive or ER-negative, HER2-positive breast cancer. Four other loci (*RALY*/*EIF2S2*, *LGR6*, 2p24.1, *FTO*-rs11075995) associated with ER-negative but not ER-positive breast cancer (9,10) may also influence TN breast cancer risk. More recently, a large study by the Breast Cancer Association Consortium (BCAC) identified 46 additional common breast cancer susceptibility loci (11-13). While 26 of these loci were associated with ER-negative as well as ER-positive breast cancer, the

influence of the loci on TN breast cancer and other histopathological subtypes of breast cancer has not yet been assessed.

Given the substantial heterogeneity in genetic risk profiles for different breast cancer subtypes that we and others have demonstrated (14-17), we hypothesized that additional genetic variants for TN breast cancer remain to be identified. These may include variants that could not be detected by previous breast cancer genome wide association studies (GWAS) conducted predominantly with ER-positive breast cancer cases, and perhaps a subset of the 42 breast cancer hits recently identified by BCAC. In addition, recent evidence has shown that risk loci are often complex and may contain multiple independent risk associated variants that influence different subtypes of breast cancer (11-13). Here we presents results from a comprehensive analysis of genetic variants and TN breast cancer within the Triple Negative Breast Cancer Consortium (TNBCC), including a two-stage GWAS of TN breast cancer, examining the contributions of known breast cancer risk loci to TN breast cancer in terms of overall associations, independent signals, and expression quantitative loci (eQTLs), and estimating the cumulative effect of all common genetic risk factors on TN breast cancer risk.

Materials and methods

Ethics statement

Study participants were recruited under protocols approved by the Institutional Review Board at each institution and all subjects provided written informed consent.

Study participants: Triple Negative Breast Cancer Consortium (TNBCC)

TNBCC subjects included in this analysis were recruited by 22 studies in seven different countries (**Table S1**). In addition, data from four publicly available control GWAS data sets (Wellcome Trust Case Control Consortium UK 1958 Birth Cohort (WTCCC), National Cancer Institute's Cancer Genetic Markers of Susceptibility (CGEMS) project, Cooperative Health Research in the Region of Augsburg (KORA) study, and the Australian Twin Cohort study from the Queensland Institute of Medical Research (QIMR)) (n=3,180) were utilized. These studies are described in more detail in Supplementary Material and have been described in detail elsewhere (8,10,14).

Pathology and tumor markers

A TN breast cancer case was defined as an individual with an ER–negative, PR–negative and HER2–negative (0 or 1 by immunohistochemical staining (IHC)) breast cancer diagnosed after age 18. Criteria used for defining ER, PR, and HER2 status varied by study and have been previously described (8,10,14).

Triple-negative breast cancer genome-wide association study (GWAS)

Stage 1 of the TNBCC GWAS has been previously described (8,10,14). Briefly, 1,529 TN breast cancer cases and 3,399 country-matched controls from 10 study sites were genotyped using the Illumina 660-Quad SNP array, CNV370 SNP array, and 550-Duo SNP array (10). GWAS data for public controls were generated using the Illumina 660-Quad (QIMR), Illumina 550(v1) (CGEMS), Illumina 550 (KORA), and Illumina 1.2M (WTCCC). Genotype data from the various GWAS were independently evaluated by an

iterative QC process as previously described (10). Common SNP genotypes were imputed to HapMap phase 2 (release 21). Quantile-quantile plots showed no substantial evidence for cryptic population substructure or differential genotype calling between cases and controls. We excluded all SNPs with a MAF <0.05, imputation quality score <0.5, and effect size (beta) with absolute value <0.3.

Triple-negative breast cancer iCOGS (Stage 2) genotyping

The design of the iCOGS array (211,155 SNPs) and genotyping methods has been previously described (11). Briefly, samples were genotyped as part of the COGS project using a custom Illumina Infinium array (iCOGS) at two genotyping centers (Mayo Clinic, Genome Quebec). In this analysis, 1,263 cases and 1,105 controls from the TNBCC were genotyped on the iCOGS array at the Mayo Clinic, and 885 cases and 204 controls were genotyped at Genome Quebec. A total of 4,628 from the 6,087 TNBCC GWAS SNPs proposed for the iCOGS array yielded high-quality genotype data. A total of 147,762 SNPs from the iCOGS array overlapped with the TNBCC Stage 1 GWAS data.

DASL expression data

Expression profiles were generated for a total of 702 TN tumors (**Table S2**) using the Illumina Whole Genome cDNA-mediated Annealing, Selection, extension, and Ligation (DASL) v4.0 assay. Tumor samples were either whole 10 micron sections or 1 millimeter (mm) cores from formalin-fixed paraffin embedded (FFPE) tumor blocks. Whole sections were macrodissected to select the tumor region on the slide, guided by a pathologist-read hematoxylin and eosin (H&E) stained slide from the same block. RNA was extracted using the Roche High Pure RNA Isolation Kit (Indianapolis, USA). Samples were plated

randomly by study on 96-well plates with two universal human reference samples and two duplicate tumor RNA samples. DASL expression profiling was performed by the Mayo Clinic Medical Genome Facility Gene Expression Core (Rochester, MN).

Statistical analyses

SNP analyses: Estimated per-allele log (odds ratios) and standard errors were calculated using unconditional logistic regression of the allele counts (dosage for imputed data). Analyses were adjusted by country of origin and principal components as previously described (10). Analyses assumed a log-additive genetic model and *P*-values were based on the one degree-of-freedom Wald test.

Expression data: Raw intensity values for tumor samples were summarized using box-plots. After $\log_2$-transformation of raw intensity values, a per-sample quality (stress) measure was calculated (18). Samples with stress >0.5, denoting a 2-fold change in the overall expression values after normalization, and replicates with the higher stress measure, were excluded (n=34). Log_2-transformed intensity values were median-quantile normalized. Probes with a p-value of detection >0.05 in all samples were excluded (n=713) for a total of 28,664 probes analyzed. Samples were median-centered by 96-well plate to correct for batch effects. Tumors with *ESR1* (ILMN_1678535) expression values more than 1.5 standard deviations from the median were excluded (n=72). Of the 596 remaining TN tumors, 486 also had genotype data from the pooled GWAS and iCOGS data and were used in subsequent analyses.

Expression quantitative trait loci (eQTL) analyses: Cis associations between SNPs and probe expression, defined as probes within 1Mb of the SNP of interest, were calculated for the 24 loci of interest (**Table 1**). Associations were evaluated using a robust linear model to appropriately account for outliers in the expression data. For the 30 TN-associated SNPs reported in this study, cis-eQTL associations at $p<0.05$ were considered significant. For all remaining SNPs, a false discovery rate (FDR) was generated using 100 permutations and cis-eQTLs were excluded at a 10% FDR threshold (equivalent to $p<1.0 \times 10^{-3}$).

Polygenic risk score: Polygenic risk scores (PRS) were calculated using a leave-one-out cross validation approach. Two scores were calculated, one using all known breast cancer risk SNPs and one using the 30 TN breast cancer-associated risk SNPs reported in this study. For the first model, a total of 74 SNPs were used (**Table S3**), including proxy SNPs ($R^2>0.8$) from three of seven loci (1p13.2, *RALY*, *MKL1*) missing genotype data for the original breast cancer risk SNPs. For the second model only the 30 SNPs associated with TN risk were included. For each subject, TN odds ratios were estimated for each SNP after dropping that subject from the data set. The log odds ratio for the tested allele for each SNP was multiplied by the number of tested alleles (0, 1, or 2) for the subject. The PRS for a subject was calculated as the sum across SNPs. Quintiles were determined based on the distribution of the PRS in controls. Odds ratios for TN breast cancer were calculated comparing each quintile to the median (3^{rd}) quintile or the lowest (1^{st}) quintile as the reference.

Cumulative risk estimates of TN breast cancer in US Caucasian women were calculated using a multi-step approach. Both age-specific SEER breast cancer incidence rates (http://seer.cancer.gov) and age-specific ratios of TN breast cancer to overall breast cancer from the California Cancer Registry (CCR) were obtained (3). Age-specific incidence rates for TN breast cancer were estimated by multiplying the overall age-specific breast cancer incidence rates from SEER by the calculated proportion of TN breast cancer among all breast cancers within age groups from the CCR. Finally, we estimated the cumulative risk of TN breast cancer by integrating these age-specific incidence rates for TN breast cancer. Changes in cumulative risk by PRS quintile were calculated using the OR estimates obtained as described above. Quintile-specific cumulative risk estimates were calculated by multiplying cumulative risk estimates by both the OR for that quintile and the attributable risk (AR) for the PRS. Attributable risk for the PRS was calculated using the following formula, where the OR for each case was assigned according to the quintile to which that case belonged:

$$AR = 1 - \frac{\sum_{i=1}^{n\ cases} OR_i^{-1}}{n\ cases}$$

Discriminatory accuracy of the PRS was assessed using receiver operating characteristic (ROC) curves and corresponding areas under the curve (AUC) and 95% confidence intervals, generated using the fitted probabilities of TN cases status from a logistic regression model using the PRS as a continuous predictor variable.

Results

TNBCC two-stage GWAS

Stage 1 of the TN GWAS (8,10,14) was comprised of 1,529 TN cases and 3,399 country-matched controls (**Table S1).** There was no evidence for genomic inflation (λ=1.04) (10), and no SNPs achieved genome-wide significance ($p < 5 \times 10^{-8}$). Candidate SNPs were selected for Stage 2 replication based on a log-additive trend-test of directly genotyped SNPs (p<0.01). A total of 4,785 SNPs were included in Stage 2 on the iCOGS genotyping array (11) and genotyped on 2,148 TN cases and 1,309 country-matched controls from the TNBCC (**Table S1**). In Stage 2 alone, no SNPs achieved significance after Bonferroni correction for 4,785 tests. However, there was substantial enrichment when comparing the observed with the expected number of SNPs at various levels of significance. Specifically, there were 357 SNPs (7.4%) at p<0.05 compared to the expected number of 240 SNPs (1.5-fold enrichment), 48 SNPs at $p<5x10^{-3}$ compared to 24 expected (2-fold enrichment) and 9 SNPs compared to 2.4 expected (3.75-fold enrichment) at $p<5x10^{-4}$.

A pooled analysis of the TNBCC GWAS and iCOGS data for a total of 3,677 TN cases and 4,708 controls was performed. SNPs in the 19p13.1 (rs2363956 OR=0.82, $p=2.33x10^{-8}$) and *PTHLH* (rs10771399 OR=0.72, $p=1.55x10^{-8}$) loci displayed genome-wide significant associations with TN breast cancer (**Table 1**). SNPs in the 19p13.1 locus have previously been specifically associated with both TN breast cancer and *BRCA1*-related breast cancer. SNPs in the *PTHLH* locus have previously been associated with breast cancer (9), but this is the first report of an association with TN breast cancer. After Bonferroni correction for 4,785 tests, an additional five SNPs in *MDM4*, *ESR1*, *PTHLH*, and 19p13.1 were significantly associated with risk of TN breast cancer (**Table S4**).

Known associations between TN breast cancer and variants in the *MDM4* and *ESR1* loci (7,9,14) were also confirmed. The 10 SNPs with the lowest p-values not located in known breast cancer loci are shown in Table S5.

Known breast cancer susceptibility loci

Next we evaluated whether any known breast cancer susceptibility SNPs that were genotyped or imputed in the combined TNBCC data were associated with risk of TN breast cancer (**Tables S3, S6**). Genotype data was available for 74 of the 78 known breast cancer risk SNPs (**Table S3**). Of these, a total of 26 SNPs were associated with risk of TN breast cancer at p<0.05 (**Table 1**). These included 11 SNPs in the 2q35, *LGR6*, *MDM4*, *TERT*, *ESR1*, *TOX3*, and 19p13.1 loci that were previously associated with TN breast cancer. Of these, rs2588809 in the *RAD51L1* locus replaced rs999737 from earlier studies as the SNP most significantly associated with TN breast cancer (**Table 1**). A further 15 SNPs at the *PEX14*, 2q14.2, 2q31.1, *ADAM29*, *EBF1*, *TCF7L2*, 11q13.1, 11q24.3, 12p13.1, *NTN4*, *PTHLH*, 12q24, *BRCA2*, and *MLK1* loci showed associations with TN breast cancer risk, which have not previously been described (**Table 1**). In contrast, SNPs in *CASP8*, *MAP3K1*, and *LSP1*, which had been marginally associated with TN breast cancer in other studies (6), were not associated with TN disease in this combined analysis. Furthermore, the *FTO* locus that was recently associated with ER-negative disease (9) was not significantly associated with TN breast cancer in our study (rs11075995 OR=1.08, 95% CI 1.00-1.17, p=0.065).

Two of the TN breast cancer risk loci we identified contained additional SNPs with lower p-values for TN breast cancer than the reported SNP (*ESR1*, *PEX14*) (**Table S7a**). In 1000 Genomes data from Caucasians (19) these new SNPs were in high linkage disequilibrium (LD) with the originally reported SNPs suggesting that the additional SNPs better capture the associations with TN breast cancer. Additionally, while the reported SNP in the *CASP8* locus was not associated with TN breast cancer risk, another highly correlated SNP (rs3731711) (R^2=0.93) was significantly associated with risk (p=1.0 x 10^{-4}) (**Table S7b**). Finally, a SNP in the *RALY* locus, for which the reported SNP was not genotyped in our study, was significantly associated with TN risk (rs6142050 p=3.8 x 10^{-3}) (**Table S7c**). The *RALY* SNP was in high LD with the reported SNP in these regions.

To better understand the patterns of risk associated with genetic variation in these TN-associated loci, we looked for independent signals in each locus by adjusting each SNP in a 250kb region for the SNP with the lowest p-value. We found evidence for additional independent associations in the 19p13.1 locus (**Figure S1**) and the *ESR1* locus (**Figure S2**). In a multivariable model for 19p13.1, including rs8100241 and rs1864112, both SNPs remained strongly associated with risk of TN breast cancer (**Table 2**). The newly identified rs1864112 is not in LD with rs8100241 (R^2= 0.025) or rs8170 (R^2= 0.093). Using data from the ENCODE project (20), we found that rs1864112 is located in a region overlapping a DNaseI hypersensitivity site and promoter-associated histone mark (H3KMe1) site in primary human mammary epithelial cells (HMEC), indicating that this SNP may a role in transcriptional regulation. In *ESR1*, both rs9397437 and rs12525163

were associated with TN risk, with the significance of the association for rs12525163 increasing in the multivariate model (**Table 2**). This SNP is not in LD with either of the *ESR1* SNPs previously associated with breast cancer risk (rs9397437, R^2=0.005; rs2046210, R^2=0.021), and does not overlap with any DNaseI hypersensitivity, H3K4Me1, or H3K4Me3 sites. These data provide evidence for two novel TN risk SNPs in 19p13.1 and *ESR1*.

Expression quantitative trait loci for TN risk loci

To better understand the potential biological mechanisms that underlie the associations between SNPs in the 25 loci (**Tables 1-2, Table S7b-c**) and risk of TN breast cancer, we conducted an expression quantitative trait locus (eQTL) analysis. Genome-wide mRNA expression data were available for 578 TN cases from corresponding clinically defined TN breast tumors, of which 62 were excluded because of *ESR1* expression in the tumors (see methods), for a total of 516 TN cases included in the eQTL analysis (**Table S2**). We then examined each of the 30 SNPs present in the 25 TN loci of interest (**Tables 1-2, Table S7b-c**) for associations with gene expression. We found evidence for 51 cis-associations with the 30 TN risk SNPs ($p<0.05$) (**Table S8**), involving 46 genes in the 25 loci. Functional annotation of the eQTL SNPs by HaploReg (21) showed that eQTL SNPs were more likely located in normal mammary epithelial cell enhancer elements (HMEC: 9 observed vs. 3.1 expected, $p=3.6\times10^{-3}$) and DNase hypersensitivity sites (HMEC: 7 observed vs. 1 expected, $p=7.5\times10^{-5}$).

A recent study functionally annotated SNPs in high LD (R^2>0.5) with 71 known breast cancer risk SNPs (22) using histone modification ChIP-seq and DNaseI-seq data published as part of the ENCODE project (20), Formaldehyde-Assisted Isolation of Regulatory Elements data, and publically available eQTL data. Twenty-three of the 25 TN risk loci we describe here were included in this report (**Table S9**); among these, 8 (34.8% in TN vs. 26.8% overall) had high-LD SNPs in transcription start site (TSS) regions, 17 (73.9% in TN vs. 77.5% overall) had high-LD SNPs in enhancers, and 6 (26.1% in TN vs. 22.5% overall) had high-LD SNPs in exons, suggesting a slight enhancement for TN risk SNPs in TSS regions. The vast majority of functional SNPs identified by Rhie, et al. were not genotyped or imputed in our data. The functional SNPs rs633800 and rs11227311 in the 11q13.1 locus were associated with *CTSW* expression, which we also observed with the correlated index SNP, rs3903072 (**Table S8**).

We next analyzed all other SNPs in the 25 TN risk loci for eQTLs (within 1Mb flanking the top risk SNP) and identified 41 candidate cis-eQTLs in 14 TN risk loci, involving 35 unique SNPs and 26 unique genes, based on a 10% false discovery rate (FDR) threshold (**Table S10**). The 35 eQTL SNPs were enriched in HMEC enhancers (6 observed vs. 1.9 expected, p=0.012) and mammary ductal adenocarcinoma DNase hypersensitivity sites (T47D: 2 observed vs. 0.4 expected, p=0.049). Notably, the *MDM4*, *TERT*, and 19p13.1 TN-specific risk loci contained cis-eQTLs (**Table S10**). Among these 35 eQTL SNPs, 8 were associated with *CTSW* expression and were in low to moderate LD ($0.084 \leq R^2 \leq 0.516$) with synonomous exonic mutations (**Table S11**), SNPs in TSS regions

(**Table S12**), and SNPs in enhancers (**Table S13**) identified by Rhie, et al. (22). No other eQTL SNPs we identified were correlated with putative functional SNPs.

Sensitivity Analysis

We conducted a sensitivity analysis of all 30 TN risk SNPs identified in this study (**Tables 1-2, Table S7b-c**) to evaluate the influence of potential misclassification with respect to ER status. We first examined the 30 SNPs in 578 TN cases with expression data and 4,638 country-matched controls. The ORs for these SNPs were very similar to the ORs observed in the overall TN analysis (**Table S14**), although the reduction in sample size produced some variability. We then repeated the analysis after excluding 62 TN cases because of *ESR1* expression in the tumors. All ORs were in the same direction and similar in magnitude for the majority of these SNPs, with the exception of 2q14.2 and *ADAM29* moving slightly closer towards the null. While the numbers are low, the results further strengthen the evidence that these 30 SNPs are associated with TN breast cancer risk.

Polygenic risk score

These results provide strong evidence that at least 24 of the 74 known breast cancer susceptibility SNPs are individually associated with risk of TN breast cancer (**Table 1**). We implemented a polygenic risk score (PRS) to approximate the combined effect of these SNPs on risk of TN disease. The PRS was calculated using all reported SNPs in known breast cancer loci for which genotype data were available (n=74, **Table S3**), both to avoid bias from data-driven SNP selection and to account for SNPs that may be

associated with TN risk that did not achieve significance in our study due to limited study size. Compared to the median quintile, an individual in the first or second quintile of the PRS was 0.51-fold or 0.76-fold less likely to have TN breast cancer, respectively (**Table 3**). In contrast, an individual in the fourth or fifth quintile of the PRS was 1.29-fold or 2.05-fold more likely to have TN breast cancer compared to subjects in the median quintile. Further, our data show that there is more than 4-fold difference in risk comparing those in the highest versus lowest quintiles (**Table S15**). The ROC curves for predicting TN breast cancer using the 74-SNP PRS produced an AUC of 0.64 (95% CI 0.63-0.65) (**Figure S3**). Applying the PRS to the population-based cumulative risk (up to age 90 years) of TN breast cancer among Caucasian women, defined as approximately 1.8% (see methods), yielded an estimated cumulative risk of TN breast cancer of 3.4% for women in the highest PRS quintile and 0.8% for women in the lowest PRS quintile (**Figure 1**).

To better understand how the additional TN risk SNPs reported in this study contribute to cumulative risk beyond the 74 overall breast cancer variants, the PRS was recalculated using all 30 TN risk SNPs identified in this study (**Tables 1-2, Table S7b-c**). Estimates were slightly stronger for each PRS quintile compared to the 74-SNP PRS (**Table 3**), and the discriminatory accuracy of the 30-SNP PRS was comparable to the 74-SNP PRS (**Figure S3**). This suggests that the identification of additional TN risk loci may improve the stratification of cumulative risk estimates for TN breast cancer (**Figure S4**). These findings also suggest that additional prospective studies are needed in order to understand the implications of these genetic data for risk prediction of TN and other subtypes of

breast cancer. Considering all known TN risk variants simultaneously is a significant step towards understanding how common genetic variants can be used for TN risk prediction, which will be enhanced by the incorporation of traditional epidemiologic risk factors in future studies.

Discussion

In this report, we present results from the first two-stage GWAS of TN breast cancer in Caucasian women. Variants in the *PTHLH* and 19p13.1 loci showed genome wide significant associations ($p<5.0 \times 10^{-8}$) with TN disease (Tables 1 and 2). Ten SNPs with near-genome associations with TN breast cancer (**Table S5)** warrant follow-up in larger studies of TN breast cancer. In addition, 26 of 74 known overall breast cancer risk SNPs were associated with TN breast cancer (**Table1, Table S6**). Specifically, this study confirmed TN associations with SNPs in ten loci (*LGR6*, *MDM4*, *CASP8*, 2q35, 2p24.1, *TERT*-rs10069690, *ESR1*, *TOX3*, 19p13.1, *RALY*) and identified TN associations with 15 other loci. Furthermore, two novel signals that are independent of previously known risk associated SNPs were identified in the *ESR1* and 19p13.1 loci (**Table 2**). Given the complexity of known breast cancer risk loci such as *CCND1* and *TERT* (12,13), further studies involving extensive fine-mapping, haplotyping, and functional characterization are needed for full understanding of the relationship between genetic variation in these loci and risk of TN breast cancer.

To gain some insight into whether the TN risk SNPs we identified have stronger effects for TN breast cancer compared to ER-negative breast cancer, we compared 25 of the SNPs in our combined analysis for which data were available from a recent ER-negative meta-analysis (9). As expected, stronger ORs were observed in our TN study compared to the ER-negative study for *MDM4*, *TERT* (rs10069690), and 19p13.1 (**Table 1**), which have previously been shown to be TN-specific loci (7-9). In addition, stronger ORs were observed in our TN study for 2q14.2, *ESR1*, *TCF7L2*, 11q13.1, 12p13.1, and *PTHLH* in TN compared to the ER-negative study. Furthermore, four of the TN loci (2q31.1, *ADAM29*, 12q24, and *RAD51L1* rs2588809) had no reported association with ER-negative breast cancer. Studies that directly compare ER-negative, non-TN to TN breast cancer are required to determine whether any of these loci are TN-specific.

In addition, we have provided evidence for SNP-mediated regulation of gene expression in these TN risk loci through cis-eQTL analyses involving over 500 TN breast tumors. Many of the 27 TN risk SNPs (**Table S8**) and an additional 35 SNPs in the TN risk loci (**Table S10**) that were associated with gene expression were located in transcriptional enhancers and DNase hypersensitivity sites in normal mammary epithelial cell lines, suggesting direct effects on gene transcription. Several interesting candidate genes were identified as cis-eQTLs. *PTHLH*, which encodes parathyroid hormone-like hormone, influences mammary gland development through regulation of epithelial to mesenchymal cellular interactions, is involved in lactation, and is expressed in 60% of breast cancers (23-25). *IGFBP2* (insulin-like growth factor binding protein 2) in the 2q35 locus displays elevated expression in breast tumors and promotes the growth and survival of breast

epithelial cells though regulation of the estrogen receptor ER-α (26,27). *TBX3* in the 12q24 locus encodes T-box 3, a transcription factor involved in developmental regulation. that is overexpressed in breast tumors (28) and can induce mammary stem-like cells and mammary gland hyperplasia in mice (29). While the cis-eQTL results suggest mechanisms by which certain loci influence TN breast cancer risk, additional functional validation of these SNP-gene expression relationships in breast cancer cell lines is needed.

Beyond etiology, the identification of 30 TN risk SNPs provides an opportunity to better understand how genetic variation may inform TN breast cancer risk prediction. As we have shown through our PRS, where we observed a 4-fold difference in risk between the highest and lowest PRS quintiles of the TN breast cancer population, it may be possible to identify women who are substantially above or below population-level risk of TN breast cancer. Our PRS had better discriminatory accuracy (AUC=0.64) compared to that of the Gail model applied in the Women's Health Initiative (overall AUC=0.58, 95% CI 0.58-0.62; ER-negative AUC=0.50, 95% CI 0.45-0.54) (30). It is also likely that the inclusion of additional TN breast cancer risk SNPs will further stratify these women with respect to cumulative incidence of TN breast cancer. It will also be important to combine these triple negative risk SNPs with known epidemiologic risk factors such as parity, age at menarche, BMI during premenopausal years, and duration of breast feeding (1,5) to understand the cumulative influence on TN breast cancer risk. An important limitation of this study was that the PRS was applied to the study population from which the TN breast cancer risk estimates were derived. While our cross-validation approach mitigates

potential bias arising from this approach, it will be important to develop a risk model with these SNPs and validate the model in an independent study population. Overall, the findings provide strong evidence that integration of SNPs into predictive models will have a substantial impact on our ability to identify women at elevated risk of TN breast cancer.

Supplementary material

Supplementary Tables 1- 15 and Supplementary Figures 1-3 can be found at http://carcin.oxfordjournals.org/

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References

1. Foulkes, W.D., *et al.* (2010) Triple-negative breast cancer. *N Engl J Med*, **363**, 1938-48.
2. (2012) American Cancer Society. Breast Cancer Facts & Figures, 2011-2012. American Cancer Society, Atlanta, GA.
3. Bauer, K.R., *et al.* (2007) Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. *Cancer*, **109**, 1721-8.
4. Nofech-Mozes, S., *et al.* (2009) Patterns of recurrence in the basal and non-basal subtypes of triple-negative breast cancers. *Breast Cancer Res Treat*, **118**, 131-7.
5. Millikan, R.C., *et al.* (2008) Epidemiology of basal-like breast cancer. *Breast Cancer Res Treat*, **109**, 123-39.
6. Stevens, K.N., *et al.* (2013) Genetic Susceptibility to Triple-Negative Breast Cancer. *Cancer research*.
7. Stevens, K.N., *et al.* (2012) 19p13.1 is a triple negative-specific breast cancer susceptibility locus. *Cancer Res*.
8. Haiman, C.A., *et al.* (2011) A common variant at the TERT-CLPTM1L locus is associated with estrogen receptor-negative breast cancer. *Nat Genet*, **43**, 1210-4.
9. Garcia-Closas, M., *et al.* (2013) Genome-wide association studies identify four ER negative-specific breast cancer risk loci. *Nature genetics*, **45**, 392-8.
10. Siddiq, A., *et al.* (2012) A meta-analysis of genome-wide association studies of breast cancer identifies two novel susceptibility loci at 6q14 and 20q11. *Hum Mol Genet*.
11. Michailidou, K., *et al.* (2013) Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nature genetics*, **45**, 353-61.
12. Bojesen, S.E., *et al.* (2013) Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. *Nature genetics*, **45**, 371-84.
13. French, J.D., *et al.* (2013) Functional Variants at the 11q13 Risk Locus for Breast Cancer Regulate Cyclin D1 Expression through Long-Range Enhancers. *American journal of human genetics*.
14. Stevens, K.N., *et al.* (2011) Common breast cancer susceptibility loci are associated with triple-negative breast cancer. *Cancer Res*, **71**, 6240-9.
15. Figueroa, J.D., *et al.* (2011) Associations of common variants at 1p11.2 and 14q24.1 (RAD51L1) with breast cancer risk and heterogeneity by tumor subtype: findings from the Breast Cancer Association Consortium. *Hum Mol Genet*, **20**, 4693-706.
16. Broeks, A., *et al.* (2011) Low penetrance breast cancer susceptibility loci are associated with specific breast tumor subtypes: findings from the Breast Cancer Association Consortium. *Hum Mol Genet*, **20**, 3289-303.
17. Milne, R.L., *et al.* (2011) Confirmation of 5p12 as a susceptibility locus for progesterone-receptor-positive, lower grade breast cancer. *Cancer Epidemiol Biomarkers Prev*, **20**, 2222-31.

18. Mahoney, D.W., *et al.* (2013) Quality assessment metrics for whole genome gene expression profiling of paraffin embedded samples. *BMC research notes*, **6**, 33.
19. Johnson, A.D., *et al.* (2008) SNAP: a web-based tool for identification and annotation of proxy SNPs using HapMap. *Bioinformatics*, **24**, 2938-9.
20. Consortium, E.P., *et al.* (2012) An integrated encyclopedia of DNA elements in the human genome. *Nature*, **489**, 57-74.
21. Ward, L.D., *et al.* (2012) HaploReg: a resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants. *Nucleic acids research*, **40**, D930-4.
22. Rhie, S.K., *et al.* (2013) Comprehensive functional annotation of seventy-one breast cancer risk Loci. *PLoS One*, **8**, e63925.
23. Fleming, N.I., *et al.* (2009) Parathyroid hormone-related protein protects against mammary tumor emergence and is associated with monocyte infiltration in ductal carcinoma in situ. *Cancer Res*, **69**, 7473-9.
24. Sowers, M.F., *et al.* (1996) Elevated parathyroid hormone-related peptide associated with lactation and bone density loss. *JAMA*, **276**, 549-54.
25. Southby, J., *et al.* (1990) Immunohistochemical localization of parathyroid hormone-related protein in human breast cancer. *Cancer Res*, **50**, 7710-6.
26. Foulstone, E.J., *et al.* (2013) Insulin-Like Growth Factor Binding Protein 2 (IGFBP-2) Promotes Growth and Survival of Breast Epithelial Cells: Novel Regulation of the Estrogen Receptor. *Endocrinology*, **154**, 1780-93.
27. Busund, L.T., *et al.* (2005) Significant expression of IGFBP2 in breast cancer compared with benign lesions. *Journal of clinical pathology*, **58**, 361-6.
28. Yarosh, W., *et al.* (2008) TBX3 is overexpressed in breast cancer and represses p14 ARF by interacting with histone deacetylases. *Cancer Res*, **68**, 693-9.
29. Liu, J., *et al.* (2011) TBX3 over-expression causes mammary gland hyperplasia and increases mammary stem-like cells in an inducible transgenic mouse model. *BMC Dev Biol*, **11**, 65.
30. Chlebowski, R.T., *et al.* (2007) Predicting risk of breast cancer in postmenopausal women by hormone receptor status. *J Natl Cancer Inst*, **99**, 1695-705.

Table 1. Known breast cancer susceptibility SNPs associated with TN breast cancer

						TN			ER-negative (9)		
SNP	**G/I**	**Chr**	**Position**	**Locus**	**Allele**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
a) Previously reported TN associations											
rs6678914	G	1	200453799	*LGR6*	A	0.90	(0.84-0.97)	3.31×10^{-3}	0.91	(0.88-0.94)	1.4×10^{-8}
rs4245739	I	1	202785465	*MDM4*	C	1.19	(1.11-1.29)	4.00×10^{-6}	1.14	(1.10-1.18)	2.1×10^{-12}
rs13387042	G	2	217614077	2q35	G	0.93	(0.87-1.00)	0.049	0.95	(0.92-0.98)	0.002
rs12710696	I	2	19184284	2p24.1	A	1.11	(1.04-1.19)	3.51×10^{-3}	1.10	(1.06-1.13)	4.6×10^{-8}
rs10069690	I	5	1332790	*TERT*	A	1.24	(1.14-1.34)	1.43×10^{-7}	1.15	(1.11-1.20)	4.5×10^{-12}
rs2736108[a]	G	5	1350488	*TERT*	T	0.77	(0.69-0.87)	8.33×10^{-6}	0.89[b]	(0.83-0.93)	1.41×10^{-8}
rs3757318	G	6	151955806	*ESR1*	A	1.33	(1.17-1.51)	9.25×10^{-6}	1.22	(1.15-1.30)	2.5×10^{-11}
rs2046210	I	6	151990059	*ESR1*	A	1.16	(1.08-1.24)	5.26×10^{-5}	1.15	(1.11-1.19)	4.9×10^{-16}
rs3803662	G	16	51143842	*TOX3*	A	1.09	(1.01-1.17)	0.022	1.14	(1.10-1.18)	5.5×10^{-13}
rs8170	G	19	17250704	19p13.1	A	1.26	(1.16-1.37)	1.26×10^{-7}	1.15	(1.11-1.20)	9.3×10^{-13}
rs2363956	G	19	17255124	19p13.1	C	0.82	(0.77-0.88)	2.33×10^{-8}	NA	NA	NA
b) Newly identified TN associations											
rs616488	G	1	10488802	*PEX14*	G	0.91	(0.85-0.98)	9.73×10^{-3}	0.91	(0.88-0.94)	1.0×10^{-8}
rs4849887	G	2	120961592	2q14.2	A	0.89	(0.79-1.00)	0.041	0.93	(0.88-0.99)	0.013
rs2016394	G	2	172681217	2q31.1	A	1.10	(1.03-1.18)	6.90×10^{-3}	1.00	(0.97-1.04)	0.85
rs6828523	I	4	176083001	*ADAM29*	A	0.84	(0.75-0.93)	1.33×10^{-3}	0.99	(0.95-1.04)	0.77
rs1432679	G	5	158176661	*EBF1*	G	1.10	(1.02-1.17)	8.62×10^{-3}	1.08	(1.04-1.11)	6.7×10^{-6}
rs7904519	G	10	114763917	*TCF7L2*	G	1.12	(1.05-1.20)	9.95×10^{-4}	1.06	(1.03-1.09)	2.9×10^{-4}
rs3903072	I	11	65339642	11q13.1	A	0.92	(0.86-0.99)	0.024	0.97	(0.94-1.00)	0.027
rs11820646	I	11	128966381	11q24.3	A	0.92	(0.86-0.98)	0.016	0.94	(0.91-0.97)	2.3×10^{-4}
rs12422552	I	12	14305198	12p13.1	C	1.13	(1.04-1.21)	2.70×10^{-3}	1.05	(1.02-1.09)	0.005
rs10771399	I	12	28046347	*PTHLH*	G	0.72	(0.64-0.80)	1.55×10^{-8}	0.83	(0.79-0.87)	2.4×10^{-12}
rs17356907	G	12	94551890	*NTN4*	G	0.90	(0.84-0.97)	7.55×10^{-3}	0.92	(0.89-0.96)	9.3×10^{-6}
rs1292011	G	12	114320905	12q24	G	1.08	(1.01-1.16)	0.035	0.99	(0.96-1.02)	0.44
rs11571833	I	13	31870626	*BRCA2*	T	1.44	(1.05-1.96)	0.023	1.52	(1.31-1.77)	6.0×10^{-6}
rs2588809	I	14	67730181	*RAD51L1*	A	0.91	(0.83-1.00)	0.041	1.00	(0.96-1.05)	0.94
rs6001930[a]	G	22	39206180	*MLK1*	C	1.21	(1.02-1.43)	0.025	1.14	(1.08-1.20)	1.6×10^{-6}

a Genotyped in stage 2 only on the iCOGS platform (2,148 cases, 1,309 controls)
b ER-negative breast cancer risk results for rs2736108 from Bojesen, et al. (12)

Table 2. Multiple independent SNPs in 19p13.1 and *ESR1*

			Single-SNP analysis			Multiple SNP regression		
Locus	**SNP**	**Previously reported**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**

19p13.1	rs8100241	Yes	0.82	0.77-0.88	$1.8x10^{-8}$	0.81	0.75-0.97	$1.8x10^{-9}$
	rs1864112	No	0.86	0.79-0.92	$6.8x10^{-5}$	0.84	0.78-0.90	$5.5x10^{-6}$
ESR1	rs9397437	Yes	1.42	1.25-1.61	$8.9x10^{-8}$	1.15	1.27-1.65	$1.6x10^{-8}$
	rs12525163	No	1.12	1.04-1.21	$3.0x10^{-3}$	1.15	1.06-1.24	$4.9x10^{-4}$

Table 3. Polygenic risk score for TN breast cancer

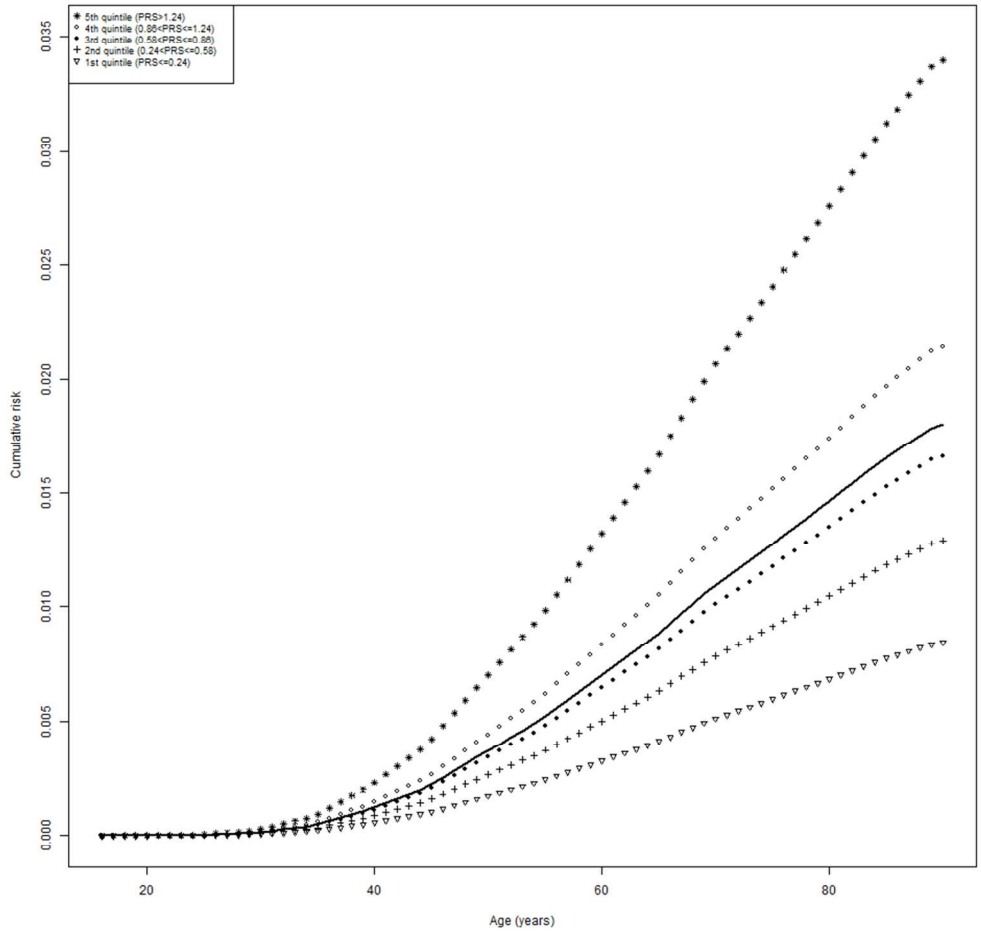
	74 SNPs				30 SNPs			
PRS Quintile	**Quintile definitions**	**OR**	**95% CI**	**p-value**	**Quintile definitions**	**OR**	**95% CI**	**p-value**
1	PRS≤0.24	0.51	0.43-0.60	$9.9x10^{-16}$	PRS≤-0.57	0.52	0.45-0.62	$3.9x10^{-15}$
2	0.24<PRS≤0.58	0.76	0.67-0.90	$1.1x10^{-3}$	-0.57<PRS≤-0.26	0.75	0.65-0.87	$1.6x10^{-4}$
3	0.58<PRS≤0.86	1.00	--	--	-0.26<PRS≤0.039	1.00	--	--
4	0.86<PRS≤1.24	1.29	1.12-1.48	$4.6x10^{-4}$	0.039<PRS≤0.40	1.37	1.20-1.57	$6.7x10^{-6}$
5	1.24<PRS	2.05	1.80-2.33	$1.8x10^{-25}$	0.40<PRS	2.13	1.87-2.43	$1.1x10^{-29}$

Figure legends

Figure 1. Cumulative incidence of TN breast cancer stratified by 74-SNP polygenic risk score.

The effect of the 74-SNP polygenic risk score (PRS) on cumulative risk of triple negative breast cancer (TNBC) among Caucasian women, stratified by PRS quintile, is shown. The population-based cumulative risk curve is shown as a solid black line, and the first through fifth quintile-specific cumulative risk estimates are shown as indicated by labels

Figure 1. Cumulative incidence of TN breast cancer stratified by 74-SNP polygenic risk score



338x338mm (72 x 72 DPI)

Table S1. Triple Negative Breast Cancer Consortium (TNBCC) studies

Stage	Study Abbreviation	Full Name	Platform	Country	Cases	Controls
Stage 1	ABCTB	Australian Breast Cancer Tissue Bank	Illumina 660-Quad	Australia	144	
	BBCC	Bavarian Breast Cancer Cases and Controls	Illumina 660-Quad	Germany	218	
	CGEMS	Cancer Genetic Markers of Susceptibility	Illumina 550 v.1	USA		947
	DFCI	Harvard Breast Cancer SPORE Blood Repository	Illumina 660-Quad	USA	246	
	FCCC	Fox Chase Cancer Center	Illumina 660-Quad	USA	120	
	GENICA	Gene Environment Interaction and Breast Cancer in Germany	Illumina 660-Quad	Germany	26	
	HEBCS	Helsinki Breast Cancer Study	Illumina HumanHap 550k DUO/ Illumina CNV370-Duo	Finland	83	219
	KORA	Cooperative Health Research in the Region of Augsburg	Illumina 550	Germany		215
	MARIE	Mammary Carcinoma Risk Factor Investigation	Illumina 660-Quad/ Illumina CNV370	Germany	148	
	MCBCS	Mayo Clinic Breast Cancer Study	Illumina 660-Quad	USA	147	
	MCCS	Melbourne Collaborative Cohort Study	Illumina 660-Quad	Australia	39	
	POSH	Prospective Study of Outcomes in Sporadic Versus Hereditary Breast Cancer	Illumina 660-Quad	UK	266	
	QIMR	Australian Twin Cohort study from the Queensland Institute of Medical Research	Illumina 610-Quad	Australia		650
	SBCS	Sheffield Breast Cancer Study	Illumina 660-Quad	UK	42	
	WTCCC	Wellcome Trust Case Control Consortium	Illumina 1.2M	UK		1368
				TOTAL	**1529**	**3399**
Stage 2	CTS	California Teachers Study	iCOGS	USA	68	71
	DEMOKRITOS	Demokritos	iCOGS	Greece	526	304
	FCCC	Fox Chase Cancer Center	iCOGS	USA	4	137
	GENICA	Gene Environment Interaction and Breast Cancer in Germany	iCOGS	Germany	33	30
	KUMC	Kansas University Medical Center	iCOGS	USA	74	
	MCBCS	Mayo Clinic Breast Cancer Study	iCOGS	USA	53	
	NBCS	Norwegian Breast Cancer Study	iCOGS	Norway	22	70
	NBHS	The Nashville Breast Health Study	iCOGS	USA	125	118
	OSU	Ohio State University	iCOGS	USA	276	279
	RPCI	Roswell Park Cancer Institute	iCOGS	USA	136	132
	SBCS	Sheffield Breast Cancer Study	iCOGS	UK	3	
	SKKDKFZS	Städtisches Klinikum Karlsruhe and Deutsches Krebsforschungszentrum Breast Cancer Study	iCOGS	Germany	136	168
	SUCCESS C	Simultaneous Study of Docetaxel Based Anthracycline Free Adjuvant Treatment Evaluation, as well as Life Style Intervention Strategies	iCOGS	Germany	605	
	WASHU	Washington University	iCOGS	USA	87	
				TOTAL	**2148**	**1309**

Table S2. TN subjects with DASL and SNP data

			Post-QC samples		Excluding ER+ samples	
	Sample type	Total	All	SNP data	All	SNP data
ABCTB	10 µm sections	101	97	86	95	84
Demokritos	10 µm sections	139	137	117	127	109
HEBCS	10 µm sections	92	89	48	79	43
KBCP*	1 mm cores	40	37	35	32	30
MCBCS	10 µm sections	31	30	28	29	27
MCCS	10 µm sections	23	23	16	22	15
NBHS	10 µm sections	18	16	15	16	15
POSH	1 mm cores	121	107	106	104	103
SBCS	10 µm sections	36	34	33	32	32
SKK	10 µm sections	101	98	94	60	58
		702	**668**	**578**	**596**	**516**

Table S3. 78 Known breast cancer susceptibility variants

Locus	SNP	Platform	Proxy	Chr.	Postion36	Alleles	AF2	Source
PEX14	rs616488	GWAS +iCOGS		1	10488802	A/G	0.33	(1)
1p13.2	rs11552449	N/A	rs3761936	1	114249912	C/T	0.17	(1)
1p11.2	rs11249433	GWAS +iCOGS		1	120982136	A/G	0.41	(2)
LGR6	rs6678914	GWAS +iCOGS		1	200453799	G/A	0.41	(3)
MDM4	rs4245739	GWAS +iCOGS		1	202785465	A/C	0.26	(3)
2p24.1	rs12710696	GWAS +iCOGS		2	19184284	C/T	0.36	(3)
2q14.2	rs4849887	GWAS +iCOGS		2	120961592	C/T	0.098	(1)
2q31.1	rs2016394	GWAS +iCOGS		2	172681217	G/A	0.48	(1)
CDCA7	rs1550623	GWAS +iCOGS		2	173921140	A/G	0.16	(1)
CASP8	rs1045485	GWAS +iCOGS		2	201857834	C/G	0.13	(4)
2q35	rs13387042	GWAS +iCOGS		2	217614077	A/G	0.47	(5)
2q35	rs16857609	GWAS +iCOGS		2	218004753	C/T	0.26	(1)
3p26.2	rs6762644	GWAS +iCOGS		3	4717276	A/G	0.4	(1)
SLC4A7	rs4973768	GWAS +iCOGS		3	27391017	C/T	0.48	(6)
TGFBR2	rs12493607	GWAS +iCOGS		3	30657943	G/C	0.35	(1)
TET2	rs9790517	GWAS +iCOGS		4	106304227	C/T	0.23	(1)
ADAM29	rs6828523	GWAS +iCOGS		4	176083001	C/A	0.13	(1)
TERT	rs10069690	GWAS +iCOGS		5	1332790	C/T	0.27	(7)
TERT	rs7705526	N/A	N/A	5	1338974	C/A	0.33	(8)
TERT	rs2736108	iCOGS	N/A	5	1350488	C/T	0.29	(8)
5p12	rs10941679	GWAS +iCOGS		5	44742255	A/G	0.27	(9)
MAP3K1	rs889312	GWAS +iCOGS		5	56067641	A/C	0.29	(10)
RAB3C	rs10472076	GWAS +iCOGS		5	58219818	T/C	0.38	(1)
PDE4D	rs1353747	GWAS +iCOGS		5	58373238	T/G	0.095	(1)
EBF1	rs1432679	GWAS +iCOGS		5	158176661	T/C	0.43	(1)
FOXQ1	rs11242675	GWAS +iCOGS		6	1263878	T/C	0.39	(1)
RANBP1	rs204247	GWAS +iCOGS		6	13830502	A/G	0.43	(1)
6q14.1	rs17529111	GWAS +iCOGS		6	82185105	T/C	0.22	(1)
ESR1	rs3757318	GWAS +iCOGS		6	151955806	G/A	0.07	(11)
ESR1	rs2046210	GWAS +iCOGS		6	151990059	G/A	0.35	(12)
7q35	rs720475	GWAS +iCOGS		7	143705862	G/A	0.25	(1)
8p21.1	rs9693444	GWAS +iCOGS		8	29565535	C/A	0.32	(1)
8q21.11	rs6472903	GWAS +iCOGS		8	76392856	T/G	0.18	(1)
HNF4G	rs2943559	GWAS +iCOGS		8	76580492	A/G	0.07	(1)
8q24	rs13281615	GWAS +iCOGS		8	128424800	A/G	0.42	(10)
8q24.21	rs11780156	GWAS +iCOGS		8	129263823	C/T	0.16	(1)
CDKN2A/B	rs1011970	GWAS +iCOGS		9	22052134	G/T	0.17	(11)
9q31.2	rs10759243	GWAS +iCOGS		9	109345936	C/A	0.39	(1)
9q31	rs865686	GWAS +iCOGS		9	109928299	T/G	0.37	(13)
ANKRD16	rs2380205	GWAS +iCOGS		10	5926740	C/T	0.44	(11)
DNAJC1	rs7072776	GWAS +iCOGS		10	22072948	G/A	0.29	(1)
DNAJC1	rs11814448	GWAS +iCOGS		10	22355849	A/C	0.02	(1)
ZNF365	rs10995190	GWAS +iCOGS		10	63948688	G/A	0.15	(11)

ZMIZ1	rs704010	GWAS +iCOGS		10	80511154	C/T	0.39	(11)
TCF7L2	rs7904519	GWAS +iCOGS		10	114763917	A/G	0.46	(1)
10q26.12	rs11199914	GWAS +iCOGS		10	123083891	C/T	0.32	(1)
FGFR2	rs2981579	GWAS +iCOGS		10	123327325	G/A	0.43	(11)
FGFR2	rs2981582	GWAS +iCOGS		10	123342307	G/A	0.41	(10)
LSP1	rs3817198	GWAS +iCOGS		11	1865582	T/C	0.32	(10)
11q13.1	rs3903072	GWAS +iCOGS		11	65339642	G/T	0.47	(1)
CCDN1	rs614367	GWAS +iCOGS		11	69037945	C/T	0.16	(11)
CCND1	rs554219	GWAS +iCOGS		11	69040823	C/G	0.14	(14)
11q24.3	rs11820646	GWAS +iCOGS		11	128966381	C/T	0.41	(1)
CCND1	rs75915166	N/A	N/A	11	69379161	A/C	0.31	(14)
12p13.1	rs12422552	GWAS +iCOGS		12	14305198	G/C	0.26	(1)
PTHLH	rs10771399	GWAS +iCOGS		12	28046347	A/G	0.11	(15)
NTN4	rs17356907	GWAS +iCOGS		12	94551890	A/G	0.3	(1)
12q24	rs1292011	GWAS +iCOGS		12	114320905	A/G	0.41	(15)
BRCA2	rs11571833	GWAS +iCOGS		13	31870626	A/T	0.008	(1)
PAX9	rs2236007	GWAS +iCOGS		14	36202520	G/A	0.21	(1)
RAD51L1	rs2588809	GWAS +iCOGS		14	67730181	C/T	0.16	(1)
RAD51L1	rs999737	GWAS +iCOGS		14	68104435	C/T	0.22	(2)
CCDC88C	rs941764	GWAS +iCOGS		14	90910822	A/G	0.34	(1)
TOX3	rs3803662	GWAS +iCOGS		16	51143842	G/A	0.29	(10)
FTO	rs17817449	GWAS +iCOGS		16	52370868	T/G	0.4	(1)
FTO	rs11075995	GWAS +iCOGS		16	52412792	T/A	0.24	(3)
CDYL2	rs13329835	GWAS +iCOGS		16	79208306	A/G	0.22	(1)
COX11	rs6504950	GWAS +iCOGS		17	50411470	G/A	0.27	(6)
18q11.2	rs527616	GWAS +iCOGS		18	22591422	G/C	0.38	(1)
CHST9	rs1436904	GWAS +iCOGS		18	22824665	T/G	0.4	(1)
MERIT40	rs8170	GWAS +iCOGS		19	17250704	G/A	0.19	(16)
MERIT40	rs2363956	GWAS +iCOGS		19	17255124	G/T	0.49	(16)
SSBP4	rs4808801	GWAS +iCOGS		19	18432141	A/G	0.35	(1)
19q13.31	rs3760982	GWAS +iCOGS		19	48978353	G/A	0.46	(1)
RALY	rs2284378	N/A	rs9753679	20	32051756	C/T	0.28	(17)
NRIP1	rs2823093	GWAS +iCOGS		21	15442703	G/A	0.26	(15)
22q12.2	rs132390	iCOGS	N/A	22	27951477	T/C	0.036	(1)
MKL1	rs6001930	iCOGS	rs6001913	22	39206180	T/C	0.11	(1)

Table S4. SNPs associated with TNBC in 2-stage GWAS

SNP	G/I	Chr.	Position	Locus	Allele	OR	95% CI	P-value
rs4245739	I	1	202785465	*MDM4*	C	1.19	1.11-1.29	4.0×10^{-06}
rs3757318	G	6	151955806	*ESR1*	A	1.33	1.17-1.51	9.2×10^{-06}
rs10484919	G	6	152016115	*ESR1*	A	1.31	1.16-1.47	5.7×10^{-06}
rs2619434	G	12	28056724	*PTHLH*	A	0.84	0.77-0.91	1.0×10^{-05}
rs8170	G	19	17250704	19p13.1	A	1.26	1.16-1.37	1.3×10^{-07}

Table S5. SNPs associated with TNBC ($p<1x10^{-3}$) in 2-stage GWAS, excluding known 78 loci

SNP	G/I	Chr.	Position	Genes	Allele	MAF	OR	95% CI	p-value
rs9761827	G	4	138635961	PCDH18	A	0.38	1.17	(1.09-1.26)	1.1x10-5
rs4425715	G	7	54233081	HPVC1	G	0.33	1.17	(1.09-1.26)	1.7 x10-5
rs1353868	G	3	174143933	SPATA16	A	0.36	1.17	(1.09-1.25)	2.6 x10-5
rs3855959	G	1	46406461	PIK3R3:TSPAN1:POMGNT1:C1orf190	A	0.40	0.86	(0.80-0.92)	3.0 x10-5
rs3810295	G	19	51830486	CALM3:PTGIR:GNG8:DACT3:PRKD2	A	0.13	1.24	(1.12-1.37)	4.3 x10-5
rs9257181	G	6	28862499	TRNAA-UGC:TRNAF-GAA:TRNAA-AGC:NOL5BP	A	0.28	1.17	(1.08-1.26)	4.9 x10-5
rs230310	G	1	40080306	TRIT1	A	0.23	1.18	(1.09-1.28)	6.0 x10-5
rs4717599	G	7	70607962	WBSCR17	G	0.27	0.85	(0.79-0.92)	6.6 x10-5
rs7020507	G	9	1705820	SMARCA2	G	0.14	0.81	(0.74-0.90)	6.9 x10-5
rs7790719	G	7	3684577	SDK1	A	0.28	0.86	(0.80-0.93)	8.0 x10-5

Table S6. 74 known breast cancer susceptibility loci and risk of TNBC compared to ER-negative and overall breast cancer risk estimates from BCAC

						TN			ER-negative (1)			Overall (1)		
SNP	G/I	Chr.	Position	Locus	Allele	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
rs616488	G	1	10488802	*PEX14*	G	0.91	(0.85-0.98)	$9.73x10^{-03}$	0.90	(0.87-0.94)	4.44×10^{-07}	0.94	(0.92-0.96)	2.13×10^{-08}
rs11249433	G	1	120982136	1p11.2	G	1.03	(0.96-1.10)	0.49	1.00	(0.96-1.04)	0.97	1.09	(1.07-1.11)	7.66×10^{-19}
rs6678914	G	1	200453799	*LGR6*	A	0.90	(0.84-0.97)	3.31×10^{-03}	0.92	(0.89-0.96)	2.83×10^{-05}	0.99	(0.97-1.01)	0.43
rs4245739	I	1	202785465	*MDM4*	C	1.19	(1.11-1.29)	4.00×10^{-06}	1.16	(1.11-1.20)	4.30×10^{-12}	1.03	(1.01-1.05)	7.03×10^{-03}
rs12710696	I	2	19184284	2p24.1	A	1.11	(1.04-1.19)	3.51×10^{-03}	1.10	(1.06-1.14)	8.56×10^{-07}	1.04	(1.02-1.06)	1.08×10^{-04}
rs4849887	G	2	120961592	2q14.2	A	0.89	(0.79-1.00)	0.041	0.91	(0.86-0.97)	5.94×10^{-03}	0.91	(0.88-0.94)	8.23×10^{-09}
rs2016394	G	2	172681217	2q31.1	A	1.10	(1.03-1.18)	6.90×10^{-03}	0.99	(0.96-1.03)	0.77	0.95	(0.93-0.97)	3.02×10^{-07}
rs1550623	G	2	173921140	*CDCA7*	G	0.94	(0.85-1.03)	0.16	0.95	(0.90-1.00)	0.046	0.94	(0.92-0.97)	2.08×10^{-05}
rs1045485	I	2	201857834	*CASP8*	C	1.00	(0.90-1.11)	0.99	0.97	(0.91-1.02)	0.22	0.97	(0.94-1.00)	0.037
rs13387042	G	2	217614077	2q35	G	0.93	(0.87-1.00)	0.049	0.96	(0.92-0.99)	0.021	0.88	(0.86-0.89)	3.04×10^{-41}
rs16857609	I	2	218004753	2q35	A	1.08	(1.00-1.16)	0.060	1.08	(1.03-1.12)	3.36×10^{-04}	1.08	(1.05-1.10)	7.23×10^{-12}
rs6762644	G	3	4717276	3p26.2	G	0.97	(0.90-1.04)	0.38	1.02	(0.98-1.06)	0.32	1.07	(1.04-1.09)	1.83×10^{-10}
rs4973768	G	3	27391017	*SLC4A7*	A	1.06	(0.99-1.14)	0.075	1.05	(1.01-1.09)	0.011	1.10	(1.08-1.12)	1.36×10^{-21}
rs12493607	I	3	30657943	*TGFBR2*	C	1.00	(0.93-1.07)	0.89	1.01	(0.97-1.05)	0.52	1.06	(1.04-1.08)	6.86×10^{-08}
rs9790517	I	4	106304227	*TET2*	A	1.00	(0.92-1.09)	0.94	1.03	(0.98-1.07)	0.22	1.05	(1.03-1.07)	2.71×10^{-05}
rs6828523	I	4	176083001	*ADAM29*	A	0.84	(0.75-0.93)	1.33×10^{-03}	1.01	(0.96-1.07)	0.66	0.89	(0.87-0.92)	1.22×10^{-13}
rs10069690	I	5	1332790	*TERT*	A	1.24	(1.14-1.34)	1.43×10^{-07}	1.16	(1.11-1.21)	1.69×10^{-12}	1.06	(1.04-1.09)	2.83×10^{-08}
rs2736108[a]	G	5	1350488	*TERT*	T	0.77	(0.69-0.87)	$8.33x10^{-6}$	0.89[b]	(0.83-0.93)	$1.41x10^{-8}$	0.94[b]	(0.92-0.95)	$6.73x10^{-9}$
rs10941679	I	5	44742255	5p12	G	1.02	(0.94-1.11)	0.59	1.04	(1.00-1.08)	0.080	1.13	(1.11-1.16)	3.57×10^{-29}
rs889312	G	5	56067641	*MAP3K1*	C	1.01	(0.94-1.09)	0.76	1.05	(1.01-1.10)	0.011	1.12	(1.10-1.15)	3.56×10^{-27}
rs10472076	I	5	58219818	*RAB3C*	G	0.96	(0.89-1.03)	0.24	1.05	(1.02-1.10)	5.87×10^{-03}	1.05	(1.03-1.07)	8.35×10^{-07}
rs1353747	G	5	58373238	*PDE4D*	C	1.01	(0.90-1.14)	0.89	0.91	(0.86-0.98)	6.65×10^{-03}	0.92	(0.89-0.95)	1.29×10^{-06}
rs1432679	G	5	158176661	*EBF1*	G	1.10	(1.02-1.17)	8.62×10^{-03}	1.08	(1.04-1.12)	2.36×10^{-05}	1.07	(1.05-1.09)	3.29×10^{-12}
rs11242675	G	6	1263878	*FOXQ1*	G	1.00	(0.93-1.07)	0.98	0.94	(0.90-0.98)	1.54×10^{-03}	0.95	(0.93-0.97)	4.29×10^{-08}
rs204247	G	6	13830502	*RANBP1*	G	1.03	(0.96-1.11)	0.36	1.01	(0.97-1.05)	0.58	1.05	(1.03-1.07)	2.67×10^{-07}
rs17529111	I	6	82185105	6q14.1	G	1.04	(0.96-1.13)	0.31	1.04	(1.00-1.09)	0.054	1.06	(1.04-1.09)	3.19×10^{-07}
rs17530068	G	6	82249828	6q14	G	1.07	(0.99-1.16)	0.093	1.05	(1.00-1.09)	0.034	1.06	(1.03-1.08)	1.97×10^{-06}
rs3757318	G	6	151955806	*ESR1*	A	1.33	(1.17-1.51)	9.25×10^{-06}	1.22	(1.14-1.31)	3.95×10^{-09}	1.16	(1.12-1.20)	1.09×10^{-15}
rs2046210	I	6	151990059	*ESR1*	A	1.16	(1.08-1.24)	5.26×10^{-05}	1.16	(1.12-1.21)	2.36×10^{-14}	1.08	(1.06-1.10)	1.38×10^{-14}
rs720475	G	7	143705862	7q35	A	1.02	(0.94-1.10)	0.62	0.99	(0.95-1.03)	0.58	0.94	(0.92-0.96)	2.49×10^{-08}
rs9693444	G	8	29565535	8p21.1	A	1.07	(0.99-1.15)	0.087	1.09	(1.05-1.13)	2.25×10^{-05}	1.07	(1.05-1.09)	4.61×10^{-11}
rs6472903	I	8	76392856	8q21.11	C	0.98	(0.90-1.08)	0.70	0.93	(0.89-0.98)	3.94×10^{-03}	0.91	(0.89-0.93)	3.08×10^{-13}
rs2943559	I	8	76580492	*HNF4G*	G	1.10	(0.97-1.24)	0.13	1.08	(1.01-1.16)	0.030	1.13	(1.09-1.17)	3.31×10^{-11}
rs13281615	G	8	128424800	8q24	G	1.01	(0.95-1.09)	0.71	1.02	(0.98-1.06)	0.28	1.10	(1.08-1.12)	1.87×10^{-20}

rs11780156	G	8	129263823	8q24.21	A	1.03	(0.95-1.13)	0.47	1.06	(1.01-1.11)	0.024	1.07	(1.05-1.10)	3.06×10^{-08}
rs1011970	G	9	22052134	*CDKN2A/B*	A	1.08	(0.99-1.18)	0.075	1.12	(1.06-1.17)	6.58×10^{-06}	1.05	(1.03-1.08)	4.04×10^{-05}
rs10759243	I	9	109345936	9q31.2	A	1.00	(0.93-1.08)	0.97	1.01	(0.97-1.05)	0.70	1.05	(1.03-1.08)	1.02×10^{-06}
rs865686	G	9	109928299	9q31	C	1.03	(0.96-1.11)	0.41	0.98	(0.95-1.02)	0.35	0.90	(0.88-0.91)	6.25×10^{-28}
rs2380205	G	10	5926740	*ANKRD16*	A	1.00	(0.94-1.07)	0.92	1.00	(0.96-1.04)	0.91	0.98	(0.96-1.00)	0.077
rs7072776	G	10	22072948	*DNAJC1*	A	0.96	(0.89-1.03)	0.24	0.94	(0.90-0.98)	3.94×10^{-03}	1.07	(1.05-1.09)	8.98×10^{-10}
rs10995190	G	10	63948688	*ZNF365*	A	0.93	(0.85-1.03)	0.16	0.87	(0.83-0.92)	2.52×10^{-07}	0.86	(0.84-0.88)	6.15×10^{-29}
rs704010	G	10	80511154	*ZMIZ1*	A	1.04	(0.97-1.12)	0.27	1.03	(0.99-1.07)	0.092	1.08	(1.06-1.10)	2.96×10^{-15}
rs7904519	G	10	114763917	*TCF7L2*	G	1.12	(1.05-1.20)	9.95×10^{-04}	1.06	(1.02-1.10)	3.18×10^{-03}	1.06	(1.04-1.08)	1.25×10^{-09}
rs11199914	G	10	123083891	10q26.12	A	1.04	(0.97-1.12)	0.28	1.02	(0.98-1.06)	0.35	0.95	(0.93-0.97)	1.44×10^{-06}
rs2981579	G	10	123327325	*FGFR2*	A	0.99	(0.93-1.06)	0.81	1.03	(0.99-1.07)	0.12	1.27	(1.24-1.29)	5.90×10^{-129}
rs2981582	I	10	123342307	*FGFR2*	A	0.98	(0.92-1.05)	0.61	1.02	(0.98-1.06)	0.27	1.26	(1.23-1.28)	1.71×10^{-117}
rs3817198	G	11	1865582	*LSP1*	G	1.06	(0.99-1.14)	0.10	1.06	(1.02-1.10)	5.81×10^{-03}	1.07	(1.05-1.09)	5.39×10^{-10}
rs3903072	I	11	65339642	11q13.1	A	0.92	(0.86-0.99)	0.024	0.97	(0.93-1.01)	0.099	0.94	(0.93-0.96)	2.89×10^{-09}
rs614367	G	11	69037945	*CCDN1*	A	1.02	(0.92-1.12)	0.75	1.02	(0.97-1.08)	0.41	1.21	(1.18-1.24)	5.21×10^{-48}
rs554219	I	11	69040823	*CCND1*	G	0.94	(0.85-1.04)	0.20	1.02	(0.96-1.08)	0.49	1.27	(1.23-1.30)	3.72×10^{-62}
rs11820646	I	11	128966381	11q24.3	A	0.92	(0.86-0.98)	0.016	0.96	(0.92-1.00)	0.028	0.95	(0.93-0.97)	2.44×10^{-07}
rs12422552	I	12	14305198	12p13.1	C	1.13	(1.04-1.21)	2.70×10^{-03}	1.04	(1.00-1.08)	0.080	1.05	(1.03-1.07)	2.47×10^{-05}
rs10771399	I	12	28046347	*PTHLH*	G	0.72	(0.64-0.80)	1.55×10^{-08}	0.83	(0.78-0.89)	3.35×10^{-09}	0.85	(0.83-0.88)	5.31×10^{-25}
rs17356907	G	12	94551890	*NTN4*	G	0.90	(0.84-0.97)	7.55×10^{-03}	0.94	(0.90-0.98)	2.27×10^{-03}	0.91	(0.89-0.93)	1.20×10^{-18}
rs1292011	G	12	114320905	12q24	G	1.08	(1.01-1.16)	0.035	0.98	(0.94-1.02)	0.31	0.92	(0.90-0.94)	6.19×10^{-17}
rs11571833	I	13	31870626	*BRCA2*	T	1.44	(1.05-1.96)	0.023	1.44	(1.20-1.71)	5.88×10^{-05}	1.26	(1.14-1.39)	5.36×10^{-06}
rs2236007	I	14	36202520	*PAX9*	A	0.99	(0.91-1.07)	0.75	0.96	(0.92-1.01)	0.096	0.93	(0.90-0.95)	1.69×10^{-10}
rs2588809	I	14	67730181	*RAD51L1*	A	0.91	(0.83-1.00)	0.041	1.01	(0.96-1.06)	0.78	1.08	(1.05-1.11)	4.71×10^{-09}
rs999737	G	14	68104435	*RAD51L1*	A	0.95	(0.88-1.03)	0.22	0.95	(0.91-0.99)	0.015	0.92	(0.90-0.94)	3.73×10^{-13}
rs941764	I	14	90910822	*CCDC88C*	G	1.03	(0.95-1.10)	0.50	1.03	(0.99-1.07)	0.091	1.06	(1.04-1.09)	1.02×10^{-09}
rs3803662	G	16	51143842	*TOX3*	A	1.09	(1.01-1.17)	0.022	1.14	(1.10-1.19)	1.16×10^{-10}	1.24	(1.21-1.27)	1.38×10^{-88}
rs17817449	I	16	52370868	*FTO*	C	0.99	(0.92-1.06)	0.68	0.91	(0.87-0.94)	5.07×10^{-07}	0.93	(0.91-0.95)	1.41×10^{-12}
rs11075995	I	16	52412792	*FTO*	A	1.08	(1.00-1.17)	0.065	1.11	(1.06-1.16)	2.13×10^{-06}	1.04	(1.02-1.07)	1.19×10^{-04}
rs13329835	G	16	79208306	*CDYL2*	G	1.03	(0.95-1.11)	0.51	1.02	(0.98-1.07)	0.30	1.08	(1.06-1.11)	1.48×10^{-11}
rs6504950	I	17	50411470	*COX11*	A	0.96	(0.89-1.04)	0.33	0.97	(0.93-1.01)	0.16	0.94	(0.92-0.96)	2.27×10^{-09}
rs527616	I	18	22591422	18q11.2	C	0.95	(0.88-1.02)	0.14	0.98	(0.94-1.02)	0.24	0.95	(0.93-0.97)	2.53×10^{-07}
rs1436904	G	18	22824665	*CHST9*	C	0.99	(0.93-1.07)	0.84	1.00	(0.96-1.04)	0.86	0.95	(0.94-0.97)	3.27×10^{-06}
rs8170	G	19	17250704	19p13.1	A	1.26	(1.16-1.37)	1.26×10^{-07}	1.14	(1.09-1.19)	1.26×10^{-08}	1.04	(1.01-1.06)	2.74×10^{-03}
rs2363956	G	19	17255124	19p13.1	C	0.82	(0.77-0.88)	2.33×10^{-08}	1.13	(1.09-1.17)	1.38×10^{-10}	1.03	(1.01-1.05)	1.86×10^{-03}
rs4808801	G	19	18432141	*SSBP4*	G	1.03	(0.96-1.11)	0.40	0.92	(0.88-0.95)	1.88×10^{-05}	0.93	(0.91-0.95)	4.70×10^{-13}
rs3760982	G	19	48978353	19q13.31	A	0.99	(0.93-1.06)	0.85	1.04	(1.00-1.08)	0.026	1.06	(1.04-1.08)	1.68×10^{-08}
rs2823093	G	21	15442703	*NRIP1*	A	1.04	(0.96-1.12)	0.35	0.97	(0.93-1.02)	0.21	0.92	(0.90-0.95)	1.57×10^{-12}
rs132390[a]	G	22	27951477	22q12.2	C	1.16	(0.89-1.52)	0.28	1.08	(0.98-1.19)	0.11	1.12	(1.07-1.18)	3.1×10^{-9}
rs6001930[a]	G	22	39206180	*MLK1*	C	1.21	(1.02-1.43)	0.025	1.10	(1.04-1.17)	1.1×10^{-3}	1.12	(1.09-1.16)	8.8×10^{-19}

a Genotyped in stage 2 only on the iCOGS platform (2,148 cases, 1,309 controls)
b Overall and ER-negative breast cancer risk results for rs2736108 from Bojesen, et al. (8)

Table S7. Additional significant SNPs in the known breast cancer susceptibility loci

Risk SNP	Reported SNP	R2 with reported SNP	G/I	Locus	Chr.	Position	Allele	OR	95% CI	P-value
a) SNPs in regions where reported SNP has p<0.05										
rs9397437	rs2046210; rs3757318	0.11; 0.38	I	*ESR1*	6	151994025	A	1.42	(1.25-1.61)	8.9×10^{-8}
rs620405	rs616488	0.73	G	*PEX14*	1	10477381	A	0.86	(0.80-0.93)	1.0×10^{-4}
b) SNPs in regions where reported SNP has p>0.05										
rs3731711	rs1045485	0.93	I	*CASP8*	2	201921306	G	0.84	(0.76-0.92)	1.4×10^{-4}
c) SNPs in regions where reported SNP not genotyped										
rs6142050	rs2284378	0.56	G	*RALY*	20	31990789	G	1.11	(1.03-1.19)	3.8×10^{-3}

Table S8. Cis-eQTL associations with known TN risk SNPs

eQTL SNP	eQTL gene	eQTL probe	chr	pos	t.stat	p.value	Risk locus
rs620405	*UBIAD1*	ILMN_1651872	1	10477381	-3.13	1.85E-03	*PEX14*
rs620405	*DFFA*	ILMN_2385220	1	10477381	-2.87	4.29E-03	*PEX14*
rs620405	*PGD*	ILMN_1794165	1	10477381	2.39	1.70E-02	*PEX14*
rs620405	*CASZ1*	ILMN_2340202	1	10477381	-2.28	2.29E-02	*PEX14*
rs620405	*CLSTN1*	ILMN_1720181	1	10477381	-2.14	3.30E-02	*PEX14*
rs620405	*C1orf200*	ILMN_1703119	1	10477381	-1.98	4.80E-02	*PEX14*
rs616488	*UBIAD1*	ILMN_1651872	1	10488802	2.67	7.72E-03	*PEX14*
rs616488	*CTNNBIP1*	ILMN_1688103	1	10488802	-2.30	2.20E-02	*PEX14*
rs616488	*CASZ1*	ILMN_2340202	1	10488802	2.08	3.76E-02	*PEX14*
rs6678914	*LGR6*	ILMN_1662362	1	200453799	2.16	3.09E-02	*LGR6*
rs3795598	*CHI3L1*	ILMN_1772289	1	200463784	-2.25	2.48E-02	*LGR6*
rs4245739	*LRRN2*	ILMN_1781841	1	202785465	-2.46	1.41E-02	*MDM4*
rs4245739	*NUAK2*	ILMN_1789793	1	202785465	-2.35	1.93E-02	*MDM4*
rs4245739	*REN*	ILMN_1742272	1	202785465	-2.06	3.99E-02	*MDM4*
rs4849887	*SCTR*	ILMN_1772537	2	120961592	-1.96	5.00E-02	2q14.2
rs2016394	*DYNC1I2*	ILMN_1773847	2	172681217	-2.85	4.51E-03	2q31.1
rs2016394	*ZAK*	ILMN_1698803	2	172681217	-2.46	1.40E-02	2q31.1
rs3731711	*AOX2P*	ILMN_1789676	2	201921306	-2.12	3.41E-02	*CASP8*
rs13387042	*TNS1*	ILMN_1807919	2	217614077	2.60	9.59E-03	2q35
rs10069690	*ZDHHC11*	ILMN_1694514	5	1332790	1.98	4.77E-02	*TERT*
rs1432679	*RNF145*	ILMN_1710906	5	158176661	2.47	1.39E-02	*EBF1*
rs9397437	*ZBTB2*	ILMN_1766247	6	151994025	2.04	4.14E-02	*ESR1*
rs2807985	*MLLT10*	ILMN_1743538	10	22270480	2.01	4.47E-02	*DNAJC1*
rs7904519	*ZDHHC6*	ILMN_2046003	10	114763917	-1.97	4.99E-02	*TCF7L2*
rs3903072	*CTSW*	ILMN_1794364	11	65339642	2.63	8.79E-03	11q13.1
rs3903072	*SART1*	ILMN_1680145	11	65339642	2.50	1.27E-02	11q13.1
rs3903072	*ACTN3*	ILMN_1665691	11	65339642	-2.32	2.09E-02	11q13.1
rs3903072	*SCYL1*	ILMN_1731991	11	65339642	-2.03	4.31E-02	11q13.1
rs3903072	*EHD1*	ILMN_1651832	11	65339642	2.00	4.65E-02	11q13.1
rs3903072	*CCDC85B*	ILMN_1657332	11	65339642	-1.97	4.96E-02	11q13.1
rs3903072	*C11orf85*	ILMN_2182850	11	65339642	1.97	4.99E-02	11q13.1
rs11820646	*ST14*	ILMN_1699887	11	128966381	3.08	2.20E-03	11q24.3
rs11820646	*APLP2*	ILMN_2081465	11	128966381	2.91	3.76E-03	11q24.3
rs11820646	*NFRKB*	ILMN_1718990	11	128966381	2.46	1.41E-02	11q24.3
rs11820646	*APLP2*	ILMN_1710482	11	128966381	2.43	1.56E-02	11q24.3
rs12422552	*GRIN2B*	ILMN_3307714	12	14305198	2.83	4.88E-03	12p13.1
rs12422552	*C12orf36*	ILMN_1755414	12	14305198	2.10	3.58E-02	12p13.1
rs11055891	*PDE6H*	ILMN_1702965	12	14312379	-2.58	1.00E-02	12p13.1
rs10771399	*REP15*	ILMN_1665884	12	28046347	-2.79	5.48E-03	*PTHLH*
rs17356907	*VEZT*	ILMN_2141398	12	94551890	-2.32	2.05E-02	*NTN4*
rs10850494	*TBX5*	ILMN_2282379	12	114311094	2.02	4.44E-02	12q24
rs2588809	*ZFYVE26*	ILMN_1798061	14	67730181	-2.07	3.87E-02	*RAD51L1*
rs8170	*PLVAP*	ILMN_2194577	19	17250704	-2.08	3.84E-02	19p13.1
rs2363956	*IL12RB1*	ILMN_1699908	19	17255124	-2.42	1.57E-02	19p13.1
rs2363956	*GTPBP3*	ILMN_1686587	19	17255124	-2.15	3.18E-02	19p13.1
rs1864112	*CPAMD8*	ILMN_1726250	19	17309960	2.38	1.78E-02	19p13.1

rs6142050	*PXMP4*	ILMN_3249742	20	31990789	-2.65	8.28E-03	*RALY*
rs6142050	*PXMP4*	ILMN_1771728	20	31990789	-2.19	2.88E-02	*RALY*
rs6142050	*PXMP4*	ILMN_3250812	20	31990789	-2.18	3.01E-02	*RALY*
rs6001913	*SLC25A17*	ILMN_1737312	22	39166699	3.02	2.64E-03	*MKL1*
rs6001913	*TNRC6B*	ILMN_1726786	22	39166699	2.98	3.00E-03	*MKL1*

Table S9. Functional annotation by Rhie, et al. (2013) in TN risk loci

							Number of SNPs in region (R2>0.5) overlapping with feature (18)		
SNP	Chr.	Positon	Locus	Allele	Description	Nearest gene	TSS	Enhancer	Exon
rs2046210	6	151990059	*ESR1*	A	intergenic	*C6orf97*	1	4	1
rs10771399	12	28046347	*PTHLH*	G	intergenic	*PTHLH*	1	62	
rs3803662	16	51143842	*TOX3*	A	intergenic	*TOX3*	1		
rs6678914	1	200453799	*LGR6*	A	intron	*LGR6*	2	10	1
rs2363956	19	17255124	19p13.1	C	exon (missense)	*ANKLE1*	2	2	2
rs3903072	11	65339642	11q13.1	A	intergenic	*SNX32; OVOL1*	2	11	3
rs2016394	2	172681217	2q31.1	A	intergenic	*CDCA7*	3		
rs4245739	1	202785465	*MDM4*	C	intron (3'utr)	*MDM4*	8	21	
rs616488	1	10488802	*PEX14*	G	intron	*PEX14*		16	1
rs1432679	5	158176661	*EBF1*	G	intron	*EBF1*			1
rs11571833	13	31870626	*BRCA2*	T	exon (nonsense)	*BRCA2*			
rs11820646	11	128966381	11q24.3	A	intergenic	*CCND1*		1	
rs17356907	12	94551890	*NTN4*	G	intergenic	*NTN4*		2	
rs4849887	2	120961592	2q14.2	A	intergenic	*INHBB*		3	
rs1292011	12	114320905	12q24	G	intergenic	*MED13L*		5	
rs12422552	12	14305198	12p13.1	C	intergenic	*ATF7IP*		9	
rs12710696	2	19184284	2p24.1	A	intergenic	*OSR1*		15	
rs13387042	2	217614077	2q35	G	intergenic	*TNP1*			
rs10069690	5	1332790	*TERT*	A	intron	*TERT*		1	
rs7904519	10	114763917	*TCF7L2*	G	intron	*TCF7L2*		36	
rs2588809	14	67730181	*RAD51L1*	A	intron	*RAD51B*		39	
rs6001930	22	39206180	*MLK1*	C	intron	*MLK1*		88	
rs6828523	4	176083001	*ADAM29*	A	intron	*ADAM29*			
Rs3757315	6	151955806	*ESR1*	A	intron	*C6orf97*			

Table S10. Cis-eQTL associations with SNPs in TN risk loci

Chr.	eQTL SNP	eQTL gene	t-statistic	eQTL p-value	Locus
1	rs11586387	*KLHDC8A*	-3.75	2.0E-04	*MDM4*
2	rs11892687	*IGFBP2*	-3.61	3.3E-04	2q35
2	rs7589722	*IGFBP2*	3.46	5.8E-04	2q35
2	rs10490444	*IGFBP2*	-3.48	5.5E-04	2q35
2	rs7579388	*PECR*	3.35	8.7E-04	2q35
2	rs6738142	*HAT1*	0.24	9.11×10^{-6}	2q31.1
2	rs2008518	*ZAK*	-0.074	9.36×10^{-5}	2q31.1
2	rs13016963	*ALS2CR12*	3.39	7.5E-04	*CASP8*
2	rs9288316	*ALS2CR12*	-3.44	6.3E-04	*CASP8*
2	rs1035142	*ALS2CR12*	3.38	7.8E-04	*CASP8*
2	rs1045494	*FZD7*	3.34	9.0E-04	*CASP8*
5	rs4246742	*SLC9A3*	3.38	7.7E-04	*TERT*
5	rs4246742	*SLC12A7*	3.33	9.4E-04	*TERT*
5	rs4246742	*SLC9A3*	3.38	7.7E-04	*TERT*
5	rs4246742	*SLC12A7*	3.33	9.4E-04	*TERT*
6	rs1871859	*AKAP12*	-3.92	1.0E-04	*ESR1*
10	rs7085532	*ACSL5*	3.64	3.0E-04	*TCF7L2*
10	rs17746916	*LOC143188*	3.60	3.5E-04	*TCF7L2*
10	rs290488	*ZDHHC6*	3.64	3.0E-04	*TCF7L2*
11	rs10896050	*SNX32*	3.78	1.8E-04	11q13.1
11	rs630303	*CTSW*	3.55	4.3E-04	11q13.1
11	rs656040	*CTSW*	-3.55	4.3E-04	11q13.1
11	rs11227332	*CTSW*	3.85	1.3E-04	11q13.1
11	rs665306	*CTSW*	-3.49	5.2E-04	11q13.1
11	rs11227306	*CTSW*	-3.45	6.1E-04	11q13.1
11	rs622614	*CTSW*	-5.61	3.3E-08	11q13.1
11	rs13817	*CTSW*	3.57	3.9E-04	11q13.1
11	rs10896050	*CTSW*	-3.90	1.1E-04	11q13.1
11	rs10896050	*MRPL11*	4.14	4.0E-05	11q13.1
12	rs11067547	*TBX3*	3.44	6.3E-04	12q24
12	rs2347230	*PTHLH*	0.47	5.67×10^{-5}	*PTHLH*
12	rs10843001	*PTHLH*	0.39	7.28×10^{-5}	*PTHLH*
12	rs16932270	*PPFIBP1*	-0.41	5.30×10^{-6}	*PTHLH*
12	rs10777711	*VEZT*	-3.38	7.8E-04	*NTN4*
12	rs7963386	*VEZT*	-3.60	3.5E-04	*NTN4*
13	rs206119	*B3GALTL*	-3.53	4.6E-04	*BRCA2*
13	rs9567670	*KL*	3.40	7.3E-04	*BRCA2*
14	rs10137893	*EXD2*	3.63	3.2E-04	*RAD51L1*
19	rs17533903	*NR2F6*	-0.34	6.45×10^{-5}	19p13.1
19	rs17454516	*FAM32A*	-0.16	6.51×10^{-5}	19p13.1
19	rs17533903	*SLC35E1*	-0.39	6.20×10^{-5}	19p13.1

Table S11. Linkage disequilibrium (R^2 >0.1) between eQTL SNPs in TN risk loci and candidate functional SNPs in exons identified by Rhie, et al.

Chr.	eQTL SNP	eQTL gene	Locus	Exon SNP	R^2 with eQTL SNP	Gene (exon)	Result
11	rs10896050	*SNX32, CTSW, MRPL11*	11q13.1	rs637571	0.174	*FOSL1*	synonomous
				rs1058068	0.124	*FOSL1*	synonomous
				rs633800	0.137	*EFEMP2*	synonomous
11	rs11227306	*CTSW*	11q13.1	rs637571	0.272	*FOSL1*	synonomous
				rs1058068	0.299	*FOSL1*	synonomous
				rs633800	0.467	*EFEMP2*	synonomous
11	rs11227332	*CTSW*	11q13.1	rs637571	0.303	*FOSL1*	synonomous
				rs1058068	0.236	*FOSL1*	synonomous
				rs633800	0.241	*EFEMP2*	synonomous
11	rs13817	*CTSW*	11q13.1	rs637571	0.188	*FOSL1*	synonomous
				rs1058068	0.278	*FOSL1*	synonomous
				rs633800	0.458	*EFEMP2*	synonomous
11	rs622614	*CTSW*	11q13.1	rs633800	0.219	*EFEMP2*	synonomous
				rs1058068	0.122	*FOSL1*	synonomous
11	rs630303	*CTSW*	11q13.1	rs637571	0.188	*FOSL1*	synonomous
				rs1058068	0.278	*FOSL1*	synonomous
				rs633800	0.458	*EFEMP2*	synonomous
11	rs656040	*CTSW*	11q13.1	rs637571	0.211	*FOSL1*	synonomous
				rs1058068	0.254	*FOSL1*	synonomous
				rs633800	0.422	*EFEMP2*	synonomous
11	rs665306	*CTSW*	11q13.1	rs637571	0.188	*FOSL1*	synonomous
				rs1058068	0.278	*FOSL1*	synonomous
				rs633800	0.458	*EFEMP2*	synonomous

Table S12. Linkage disequilibrium (R^2 >0.1) between eQTL SNPs in TN risk loci and candidate functional SNPs in transcroiption start sites identified by Rhie, et al.

Chr.	eQTL SNP	eQTL gene	Locus	TSS snp	R^2 with eQTL SNP
11	rs10896050	SNX32, CTSW, MRPL11	11q13.1	rs633800	0.137
				rs10896064	0.2
11	rs11227306	CTSW	11q13.1	rs633800	0.467
				rs10896064	0.317
11	rs11227332	CTSW	11q13.1	rs633800	0.241
				rs10896064	0.256
11	rs13817	CTSW	11q13.1	rs633800	0.458
				rs10896064	0.478
11	rs622614	CTSW	11q13.1	rs633800	0.219
				rs10896064	0.228
11	rs630303	CTSW	11q13.1	rs633800	0.458
				rs10896064	0.478
11	rs656040	CTSW	11q13.1	rs633800	0.422
				rs10896064	0.516
11	rs665306	CTSW	11q13.1	rs633800	0.458
				rs10896064	0.478

Table S13. Linkage disequilibrium (R^2 >0.1) between eQTL SNPs in TN risk loci and candidate functional SNPs in enhancers identified by Rhie, et al.

Chr.	eQTL SNP	eQTL gene	Locus	Enhancer SNP	R^2 with eQTL SNP
11	rs10896050	SNX32, CTSW, MRPL11	11q13.1	rs10160792	0.102
				rs1058068	0.124
				rs11227309	0.133
				rs11227311	0.133
				rs526631	0.105
				rs637571	0.174
				rs677029	0.124
				rs689274	0.112
11	rs630303	CTSW	11q13.1	rs10160792	0.198
				rs1058068	0.278
				rs11227309	0.443
				rs11227311	0.443
				rs1151523	0.218
				rs526631	0.244
				rs634534	0.218
				rs637571	0.188
				rs677029	0.235
				rs689274	0.248
11	rs656040	CTSW	11q13.1	rs10160792	0.175
				rs1058068	0.254
				rs11227309	0.427
				rs11227311	0.427
				rs1151523	0.198
				rs526631	0.222
				rs634534	0.198
				rs637571	0.211
				rs677029	0.212
				rs689274	0.227
11	rs11227332	CTSW	11q13.1	rs10160792	0.218
				rs1058068	0.236
				rs11227309	0.233
				rs11227311	0.233
				rs1151523	0.197
				rs526631	0.215
				rs634534	0.197
				rs637571	0.303
				rs677029	0.239
				rs689274	0.219
11	rs665306	CTSW	11q13.1	rs10160792	0.198
				rs1058068	0.278
				rs11227309	0.443
				rs11227311	0.443
				rs1151523	0.218
				rs526631	0.244
				rs634534	0.218

				rs637571	0.188
				rs677029	0.235
				rs689274	0.248
11	rs11227306	CTSW	11q13.1	rs10160792	0.275
				rs1058068	0.299
				rs11227309	0.45
				rs11227311	0.45
				rs1151523	0.268
				rs526631	0.305
				rs634534	0.268
				rs637571	0.272
				rs677029	0.35
				rs689274	0.309
11	rs622614	CTSW	11q13.1	rs10160792	0.107
				rs1058068	0.122
				rs11227309	0.212
				rs11227311	0.212
				rs526631	0.105
				rs677029	0.122
				rs689274	0.111
11	rs13817	CTSW	11q13.1	rs10160792	0.198
				rs1058068	0.278
				rs11227309	0.443
				rs11227311	0.443
				rs1151523	0.218
				rs526631	0.244
				rs634534	0.218
				rs637571	0.188
				rs677029	0.235
				rs689274	0.248

Table S14. Comparison of ORs for a subset of TNBCC subjects with expression data, stratified by DASL-defined ER status

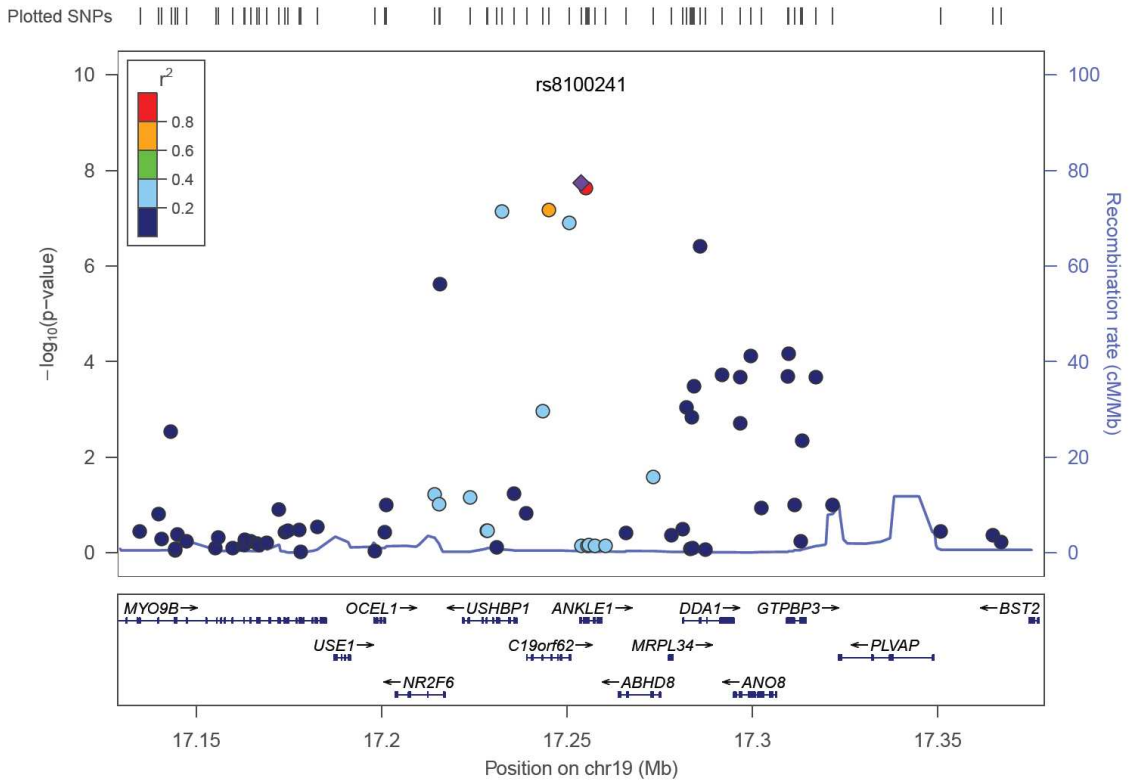
						Overall TN 3,677 cases 4,708 controls		TN with DASL 578 cases 4,638 controls			TN excluding ER+ 516 cases 4,638 controls			DASL-defined ER+ 62 cases 4,638 controls		
SNP	**G/I**	**Chr.**	**Position**	**Locus**	**Allele**	**OR**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
rs616488	G	1	10488802	*PEX14*	G	0.91	$9.7x10^{-3}$	0.99	(0.86-1.13)	0.85	0.99	(0.85-1.14)	0.84	1.00	(0.67-1.49)	0.99
rs6678914	G	1	200453799	*LGR6*	A	0.90	$3.3 x10^{-3}$	0.97	(0.85-1.12)	0.7	0.96	(0.84-1.11)	0.62	1.07	(0.73-1.57)	0.74
rs4245739	I	1	202785465	*MDM4*	C	1.19	$4.0 x10^{-6}$	1.19	(1.03-1.38)	0.017	1.16	(0.99-1.35)	0.061	1.56	(1.05-2.33)	0.029
rs12710696	I	2	19184284	2p24.1	A	1.11	$3.5 x10^{-3}$	1.07	(0.93-1.23)	0.34	1.08	(0.94-1.25)	0.27	0.92	(0.62-1.36)	0.68
rs4849887	G	2	120961592	2q14.2	A	0.89	0.041	0.93	(0.75-1.15)	0.5	0.97	(0.78-1.22)	0.77	0.72	(0.42-1.27)	0.26
rs2016394	G	2	172681217	2q31.1	A	1.10	$6.9x10^{-3}$	1.13	(0.99-1.29)	0.074	1.12	(0.97-1.29)	0.11	1.21	(0.83-1.74)	0.32
rs3731711	I	2	201921306	*CASP8*	G	0.84	1.4x10-4	0.94	(0.79-1.12)	0.51	0.92	(0.76-1.11)	0.38	1.02	(0.62-1.69)	0.93
rs13387042	G	2	217614077	2q35	G	0.93	0.049	0.92	(0.80-1.04)	0.19	0.93	(0.81-1.07)	0.29	0.85	(0.59-1.22)	0.38
rs6828523	I	4	176083001	*ADAM29*	A	0.84	$1.3x10^{-3}$	0.88	(0.71-1.08)	0.22	0.94	(0.75-1.17)	0.56	0.45	(0.20-1.00)	0.049
rs10069690	I	5	1332790	*TERT*	A	1.24	$1.4 x10^{-7}$	1.27	(1.08-1.48)	$3.1x10^{-3}$	1.32	(1.12-1.56)	$8.4x10^{-4}$	0.91	(0.57-1.45)	0.69
rs2735845	I	5	1353584	*TERT*	G	0.80	$2.5x10^{-7}$	0.93	(0.80-1.09)	0.39	0.95	(0.81-1.12)	0.54	0.71	(0.44-1.15)	0.16
rs1432679	G	5	158176661	*EBF1*	G	1.10	$8.6x10^{-3}$	1.06	(0.93-1.22)	0.36	1.05	(0.91-1.21)	0.51	1.30	(0.89-1.90)	0.17
rs3757318	G	6	151955806	*ESR1*	A	1.33	$9.2 x10^{-6}$	1.57	(1.25-1.98)	$1.2x10^{-4}$	1.58	(1.25-2.01)	$1.5x10^{-4}$	1.48	(0.75-2.92)	0.26
rs2046210	I	6	151990059	*ESR1*	A	1.16	$5.3 x10^{-5}$	1.25	(1.09-1.43)	$1.5x10^{-3}$	1.22	(1.06-1.41)	$6.8x10^{-3}$	1.54	(1.04-2.27)	0.031
rs12525163	I	6	152081984	*ESR1*	C	1.15	$4.9x10^{-4}$	1.08	(0.93-1.25)	0.31	1.1	(0.94-1.28)	0.24	0.94	(0.61-1.46)	0.78
rs7904519	G	10	114763917	*TCF7L2*	G	1.12	$9.9x10^{-4}$	1.10	(0.97-1.26)	0.15	1.09	(0.95-1.26)	0.2	1.17	(0.80-1.71)	0.43
rs3903072	I	11	65339642	11q13.1	A	0.92	0.024	0.95	(0.83-1.08)	0.42	0.95	(0.82-1.09)	0.43	0.97	(0.66-1.43)	0.88
rs11820646	I	11	128966381	11q24.3	A	0.92	0.016	0.91	(0.79-1.04)	0.17	0.88	(0.77-1.02)	0.084	1.17	(0.80-1.72)	0.42
rs12422552	I	12	14305198	12p13.1	C	1.13	$2.7x10^{-3}$	1.15	(0.99-1.34)	0.06	1.16	(0.99-1.36)	0.059	1.07	(0.70-1.64)	0.74
rs10771399	I	12	28046347	*PTHLH*	G	0.72	$1.5x10^{-8}$	0.77	(0.61-0.96)	0.022	0.74	(0.58-0.94)	0.015	1.01	(0.57-1.80)	0.97
rs17356907	G	12	94551890	*NTN4*	G	0.90	$7.5x10^{-3}$	1.15	(0.93-1.22)	0.061	1.16	(0.99-1.35)	0.066	1.14	(0.74-1.75)	0.56
rs1292011	G	12	114320905	12q24	G	1.08	0.035	1.06	(0.93-1.22)	0.4	1.03	(0.90-1.19)	0.64	1.25	(0.84-1.89)	0.27
rs11571833	I	13	31870626	*BRCA2*	T	1.44	0.023	1.62	(0.92-2.86)	0.094	1.70	(0.96-3.03)	0.07	1.01	(0.15-6.72)	0.99
rs2588809	I	14	67730181	*RAD51L1*	A	0.91	0.041	0.87	(0.72-1.05)	0.14	0.85	(0.70-1.04)	0.11	1.00	(0.61-1.65)	1
rs3803662	G	16	51143842	*TOX3*	A	1.09	0.022	1.06	(0.91-1.22)	0.46	1.07	(0.92-1.25)	0.38	0.9	(0.59-1.37)	0.62
rs8170	G	19	17250704	19p13.1	A	1.26	$1.3 x10^{-7}$	1.22	(1.04-1.44)	0.017	1.26	(1.06-1.49)	$7.3x10^{-3}$	1.03	(0.62-1.71)	0.9
rs2363956	G	19	17255124	19p13.1	C	0.82	$2.3 x10^{-8}$	0.83	(0.72-0.94)	$4.8x10^{-3}$	0.82	(0.71-0.94)	$5.4x10^{-3}$	0.81	(0.56-1.17)	0.26
rs1864112	I	19	17309960	19p13.1	A	0.84	$5.5x10^{-6}$	0.81	(0.70-0.94)	$7.1x10^{-3}$	0.79	(0.67-0.93)	$4.7x10^{-3}$	0.9	(0.59-1.36)	0.61
rs6142050	G	20	31990789	*RALY*	G	1.11	$3.8x10^{-3}$	1.11	(0.97-1.27)	0.14	1.11	(0.96-1.28)	0.14	1.07	(0.72-1.59)	0.73
rs6001913	G	22	39166699	*MKL1*	A	1.20	$1.8x10^{-3}$	1.46	(1.17-1.82)	$6.6x10^{-4}$	1.45	(1.16-1.82)	$1.3x10^{-3}$	1.5	(0.82-2.77)	0.19

Table S15. Polygenic risk score and TNBC risk using the first quintile as the reference

	74 SNPs				27 SNPs			
PRS Quintile	**Quintile definitions**	**OR**	**95% CI**	**p-value**	**Quintile definitions**	**OR**	**95% CI**	**p-value**
1	PRS≤0.24	1.00	--	--	PRS≤-0.57	1.00	--	--
2	0.24<PRS≤0.58	1.53	1.29-1.81	$1.1x10^{-6}$	-0.57<PRS≤-0.26	1.43	1.21-1.69	$2.8x10^{-5}$
3	0.58<PRS≤0.86	1.97	1.68-2.32	$9.9x10^{-16}$	-0.26<PRS≤0.039	1.91	1.63-2.25	$3.9x10^{-15}$
4	0.86<PRS≤1.24	2.54	2.17-2.97	$1.3x10^{-29}$	0.039<PRS≤0.40	2.62	2.24-3.06	$1.4x10^{-33}$
5	1.24<PRS	4.03	3.46-4.70	$4.8x10^{-69}$	0.40<PRS	4.08	3.50-4.75	$2.5x10^{-74}$

Figure S1. Association between 19p13.1 variants (n=170) and TN breast cancer risk

a) TNBC associations in a 250kb region



b) Adjusted for rs8100241

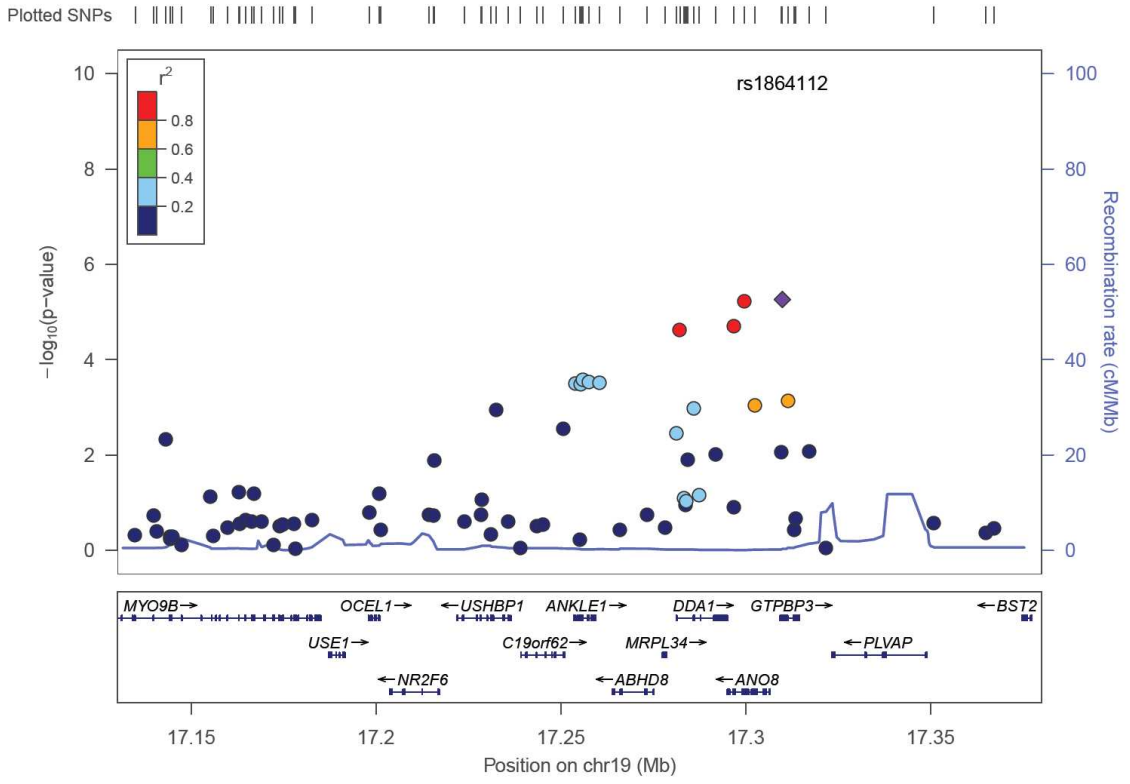
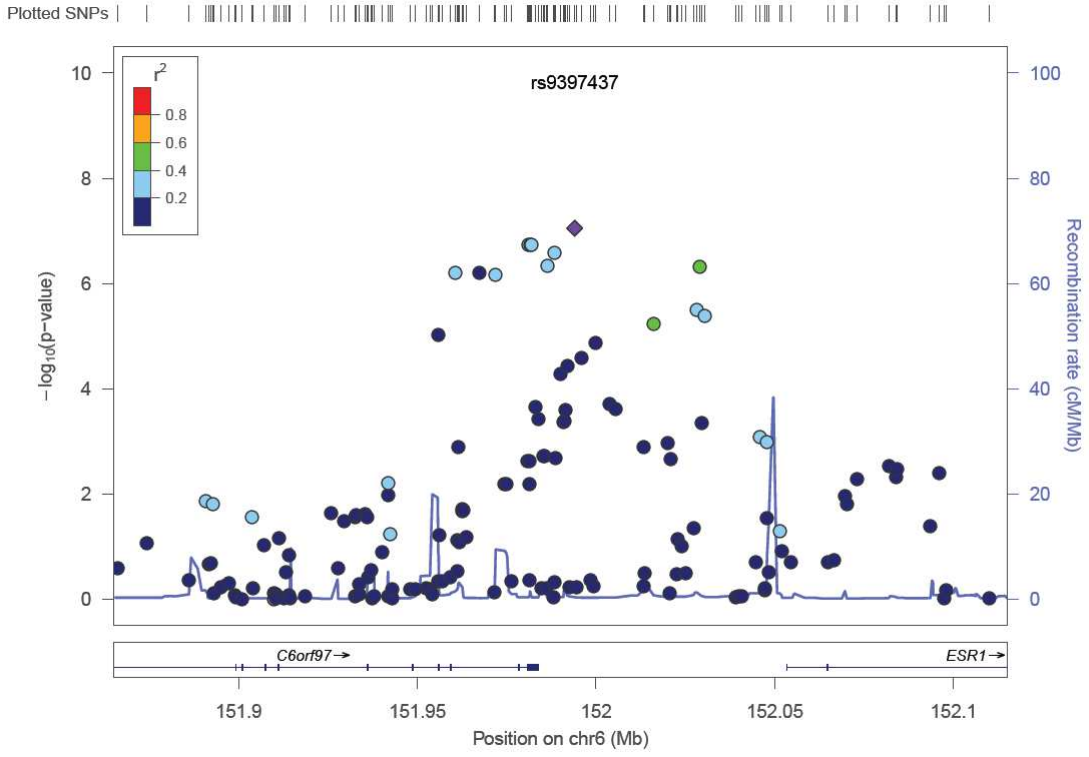


Figure S2. Association between *ESR1* variants (n=448) and TN breast cancer risk

a) TNBC associations in a 250kb region



b) Adjusted for rs9397437

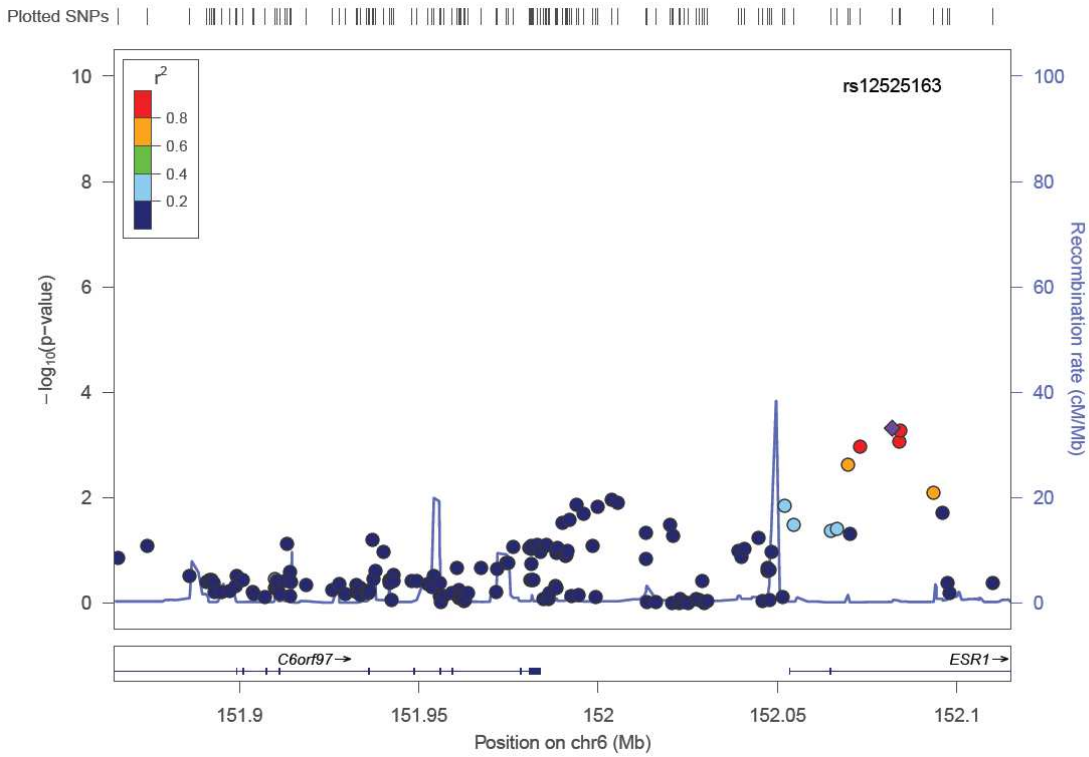


Figure S3. ROC curves for TN breast cancer risk by 74-SNP and 30-SNP PRS

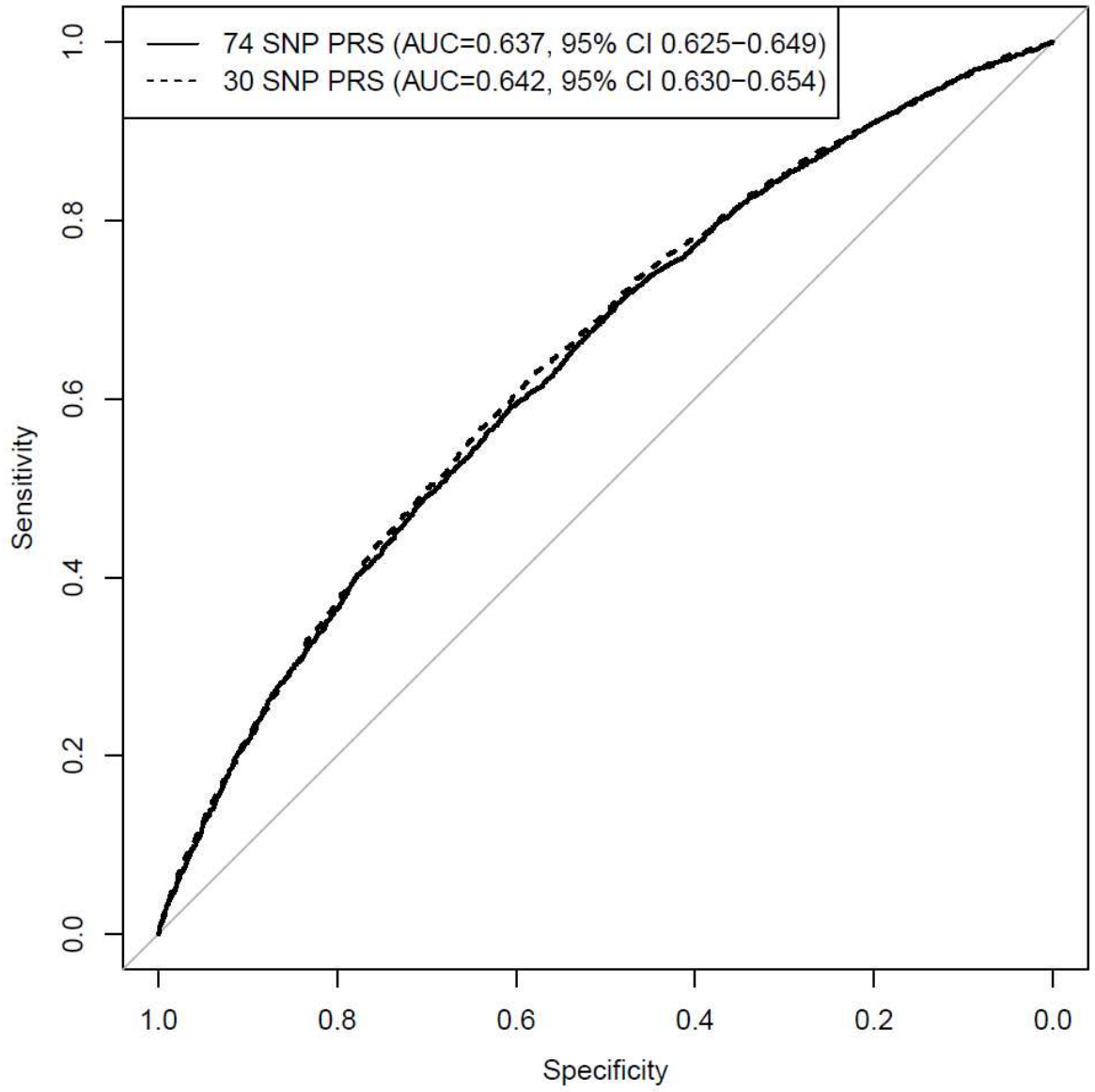


Figure S4. Cumulative risk of TNBC stratified by a 30-SNP polygenic risk score

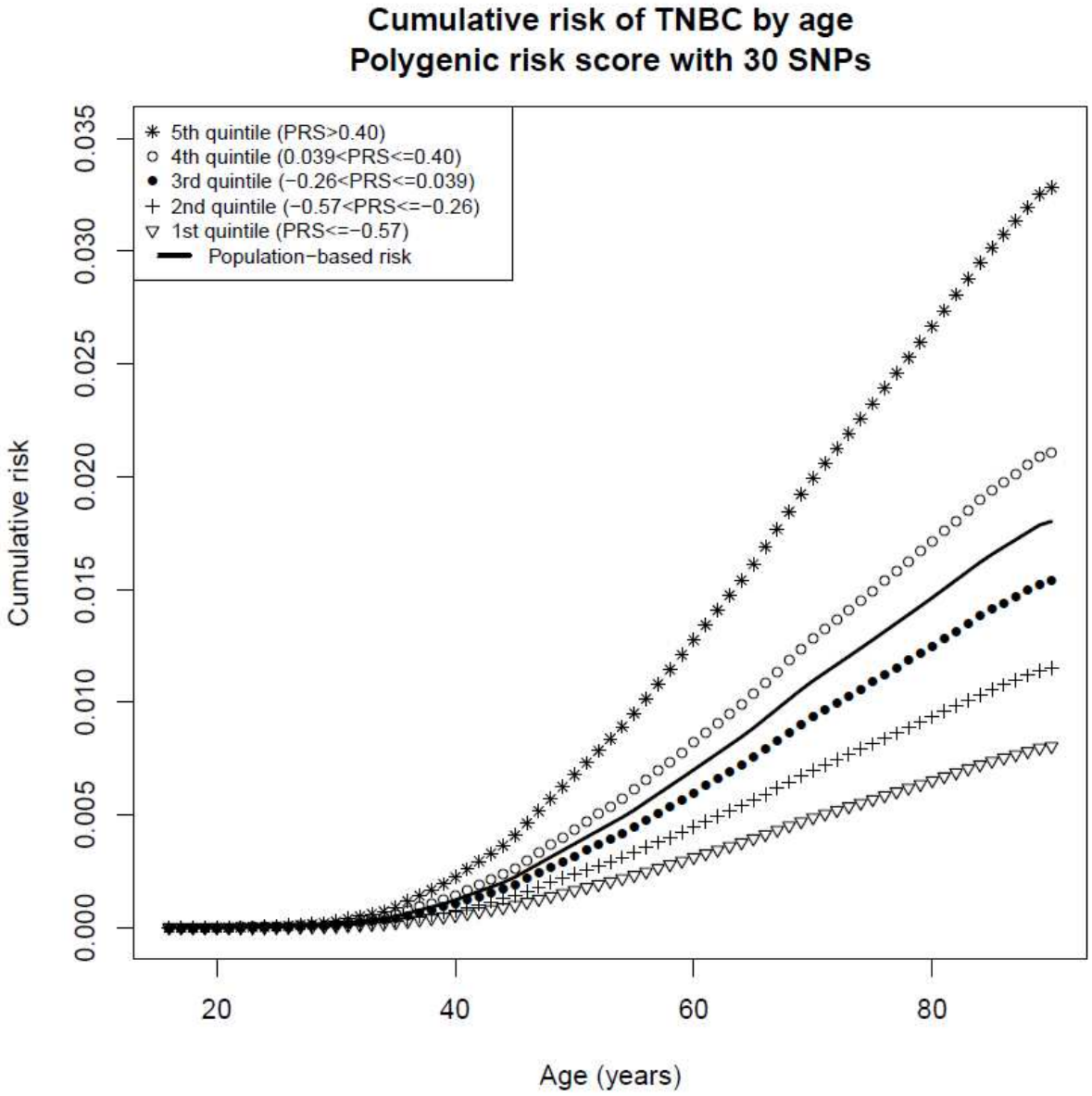


Figure legends

Figure S1. Association between 19p13.1 variants (n=170) and TN breast cancer risk

a) The association between 170 variants from the combined 19p13.1 analyses in stages 1 and 2 is shown. The most significant SNP (rs8100241) is shown as the purple diamond ($p=1.8 \times 10^{-8}$). The remaining variants are shown as circles, colored by the degree of linkage disequilibrium (R^2) between each SNP and rs8100241. The continuous blue line represents the recombination rate (cM/Mb). b) The association between 19p13.1 variants adjusted for rs8100241 is shown. The most significant SNP after adjustment for rs8100241 (rs1864112) is shown as the purple diamond ($p=5.5 \times 10^{-6}$).

Figure S2. Association between *ESR1* variants (n=448) and TN breast cancer risk

a) The association between 448 variants from the combined *ESR1* analyses in stages 1 and 2 is shown. The most significant SNP (rs9397437) is shown as the purple diamond ($p=8.9 \times 10^{-8}$). The remaining variants are shown as circles, colored by the degree of linkage disequilibrium (R^2) between each SNP and rs9397437. The continuous blue line represents the recombination rate (cM/Mb). b) The association between *ESR1* variants adjusted for rs9397437is shown. The most significant SNP after adjustment for rs9397437 (rs12525163) is shown as the purple diamond ($p=4.9 \times 10^{-4}$).

Figure S3. ROC curves for TN breast cancer risk by 74-SNP and 30-SNP PRS

Receiver operating characteristic (ROC) curves are shown for the 74-SNP PRS (solid black line) and the 30-SNP PRS (dashed black line). The area under the curve (AUC) for the 74-SNP PRS

was 0.637 (95% CI 0.625-0.649) while the AUC for the 30-SNP PRS was 0.642 (95% CI 0.630-0.654).

Figure S4. Cumulative risk of TNBC stratified by a 30-SNP polygenic risk score

The effect of the 30-SNP polygenic risk score (PRS) on cumulative risk of triple negative (TN) breast cancer among Caucasian women, stratified by PRS quintile, is shown. The population-based cumulative risk curve is shown as a solid black line, and the first through fifth quintile-specific cumulative risk estimates are presented according to labels.

The Triple-Negative Breast Cancer Consortium (TNBCC)

Australia Breast Cancer Tissue Bank (ABCTB): Breast cancer cases were collected from six hospitals in New South Wales, Australia: Royal Prince Alfred Hospital, Westmead Hospital, Royal North Shore Hospital, St. Vincent's Hospital, Hunter Area Hospitals, and Port Macquarie beginning in 2006.

Bavarian Breast Cancer Cases and Controls (BBCC): This is a consecutive series of cases with invasive breast cancer recruited at the University Breast Centre, Franconia in Northern Bavaria, Germany from 2002-2006. Cases were between 22-96 years of age. Controls were population-based unaffected women from the same geographical area.

California Teachers Study (CTS): Breast cancer cases from the CTS cohort, composed of women who were active or retired California teachers or administrators at the time the cohort was established in 1995. Cancer outcomes were identified through annual linkage with the California Cancer Registry (CCR). Unaffected individuals from the CTS cohort were sampled for controls.

Cancer Genetic Markers of Susceptibility (CGEMS): The Nurses' Health Study (NHS) is a longitudinal study of 121,700 women enrolled in 1976. The CGEMS nested case-control study is derived from 32,826 participants who provided a blood sample between 1989 and 1990 and were free of diagnosed breast cancer at blood collection and followed for incident disease until June 1, 2004. Controls were not diagnosed with breast cancer during follow-up, and were matched to cases based on age at diagnosis, blood collection variables (time of day, season, and

year of blood collection, as well as recent (<3 months) use of postmenopausal hormones), ethnicity (all cases and controls are self-reported Caucasians), and menopausal status (all cases were postmenopausal at diagnosis).

Dana Farber Cancer Institute (DFCI): Cases were obtained from an unselected series of breast tumors patients from the Dana Farber Cancer Institute. DNA samples from residual bloods from triple negative breast cancer patients were genotyped.

DEMOKRITOS: Cases were enrolled from 1997 until 2010 in several major hospitals covering most geographical areas of Greece, such as Athens metropolitan area, Thessaloniki, Ioannina, Patras, and Crete (Chania), in collaboration with the Hellenic Cooperative Oncology Group (HECOG). Cases had an age range of 20-87 years. Controls were population-based unaffected women of the same age range.

Fox Chase Cancer Center (FCCC): Cases were seen at FCCC and 28-80 years of age at diagnosis. Comprehensive clinical data including histology, staging, treatment and outcomes was provided for all cases. Controls were healthy females with no personal cancer history matched geographically and by gender, race and age. DNA was obtained from peripheral blood samples.

Gene Environment Interaction and Breast Cancer in Germany (GENICA): This is a population-based case-control study of breast cancer in the Greater Bonn area of Germany. Cases were incident breast cancer cases enrolled between 2000 and 2004 (reported from 14 hospitals within the study region), all of which were enrolled within 6 months of diagnosis. Cases were between

23-80 years of age. Controls were selected from population registries from 31 communities in the greater Bonn area and matched to cases in 5-year age classes between 2001 and 2004.

University of Kansas Medical Center (KUMC): Cases were obtained from an unselected series of breast tumors patients from the University of Kansas Medical Center. DNA samples from residual bloods from triple negative breast cancer patients were genotyped.

Helsinki Breast Cancer Study (HEBCS): Cases from this hospital-based case-control study in Southern Finland were consecutive breast cancer cases from the 1) Department of Oncology, Helsinki University Central Hospital 1997-8 and 2000, 2) consecutive cases from the Department of Surgery, Helsinki University Central Hospital 2001 – 2004, or 3) Familial breast cancer patients from the Helsinki University Central Hospital, Departments of Oncology and Clinical Genetics (from 1995). Cases were between 22 and 96 years of age. The population allele and genotype frequencies were obtained from the Finnish Genome Centre on 221 healthy population controls in the NordicDB, a Nordic pool and portal for genome-wide control data (19).

Cooperative Health Research in the Region of Augsburg (KORA): In total, four population based health surveys have been conducted between 1984 and 2000 with 18,000 participants between the age of 25 to 74 years, and a biological specimen bank was established in order to enable the researchers to perform epidemiologic research with respect to molecular and genetic factors. The KORA study center conducts regular follow-up investigations and has collected a

wealth of information on sociodemography, general medical history, environmental factors, smoking, nutrition, alcohol consumption, and various laboratory parameters. Follow-up activities include address inquiry for all participants (incl. assessment of vital status and cause of death), postal questionnaires focusing on chronic diseases, and complete follow-up studies with interviews and physical examination.

Mammary Carcinoma Risk Factor Investigation (MARIE): This is a population-based case-control study of breast cancer in Northern and Southern Germany. Cases from this study were incident and prevalent cases diagnosed from 2001-2005 in the study region of Hamburg in Northern Germany and from 2002-2005 in the study region of Rhein-Neckar-Karlsruhe in Southern Germany. Controls were randomly drawn from population registries and frequency matched by birth year and study region to the case. Controls were recruited from 2002 to 2006.

Mayo Clinic Breast Cancer Study (MCBCS): This is a clinic-based breast cancer case-control study at the Mayo Clinic. Subjects were enrolled between February 1, 2001 and June 30, 2005. Cases were comprised of Caucasian women with primary invasive breast cancer ascertained with 6 months of diagnosis. Controls were comprised of Caucasian women visiting the Mayo Clinic for general medical exams in the Department of Internal Medicine with no prior history of cancer. Controls were frequency matched to cases on region of residence, race, and 5-year age group.

Melbourne Collaborative Cohort Study (MCCS): Incident cases of breast cancer were diagnosed within the Melbourne Collaborative Cohort Study in Melbourne, Australia during the follow-up

from baseline (1990-1994) to 2008 of the 24,469 participating women, and controls were randomly sampled from the initial cohort among members not diagnosed with breast cancer at the end of follow-up.

Norwegian Breast Cancer Study (NBCS): Cases were comprised of Incidence cases from three different hospitals: 1) Cases (114) mean age 64 (28-92) at Ullevål Univ. Hospital 1990-94, 2) cases (182) mean age 59 (26-75) referred to Norwegian Radium Hospital 1975-1986, 3) cases (124), mean age 56 (29-82)) with stage I or II disease, in the Oslo micro-metastases study at Norwegian Radium Hospital between 1995-1998, 4) cases (71) mean age 67 (37–82) with locally advanced disease at Haukeland University Hospital. Control subjects were healthy women, age 55-71, residing in Tromsø (440), and Bergen (109) attending the Norwegian Breast Cancer Screening Program.

The Nashville Breast Health Study (NBHS): The NBHS is a population-based case-control study of breast cancer conducted in Tennessee. The study was initiated in 2001 to recruit patients with invasive breast cancer or ductal carcinoma in situ between the ages of 25 and 75 years. Cases were identified from participating hospitals in and around the Nashville Metropolitan area as well as from the Tennessee Cancer Registry (TCR). Diagnosis and tumor pathology were confirmed via medical record abstraction and ascertainment from the TCR. Controls were recruited through random digit dialing.

Ohio State University (OSU): Cases were obtained from an unselected series of breast tumors patients from the Ohio State University Stefanie Spielman Breast Bank. DNA samples isolated

from blood of triple negative breast cancer patients were genotyped. Controls were selected from the Columbus Area Control Sample Bank and were frequency matched for age and ethnicity to the cases.

Prospective Study of Outcomes in Sporadic Versus Hereditary Breast Cancer (POSH): Cases from this prospective cohort study in the United Kingdom were aged 40 or younger at breast cancer diagnosis, recruited across the UK, and diagnosed between January 2000 and December 2007.

Australian Twin Cohort study from the Queensland Institute of Medical Research (QIMR): Two cohorts of Australian twins and their families (parents, children, spouses and siblings), were recruited to a Health and Lifestyle study in 1988 and 1990. The total number of participants was over 27,000, with an age range of 17 to 96 (M = 39.7, SD = 15.3). Phenotypic data were available for 20,464 individuals, of which 5117 (1727 males and 3390 females) from 2567 independent families were genotyped. Phenotypic and genotypic data collection was approved by the Queensland Institute of Medical Research (QIMR) Ethics Committee and informed consent was obtained from all participants.

Sheffield Breast Cancer Study (SBCS): This is a hospital-based case-control study of breast cancer. The study consists of women with pathologically confirmed breast cancer recruited from surgical outpatient clinics at the Royal Hallamshire Hospital, Sheffield, 1998 – 2005 and unselected women attending the Sheffield Mammography Screening Service between Sep 2000 -

Aug 2004 if their mammograms showed no evidence of a breast lesion. Cases are a mixture of prevalent and incident disease.

Städtisches Klinikum Karlsruhe and Deutsches Krebsforschungszentrum Breast Cancer Study (SKKDKFZS): This breast cancer case cohort study consists of women with pathologically confirmed breast cancer recruited at the Städtisches Klinikum Karlruhe, Karlsruhe, Germany from 1993 - 2005. Cases were between 21-93 years of age. Controls for the subgroup of TN breast cancer cases were from an unselected series of unaffected women from the same geographical area.

Simultaneous Study of Docetaxel Based Anthracycline Free Adjuvant treatment Evaluation, as well as Life Style Intervention Strategies (SUCCESS C): is a prospectively randomized trial for high risk breast cancer patients without metastases. All patients had to be at least 18 years of age, HER2 negative with an otherwise high risk of recurrence. A total of 3642 patients were recuited from March 2009 to August 2011. Of 3256 patients whole blood samples could be collected, of which 742 were from patients with triple negative tumors.

Washington University Young Women's Breast Cancer Study (WASHU): This breast cancer case cohort study consists of women with pathologically confirmed breast cancer identified through the Young Women's Breast Cancer Program at Washington University Siteman Cancer Center.

Wellcome Trust Case Control Consortium (WTCCC): The 1958 Birth Cohort (also known as the National Child Development Study) includes all births in England, Wales and Scotland, during

one week in 1958. From an original sample of over 17,000 births, survivors were followed up at ages 7, 11, 16, 23, 33 and 42 yrs. In a biomedical examination at 44-45 yrs, 9,377 cohort members were visited at home providing 7,692 blood samples with consent for future Epstein–Barr virus (EBV)-transformed cell lines. DNA samples extracted from 1,500 cell lines of self-reported white ethnicity and representative of gender and each geographical region were selected for use as controls.

References

1. Michailidou, K., *et al.* (2013) Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nature genetics*, **45**, 353-61.
2. Thomas, G., *et al.* (2009) A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 (RAD51L1). *Nat Genet*, **41**, 579-84.
3. Garcia-Closas, M., *et al.* (2013) Genome-wide association studies identify four ER negative-specific breast cancer risk loci. *Nature genetics*, **45**, 392-8.
4. Cox, A., *et al.* (2007) A common coding variant in CASP8 is associated with breast cancer risk. *Nat Genet*, **39**, 352-8.
5. Stacey, S.N., *et al.* (2007) Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor-positive breast cancer. *Nat Genet*, **39**, 865-9.
6. Ahmed, S., *et al.* (2009) Newly discovered breast cancer susceptibility loci on 3p24 and 17q23.2. *Nat Genet*, **41**, 585-90.
7. Haiman, C.A., *et al.* (2011) A common variant at the TERT-CLPTM1L locus is associated with estrogen receptor-negative breast cancer. *Nat Genet*, **43**, 1210-4.
8. Bojesen, S.E., *et al.* (2013) Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. *Nature genetics*, **45**, 371-84.
9. Stacey, S.N., *et al.* (2008) Common variants on chromosome 5p12 confer susceptibility to estrogen receptor-positive breast cancer. *Nat Genet*, **40**, 703-6.
10. Easton, D.F., *et al.* (2007) Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature*, **447**, 1087-93.
11. Turnbull, C., *et al.* (2010) Genome-wide association study identifies five new breast cancer susceptibility loci. *Nat Genet*, **42**, 504-7.
12. Zheng, W., *et al.* (2009) Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25.1. *Nat Genet*, **41**, 324-8.
13. Fletcher, O., *et al.* (2011) Novel Breast Cancer Susceptibility Locus at 9q31.2: Results of a Genome-Wide Association Study. *J Natl Cancer Inst*.
14. French, J.D., *et al.* (2013) Functional Variants at the 11q13 Risk Locus for Breast Cancer Regulate Cyclin D1 Expression through Long-Range Enhancers. *American journal of human genetics*.
15. Ghoussaini, M., *et al.* (2012) Genome-wide association analysis identifies three new breast cancer susceptibility loci. *Nat Genet*, **44**, 312-318.
16. Antoniou, A.C., *et al.* (2010) A locus on 19p13 modifies risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population. *Nat Genet*, **42**, 885-92.
17. Siddiq, A., *et al.* (2012) A meta-analysis of genome-wide association studies of breast cancer identifies two novel susceptibility loci at 6q14 and 20q11. *Hum Mol Genet*.
18. Rhie, S.K., *et al.* (2013) Comprehensive functional annotation of seventy-one breast cancer risk Loci. *PLoS One*, **8**, e63925.
19. Leu, M., *et al.* (2010) NordicDB: a Nordic pool and portal for genome-wide control data. *Eur J Hum Genet*, **18**, 1322-6.