**Associations of a Breast Cancer Polygenic Risk Score with Tumor Characteristics and Survival**

Josephine M.N. Lopes Cardozo1, 2, Irene L. Andrulis3, 4, Stig E. Bojesen5-7, Thilo Dörk8, Diana M. Eccles9, Peter A. Fasching10, Maartje J. Hooning11, Renske Keeman12, Heli Nevanlinna13, Emiel J.T. Rutgers1, Thomas U. Ahearn14, Hoda Anton-Culver15, Volker Arndt16, Paul L. Auer17, Annelie Augustinsson18, Laura E. Beane Freeman14, Heiko Becher19, Matthias W. Beckmann10, Sabine Behrens20, Javier Benitez21, 22, Marina Bermisheva23, Carl Blomqvist24, Manjeet K. Bolla25, Bernardo Bonanni26, Terry Boyle27, Hermann Brenner16, 28, 29, Sara Y. Brucker30, Thomas Brüning31, Barbara Burwinkel32, 33, Saundra S. Buys34, Nicola J. Camp34, Federico Canzian35, Fatima Cardoso36, Jose E. Castelao37, Melissa H. Cessna38, Tsun L. Chan39, 40, Jenny Chang-Claude20, 41, Georgia Chenevix-Trench42, Ji-Yeob Choi43-45, NBCS Collaborators46-57, Sarah V. Colonna34, CTS Consortium58, 59, Ellen Copson60, Fergus J. Couch61, Angela Cox62, Simon S. Cross63, Kamila Czene64, Mary B. Daly65, Joe Dennis25, Peter Devilee66, 67, Caroline A. Drukker1, Alison M. Dunning68, Miriam Dwek69, A. Heather Eliassen70-72, Christoph Engel73, 74, D. Gareth Evans75, 76, Jonine D. Figueroa14, 77, 78, Olivia Fletcher79, Henrik Flyger80, Manuela Gago-Dominguez81, Montserrat García-Closas14, José A. García-Sáenz82, Jeanine Genkinger83, 84, Graham G. Giles85-87, Anna González-Neira88, Pascal Guénel89, Melanie Gündert32, 33, 90, Eric Hahnen91, 92, Christopher A. Haiman93, Niclas Håkansson94, Ute Hamann95, Mikael Hartman96-98, Bernadette A.M. Heemskerk-Gerritsen11, Alexander Hein10, Weang-Kee Ho99, 100, Reiner Hoppe101, 102, John L. Hopper86, Richard S. Houlston103, Anthony Howell104, David J. Hunter71, 105, kConFab Investigators106, 107, ABCTB Investigators108, SGBCC Investigators96, 97, 109-119, Hidemi Ito120, 121, Anna Jakubowska122, 123, Helena Jernström18, Esther M. John124, 125, Nichola Johnson79, Michael E. Jones103, Vijai Joseph126, 127, Rudolf Kaaks20, Daehee Kang44, 128, Sung-Won Kim129, Cari M. Kitahara130, Linetta B. Koppert131, Veli-Matti Kosma132-134, Peter Kraft71, 135, Vessela N. Kristensen47, 57, Katerina Kubelka-Sabit136, Stella Koutros14, Allison W. Kurian124, 125, Ava Kwong39, 137, 138, James V. Lacey58, 59, Diether Lambrechts139, 140, Loic Le Marchand141, Jingmei Li109, Jan Lubiński122, Michael Lush25, Arto Mannermaa132-134, Mehdi Manoochehri95, Sara Margolin142, 143, Keitaro Matsuo121, 144, Dimitrios Mavroudis145, Kyriaki Michailidou25, 146, Roger L. Milne85-87, Nur Aishah Mohd Taib147, Anna Marie Mulligan148, 149, Patrick Neven150, William G. Newman75, 76, Nadia Obi19, Kenneth Offit126, 127, Andrew F. Olshan151, Sue K. Park44, 128, 152, Tjoung-Won Park-Simon8, Alpa V. Patel153, Dijana Plaseska-Karanfilska154, Coralie Poncet2, Ross L. Prentice155, Nadege Presneau69, Renate Prevos150, Katri Pylkäs156, 157, Paolo Radice158, Gad Rennert159, Hedy S. Rennert159, Atocha Romero160, Emmanouil Saloustros161, Elinor J. Sawyer162, Rita K. Schmutzler91, 92, 163, Lukas Schwentner164, Christopher Scott165, Mitul Shah68, Chen-Yang Shen166, 167, Xiao-Ou Shu168, Xueling Sim96, Melissa C. Southey85, 87, 169, Jennifer Stone86, 170, Daniel O. Stram93, Rulla M. Tamimi71, 171, Soo Hwang Teo147, 172, Lauren R. Teras153, Mary Beth Terry83, Katarzyna Tomczyk79, Ian Tomlinson173, Melissa A. Troester151, Thérèse Truong89, Celine M. Vachon174, Chantal van Ongeval150, Qin Wang25, Barbara Wappenschmidt91, 92, Camilla Wendt143, Robert Winqvist156, 157, Alicja Wolk94, Anna H. Wu175, Siddhartha Yadav176, Cheng Har Yip147, 177, Wei Zheng168, Argyrios Ziogas15, Douglas F. Easton25, 68, Per Hall64, 142, Paul D.P. Pharoah25, 68, Laura J. van 't Veer178, Marjanka K. Schmidt12, 179, 180

Corresponding author: Prof. Marjanka K. Schmidt, Division of Molecular Pathology Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands *Telephone number:* +31 20 512 2767 *Email address:* [mk.schmidt@nki.nl](mailto:mk.schmidt@nki.nl)

**Running head:** Polygenic Risk Score and Breast Cancer Outcome

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1. Department of Surgery. The Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital. Amsterdam: the Netherlands

2. European Organisation for Research and Treatment of Cancer Headquarters. Brussels: Belgium

3. Fred A. Litwin Center for Cancer Genetics. Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital. Toronto, Ontario: Canada

4. Department of Molecular Genetics. University of Toronto. Toronto, Ontario: Canada

5. Copenhagen General Population Study, Herlev and Gentofte Hospital. Copenhagen University Hospital. Herlev: Denmark

6. Department of Clinical Biochemistry, Herlev and Gentofte Hospital. Copenhagen University Hospital. Herlev: Denmark

7. Faculty of Health and Medical Sciences. University of Copenhagen. Copenhagen: Denmark

8. Gynaecology Research Unit. Hannover Medical School. Hannover: Germany

9. Faculty of Medicine. University of Southampton. Southampton: UK

10. Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg. University Hospital Erlangen. Erlangen: Germany

11. Department of Medical Oncology. Erasmus MC Cancer Institute. Rotterdam: the Netherlands

12. Division of Molecular Pathology. The Netherlands Cancer Institute. Amsterdam: the Netherlands

13. Department of Obstetrics and Gynecology, Helsinki University Hospital. University of Helsinki. Helsinki: Finland

14. Division of Cancer Epidemiology and Genetics. National Cancer Institute, National Institutes of Health, Department of Health and Human Services. Bethesda, MD: USA

15. Department of Medicine, Genetic Epidemiology Research Institute. University of California Irvine. Irvine, CA: USA

16. Division of Clinical Epidemiology and Aging Research. German Cancer Research Center (DKFZ). Heidelberg: Germany

17. Division of Biostatistics, Institute for Health and Equity, and Cancer Center. Medical College of Wisconsin. Milwaukee, WI: USA

18. Oncology, Department of Clinical Sciences in Lund. Lund University. Lund: Sweden

19. Institute for Medical Biometry and Epidemiology. University Medical Center Hamburg-Eppendorf. Hamburg: Germany

20. Division of Cancer Epidemiology. German Cancer Research Center (DKFZ). Heidelberg: Germany

21. Human Genetics Group. Spanish National Cancer Research Centre (CNIO). Madrid: Spain

22. Centre for Biomedical Network Research on Rare Diseases (CIBERER), Instituto de Salud Carlos III. Madrid: Spain

23. Institute of Biochemistry and Genetics of the Ufa Federal Research Centre of the Russian Academy of Sciences. Ufa: Russia

24. Department of Oncology, Helsinki University Hospital. University of Helsinki. Helsinki: Finland

25. Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care. University of Cambridge. Cambridge: UK

26. Division of Cancer Prevention and Genetics. IEO, European Institute of Oncology IRCCS. Milan: Italy

27. Australian Centre for Precision Health. University of South Australia. Adelaide, SA: Australia

28. Division of Preventive Oncology. German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT). Heidelberg: Germany

29. German Cancer Consortium (DKTK). German Cancer Research Center (DKFZ). Heidelberg: Germany

30. Department of Women's Health. Tuebingen University Hospital. Tuebingen: Germany

31. Institute for Prevention and Occupational Medicine of the German Social Accident Insurance. Institute of the Ruhr University Bochum. Bochum: Germany

32. Molecular Epidemiology Group, C080. German Cancer Research Center (DKFZ). Heidelberg: Germany

33. Molecular Biology of Breast Cancer, University Womens Clinic Heidelberg. University of Heidelberg. Heidelberg: Germany

34. Department of Internal Medicine and Huntsman Cancer Institute. University of Utah. Salt Lake City, UT: USA

35. Genomic Epidemiology Group. German Cancer Research Center (DKFZ). Heidelberg: Germany

36. Breast Unit, Champalimaud Clinical Center, Champalimaud Foundation. Lisbon: Portugal

37. Oncology and Genetics Unit. Instituto de Investigación Sanitaria Galicia Sur (IISGS), Xerencia de Xestion Integrada de Vigo-SERGAS. Vigo: Spain

38. Intermountain Healthcare. Salt Lake City, UT: USA

39. Hong Kong Hereditary Breast Cancer Family Registry: Hong Kong

40. Department of Molecular Pathology. Hong Kong Sanatorium and Hospital: Hong Kong

41. Cancer Epidemiology Group, University Cancer Center Hamburg (UCCH). University Medical Center Hamburg-Eppendorf. Hamburg: Germany

42. Cancer Division. QIMR Berghofer Medical Research Institute. Brisbane, Queensland: Australia

43. Department of Biomedical Sciences. Seoul National University Graduate School. Seoul: Korea

44. Cancer Research Institute. Seoul National University. Seoul: Korea

45. Institute of Health Policy and Management. Seoul National University Medical Research Center. Seoul: Korea

46. Department of Cancer Genetics, Institute for Cancer Research. Oslo University Hospital-Radiumhospitalet. Oslo: Norway

47. Institute of Clinical Medicine, Faculty of Medicine. University of Oslo. Oslo: Norway

48. Department of Research. Vestre Viken Hospital. Drammen: Norway

49. Section for Breast- and Endocrine Surgery, Department of Cancer, Division of Surgery, Cancer and Transplantation Medicine. Oslo University Hospital-Ullevål. Oslo: Norway

50. Department of Radiology and Nuclear Medicine. Oslo University Hospital. Oslo: Norway

51. Department of Pathology. Akershus University Hospital. Lørenskog: Norway

52. Department of Tumor Biology, Institute for Cancer Research. Oslo University Hospital. Oslo: Norway

53. Department of Oncology, Division of Surgery, Cancer and Transplantation Medicine. Oslo University Hospital-Radiumhospitalet. Oslo: Norway

54. National Advisory Unit on Late Effects after Cancer Treatment. Oslo University Hospital. Oslo: Norway

55. Department of Oncology. Akershus University Hospital. Lørenskog: Norway

56. Oslo Breast Cancer Research Consortium. Oslo University Hospital. Oslo: Norway

57. Department of Medical Genetics. Oslo University Hospital and University of Oslo. Oslo: Norway

58. Department of Computational and Quantitative Medicine. City of Hope. Duarte, CA: USA

59. City of Hope Comprehensive Cancer Center. City of Hope. Duarte, CA: USA

60. Department of Medical Oncology. University of Southampton. Southampton: UK

61. Department of Laboratory Medicine and Pathology. Mayo Clinic. Rochester, MN: USA

62. Sheffield Institute for Nucleic Acids (SInFoNiA), Department of Oncology and Metabolism. University of Sheffield. Sheffield: UK

63. Academic Unit of Pathology, Department of Neuroscience. University of Sheffield. Sheffield: UK

64. Department of Medical Epidemiology and Biostatistics. Karolinska Institutet. Stockholm: Sweden

65. Department of Clinical Genetics. Fox Chase Cancer Center. Philadelphia, PA: USA

66. Department of Pathology. Leiden University Medical Center. Leiden: the Netherlands

67. Department of Human Genetics. Leiden University Medical Center. Leiden: the Netherlands

68. Centre for Cancer Genetic Epidemiology, Department of Oncology. University of Cambridge. Cambridge: UK

69. School of Life Sciences. University of Westminster. London: UK

70. Channing Division of Network Medicine, Department of Medicine. Brigham and Women's Hospital and Harvard Medical School. Boston, MA: USA

71. Department of Epidemiology. Harvard TH Chan School of Public Health. Boston, MA: USA

72. Department of Nutrition. Harvard TH Chan School of Public Health. Boston, MA: USA

73. Institute for Medical Informatics, Statistics and Epidemiology. University of Leipzig. Leipzig: Germany

74. LIFE - Leipzig Research Centre for Civilization Diseases. University of Leipzig. Leipzig: Germany

75. Division of Evolution and Genomic Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health. University of Manchester, Manchester Academic Health Science Centre. Manchester: UK

76. North West Genomics Laboratory Hub, Manchester Centre for Genomic Medicine. St Mary’s Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre. Manchester: UK

77. Usher Institute of Population Health Sciences and Informatics. The University of Edinburgh. Edinburgh: UK

78. Cancer Research UK Edinburgh Centre. The University of Edinburgh. Edinburgh: UK

79. The Breast Cancer Now Toby Robins Research Centre. The Institute of Cancer Research. London: UK

80. Department of Breast Surgery, Herlev and Gentofte Hospital. Copenhagen University Hospital. Herlev: Denmark

81. Genomic Medicine Group, International Cancer Genetics and Epidemiology Group. Fundación Pública Galega de Medicina Xenómica, Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Complejo Hospitalario Universitario de Santiago, SERGAS. Santiago de Compostela: Spain

82. Medical Oncology Department, Hospital Clínico San Carlos. Instituto de Investigación Sanitaria San Carlos (IdISSC), Centro Investigación Biomédica en Red de Cáncer (CIBERONC). Madrid: Spain

83. Department of Epidemiology, Mailman School of Public Health. Columbia University. New York, NY: USA

84. Herbert Irving Comprehensive Cancer Center. New York, NY: USA

85. Cancer Epidemiology Division. Cancer Council Victoria. Melbourne, Victoria: Australia

86. Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health. The University of Melbourne. Melbourne, Victoria: Australia

87. Precision Medicine, School of Clinical Sciences at Monash Health. Monash University. Clayton, Victoria: Australia

88. Human Genotyping Unit-CeGen. Spanish National Cancer Research Centre (CNIO). Madrid: Spain

89. Team 'Exposome and Heredity', CESP, Gustave Roussy. INSERM, University Paris-Saclay, UVSQ. Villejuif: France

90. Institute of Diabetes Research. Helmholtz Zentrum München, German Research Center for Environmental Health. Neuherberg: Germany

91. Center for Familial Breast and Ovarian Cancer. Faculty of Medicine and University Hospital Cologne, University of Cologne. Cologne: Germany

92. Center for Integrated Oncology (CIO). Faculty of Medicine and University Hospital Cologne, University of Cologne. Cologne: Germany

93. Department of Preventive Medicine, Keck School of Medicine. University of Southern California. Los Angeles, CA: USA

94. Institute of Environmental Medicine. Karolinska Institutet. Stockholm: Sweden

95. Molecular Genetics of Breast Cancer. German Cancer Research Center (DKFZ). Heidelberg: Germany

96. Saw Swee Hock School of Public Health. National University of Singapore and National University Health System. Singapore: Singapore

97. Department of Surgery. National University Health System. Singapore: Singapore

98. Department of Pathology, Yong Loo Lin School of Medicine. National University of Singapore. Singapore: Singapore

99. Department of Mathematical Sciences, Faculty of Science and Engineering. University of Nottingham Malaysia Campus. Semenyih, Selangor: Malaysia

100. Breast Cancer Research Programme. Cancer Research Malaysia. Subang Jaya, Selangor: Malaysia

101. Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology. Stuttgart: Germany

102. University of Tübingen. Tübingen: Germany

103. Division of Genetics and Epidemiology. The Institute of Cancer Research. London: UK

104. Division of Cancer Sciences. University of Manchester. Manchester: UK

105. Nuffield Department of Population Health. University of Oxford. Oxford: UK

106. Research Department. Peter MacCallum Cancer Center. Melbourne, Victoria: Australia

107. Sir Peter MacCallum Department of Oncology. The University of Melbourne. Melbourne, Victoria: Australia

108. Australian Breast Cancer Tissue Bank, Westmead Institute for Medical Research. University of Sydney. Sydney, New South Wales: Australia

109. Human Genetics Division. Genome Institute of Singapore. Singapore: Singapore

110. Department of Medicine, Yong Loo Lin School of Medicine. National University of Singapore and National University Health System. Singapore: Singapore

111. Cancer Genetics Service. National Cancer Centre. Singapore: Singapore

112. Breast Department. KK Women's and Children's Hospital. Singapore: Singapore

113. SingHealth Duke-NUS Breast Centre. Singapore: Singapore

114. Department of General Surgery. Tan Tock Seng Hospital. Singapore: Singapore

115. Division of Surgical Oncology. National Cancer Centre. Singapore: Singapore

116. Department of General Surgery. Singapore General Hospital. Singapore: Singapore

117. Division of Breast Surgery, Department of General Surgery. Changi General Hospital. Singapore: Singapore

118. Division of Radiation Oncology. National Cancer Centre. Singapore: Singapore

119. Division of Medical Oncology. National Cancer Centre. Singapore: Singapore

120. Division of Cancer Information and Control. Aichi Cancer Center Research Institute. Nagoya: Japan

121. Division of Cancer Epidemiology. Nagoya University Graduate School of Medicine. Nagoya: Japan

122. Department of Genetics and Pathology. Pomeranian Medical University, Unii Lubelskiej. Szczecin: Poland

123. Independent Laboratory of Molecular Biology and Genetic Diagnostics. Pomeranian Medical University, Unii Lubelskiej. Szczecin: Poland

124. Department of Epidemiology and Population Health. Stanford University School of Medicine. Stanford, CA: USA

125. Department of Medicine, Division of Oncology. Stanford Cancer Institute, Stanford University School of Medicine. Stanford, CA: USA

126. Clinical Genetics Research Lab, Department of Cancer Biology and Genetics. Memorial Sloan Kettering Cancer Center. New York, NY: USA

127. Clinical Genetics Service, Department of Medicine. Memorial Sloan Kettering Cancer Center. New York, NY: USA

128. Department of Preventive Medicine. Seoul National University College of Medicine. Seoul: Korea

129. Department of Surgery. Daerim Saint Mary's Hospital. Seoul: Korea

130. Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics. National Cancer Institute. Bethesda, MD: USA

131. Department of Surgical Oncology, Family Cancer Clinic. Erasmus MC Cancer Institute. Rotterdam: the Netherlands

132. Translational Cancer Research Area. University of Eastern Finland. Kuopio: Finland

133. Institute of Clinical Medicine, Pathology and Forensic Medicine. University of Eastern Finland. Kuopio: Finland

134. Biobank of Eastern Finland. Kuopio University Hospital. Kuopio: Finland

135. Program in Genetic Epidemiology and Statistical Genetics. Harvard TH Chan School of Public Health. Boston, MA: USA

136. Department of Histopathology and Cytology. Clinical Hospital Acibadem Sistina. Skopje: Republic of North Macedonia

137. Department of Surgery. The University of Hong Kong: Hong Kong

138. Department of Surgery and Cancer Genetics Center. Hong Kong Sanatorium and Hospital: Hong Kong

139. Laboratory for Translational Genetics, Department of Human Genetics. KU Leuven. Leuven: Belgium

140. VIB Center for Cancer Biology, VIB. Leuven: Belgium

141. Epidemiology Program. University of Hawaii Cancer Center. Honolulu, HI: USA

142. Department of Oncology. Södersjukhuset. Stockholm: Sweden

143. Department of Clinical Science and Education, Södersjukhuset. Karolinska Institutet. Stockholm: Sweden

144. Division of Cancer Epidemiology and Prevention. Aichi Cancer Center Research Institute. Nagoya: Japan

145. Department of Medical Oncology. University Hospital of Heraklion. Heraklion: Greece

146. Biostatistics Unit. The Cyprus Institute of Neurology & Genetics. Nicosia: Cyprus

147. Department of Surgery, Faculty of Medicine. University of Malaya, UM Cancer Research Institute. Kuala Lumpur: Malaysia

148. Department of Laboratory Medicine and Pathobiology. University of Toronto. Toronto, Ontario: Canada

149. Laboratory Medicine Program. University Health Network. Toronto, Ontario: Canada

150. Leuven Multidisciplinary Breast Center, Department of Oncology. Leuven Cancer Institute, University Hospitals Leuven. Leuven: Belgium

151. Department of Epidemiology, Gillings School of Global Public Health and UNC Lineberger Comprehensive Cancer Center. University of North Carolina at Chapel Hill. Chapel Hill, NC: USA

152. Integrated Major in Innovative Medical Science. Seoul National University College of Medicine. Seoul: Korea

153. Department of Population Science. American Cancer Society. Atlanta, GA: USA

154. Research Centre for Genetic Engineering and Biotechnology 'Georgi D. Efremov'. MASA. Skopje: Republic of North Macedonia

155. Cancer Prevention Program. Fred Hutchinson Cancer Research Center. Seattle, WA: USA

156. Laboratory of Cancer Genetics and Tumor Biology, Translational Medicine Research Unit, Biocenter Oulu. University of Oulu. Oulu: Finland

157. Laboratory of Cancer Genetics and Tumor Biology. Northern Finland Laboratory Centre Oulu. Oulu: Finland

158. Unit of Molecular Bases of Genetic Risk and Genetic Testing, Department of Research. Fondazione IRCCS Istituto Nazionale dei Tumori (INT). Milan: Italy

159. Clalit National Cancer Control Center. Carmel Medical Center and Technion Faculty of Medicine. Haifa: Israel

160. Medical Oncology Department. Hospital Universitario Puerta de Hierro. Madrid: Spain

161. Department of Oncology. University Hospital of Larissa. Larissa: Greece

162. School of Cancer & Pharmaceutical Sciences, Comprehensive Cancer Centre, Guy’s Campus. King's College London. London: UK

163. Center for Molecular Medicine Cologne (CMMC). Faculty of Medicine and University Hospital Cologne, University of Cologne. Cologne: Germany

164. Department of Gynaecology and Obstetrics. University Hospital Ulm. Ulm: Germany

165. Department of Health Sciences Research. Mayo Clinic. Rochester, MN: USA

166. Institute of Biomedical Sciences. Academia Sinica. Taipei: Taiwan

167. School of Public Health. China Medical University. Taichung: Taiwan

168. Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center. Vanderbilt University School of Medicine. Nashville, TN: USA

169. Department of Clinical Pathology. The University of Melbourne. Melbourne, Victoria: Australia

170. Genetic Epidemiology Group, School of Population and Global Health. University of Western Australia. Perth, Western Australia: Australia

171. Department of Population Health Sciences. Weill Cornell Medicine. New York, NY: USA

172. Breast Cancer Research Programme. Cancer Research Malaysia. Subang Jaya, Selangor: Malaysia

173. Cancer Research Centre. The University of Edinburgh. Edinburgh: UK

174. Department of Quantitative Health Sciences, Division of Epidemiology. Mayo Clinic. Rochester, MN: USA

175. Department of Population Health and Public Health Sciences, Keck School of Medicine. University of Southern California Norris Comprehensive Cancer Center. Los Angeles, CA: USA

176. Department of Medical Oncology. Mayo Clinic. Rochester, MN: USA

177. Subang Jaya Medical Centre. Subang Jaya, Selangor: Malaysia

178. UCSF Helen Diller Family Comprehensive Cancer Center, University of California San Francisco. San Francisco, CA: USA

179. Division of Psychosocial Research and Epidemiology. The Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital. Amsterdam: the Netherlands

180. Department of Clinical Genetics. Leiden University Medical Center. Leiden: the Netherlands

**ABSTRACT**

**PURPOSE:** A polygenic risk score (PRS) consisting of 313 common genetic variants (PRS313) is associated with risk of breast cancer and contralateral breast cancer. This study aimed to evaluate the association of the PRS313 with clinical-pathological characteristics of, and survival following, breast cancer.

**PATIENTS AND METHODS:** Women with invasive breast cancer were included, 98,397 of European ancestry and 12,920 of Asian ancestry, from the Breast Cancer Association Consortium (BCAC), and 683 women from the European MINDACT trial. Associations between PRS313 and clinical-pathological characteristics, including the 70-gene signature for MINDACT, were evaluated using logistic regression analyses. Associations of PRS313 (continuous, per SD) with overall survival (OS) and breast cancer-specific survival (BCSS) were evaluated with Cox regression, adjusted for clinical-pathological characteristics and treatment.

**RESULTS:** The PRS313 was associated with more favorable tumor characteristics. In BCAC, increasing PRS313 was associated with lower grade, hormone receptor-positive status, and smaller tumor size. In MINDACT, PRS313 was associated with a low risk 70-gene signature. In European women from BCAC, higher PRS313 was associated with better OS and BCSS: hazard ratio (HR) 0.96 (95% confidence interval (CI):0.94-0.97) and 0.96 (95%CI:0.94-0.98), but the association disappeared after adjustment for clinical-pathological characteristics (and treatment): OS HR:1.01 (95%CI:0.98-1.05) and BCSS HR:1.02 (95%CI:0.98-1.07). Results in MINDACT and Asian women from BCAC were consistent.

**CONCLUSION:** An increased PRS313 is associated with favorable tumor characteristics, but is not independently associated with prognosis. Thus, PRS313 has no role in the clinical management of primary breast cancer at time of diagnosis. Nevertheless, breast cancer mortality rates will be higher for women with higher PRS313 as increasing PRS313 is associated with an increased risk of disease. This information is crucial for modelling effective stratified screening programs.

**CONTEXT SUMMARY**

**Key objective**

An optimized and extensively validated polygenic risk score (PRS) consisting of 313 common genetic variants (PRS313) has been associated with risk of first breast cancer and contralateral breast cancer, and has a promising role for risk stratification in screening and prevention programs. Whether PRS313 affects breast cancer prognosis has not yet been addressed, and is important for incorporating PRS into clinical practice.

**Knowledge generated**

PRS313 was associated with more favorable tumor characteristics. PRS313 was not independently associated with prognosis. Nevertheless, breast cancer mortality rates will be higher for women with higher PRS313 as increasing PRS313 is associated with an increased risk of disease.

**INTRODUCTION**

Over recent years there has been an increased understanding of genetic factors that contribute to risk of breast cancer.1–6 Large scale genome-wide association studies (GWAS) have identified hundreds of common genetic variants (mostly single nucleotide polymorphisms (SNPs)) that are associated with breast cancer risk.5–12 Together these common genetic variants explain approximately 20% of the hereditary component of breast cancer risk.11

Individual SNPs have a small effect on risk, but their joint effects can be substantial, and can be efficiently summarized in terms of polygenic risk scores (PRS), which are the weighted sum of risk alleles.6,7,12 We previously reported the association between an optimized and validated PRS consisting of 313 SNPs (PRS313) and the risk of breast cancer using data from the Breast Cancer Association Consortium (BCAC).6,12 PRS313 is predictive of overall breast cancer risk, with an odds ratio (OR) per standard deviation (SD) of 1.61 (95% confidence interval (95%CI): 1.57–1.65).12 PRS313 is also associated with a higher risk of contralateral breast cancer with a hazard ratio (HR) per SD of 1.25 (95%CI: 1.18-1.33).13 PRS for subtype-specific disease (estrogen receptor (ER)-positive and ER-negative disease) have also been established, although currently the risk prediction for ER-positive disease is better than for ER-negative disease.7,12

One of the most promising clinical applications for PRS is to provide a personalized risk assessment in order to individualize breast cancer screening. For women with a higher risk of developing breast cancer, this could involve starting screening at a younger age and offering more frequent screening, while women at lower risk could be offered less frequent screening.7,14 Currently, several large studies are investigating the feasibility and effectiveness of incorporating risk-based screening based on PRS and other risk factors into breast cancer screening programs.15–19 Since the ultimate goal of screening programs is to reduce mortality, an important question is whether PRS are associated with survival of women with breast cancer. The aim of this study was to investigate the association between PRS313 and clinical-pathological characteristics of breast cancer and disease outcome. In a subgroup of patients from the MINDACT study, we also explored associations of PRS313 with the 70-gene signature (MammaPrint), which has been shown to predict distant metastasis within 5 years of breast cancer diagnosis.20

**METHODS**

**Study subjects and SNP genotyping**

***BCAC***  
We selected women diagnosed with a first invasive breast cancer from the BCAC database version 13. All women of European and Asian ancestry, based on genotyping, who were 18 years and older were included, including 98,397 European women (74 studies) and 12,920 Asian women (10 studies) (Figure S1A). SNP genotyping was performed using the iCOGS array21,22 or the OncoArray10,11. Genotypes for variants that were not on the arrays were estimated by imputation.11,22 For samples that were genotyped with both arrays, OncoArray data were used. As previously described, adjustment for type of array was not needed because of the high correlation of PRS313 between the two platforms.12,13 All participants provided written informed consent, and all studies were approved by the relevant institutional review boards. BCAC data were centrally harmonized and cleaned in consultation with the study data managers and principal investigators.

***MINDACT***A selection of 1,139 women who were screened for participation in the EORTC 10041/BIG 3-04 MINDACT study also participated in the iCOGS project. In this project, genotyping was performed using the iCOGS array.21,22 Of these, 683 women were eventually enrolled in the MINDACT trial, for whom clinical and outcome data were available (Figure S1B). MINDACT included women aged 18-70 years with operable invasive breast cancer (T1-3), 0-3 positive lymph nodes (N0-1) and no distant metastasis (M0).23,24 Further details on the MINDACT study design and the trial results have been previously described.23,24 For all patients enrolled in the MINDACT trial, a tumor sample was shipped to Agendia (Amsterdam, Netherlands) for 70-gene signature testing.23,24 The 70-gene signature classifies tumors as high or low risk of developing distant metastasis within 5 years after breast cancer diagnosis.20 All patients provided written informed consent for participation in the iCOGS project as part of the informed consent for the MINDACT study, which allowed linkage of the PRS313 results to the MINDACT study database.

**Polygenic risk scores (PRSs)**The PRS313 and the ER-specific PRSs (hybrid method) were calculated and validated as described by Mavaddat et al;12 MINDACT and the Asian BCAC set were not included in that study, but the BCAC European data were. For consistency with other PRS analyses, we standardized the PRS by dividing it by the standard deviation of PRS313 of the control subjects (PRS313 SD=0.61; ER-positive PRS313 SD=0.65; ER-negative PRS313 SD=0.59).12,13

**Statistical analysis**All analyses were performed separately in the BCAC and MINDACT databases. Univariable logistic regression models were used to test the association between the PRS313 and clinical-pathological characteristics including the 70-gene signature. In BCAC, models were adjusted for country.

The primary outcome was to evaluate the association between PRS313 (per SD) and outcome after breast cancer. This was assessed for three different endpoints; overall survival (OS), breast cancer-specific survival (BCSS) and distant metastasis-free interval (DMFI). OS was defined as the time from breast cancer diagnosis until death from any cause. BCSS was defined as the time from breast cancer diagnosis until death due to breast cancer. DMFI was defined as the time from breast cancer diagnosis until first distant metastasis or death due to breast cancer. Patients who developed a contralateral breast cancer during follow-up were not censored. For MINDACT, death from unknown cause was included as an event for DMFI. For BCAC, death from unknown cause was not included as an event for DMFI, because of the high number of patients with unknown causes of death.

Cox proportional hazards models were used to test the association between PRS313 and survival endpoints in univariable models and in multivariable models adjusted for clinical-pathological characteristics and treatment (chemotherapy and endocrine therapy). Additionally, in a univariable Cox model, the association between the PRS313 and BCSS was evaluated in subgroups based on clinical-pathological characteristics.

In BCAC, all analyses were stratified by country, and for the survival analyses patients with stage IV breast cancer (n=1,379) were excluded to allow for comparison to MINDACT. The entire follow-up duration was considered for the analyses in MINDACT. For BCAC, follow-up was right censored at 15 years, accounting for the large variation in follow-up durations for different studies; this did not lead to different conclusions compared to the analyses when all follow-up was considered. Analyses in BCAC allowed for delayed study entry (after breast cancer diagnosis) using left truncation. Cases with missing data for a given variable were excluded for any analysis using that variable. A sensitivity analysis was performed in BCAC including only cases with complete data for all variables. Details on the different studies included in BCAC, including information on number of patients and collection of follow-up per study, have been described previously.25,26 Women of Asian ancestry were analyzed separately and this analysis was limited to the main analyses of the association between PRS313 and clinical-pathological characteristics and survival endpoints, because of the smaller size of the dataset with shorter follow-up time than for the European BCAC studies, and because 26 variants of the PRS313 were imputed with a low (<.9) imputation score.27 Similarly, analysis in MINDACT were also limited to the main analyses, because of the smaller dataset.

All analyses in MINDACT were performed using SPSS (version 27.0) or R (version 3.6.3). All analyses in BCAC were performed using STATA/SE (version 15.1). All plots were made using R (version 3.6.3). All tests of statistical significance were two-sided, with the level of significance defined as a *P* value of <.05.

**RESULTS**

**Association between PRS313 and clinical-pathological characteristics**

The association between the PRS313 and individual clinical-pathological characteristics was evaluated for 98,397 women of European ancestry and 12,920 women of Asian ancestry with invasive breast cancer included in BCAC and 683 women included in MINDACT. Patient, tumor and treatment characteristics are shown in Table 1. BCAC included more patients with tumors of larger size and positive lymph nodes than MINDACT. The distribution of other tumor and treatment characteristics were similar for BCAC and MINDACT; although there was substantial missing information in BCAC for some variables. Table 2 and Figure 1 show the association between specific tumor characteristics and PRS313. Generally, an increase in PRS313 was associated with a decreased probability of unfavorable tumor characteristics. Patients with a higher PRS313 were less likely to have ER-negative or progesterone receptor (PR)-negative tumors, higher grade tumors or larger tumors. However, a higher PRS313 was associated with a higher probability of lymph node positive tumors, and with a younger age at diagnosis. In the MINDACT study, a higher PRS313 was associated with a lower probability of a high-risk 70-gene signature, and the association was attenuated after adjusting for other clinical-pathological characteristics (adjusted OR 0.97 (95%CI: 0.78-1.21)). This is not unexpected, as we know from previous studies that 70-gene signature low risk tumors are mostly hormone receptor positive, with favorable tumor characteristics. The estimates in BCAC and MINDACT were in the same direction for most factors, although results in the smaller MINDACT study and the subset of women of Asian ancestry in BCAC were statistically non-significant.

**Association between PRS313 and breast cancer outcome**

Data from 95,955 women of European ancestry with primary invasive breast cancer with 16,582 deaths (7,635 known breast cancer deaths) within 15 years from BCAC and 683 women with 61 deaths (31 breast cancer deaths) from MINDACT were included for the primary survival analysis. Median follow-up for overall survival was 7.7 years in BCAC and 8.3 years in MINDACT. In BCAC, an increase in PRS313 was associated with a slightly better OS, HR per unit SD of PRS313 0.96 (95%CI: 0.94-0.97); BCSS, 0.96 (95%CI: 0.94-0.98); and DMFI, 0.98 (95%CI: 0.96-1.00) (Table 3 and Figure 2). For all endpoints, the associations disappeared after adjusting for clinical-pathological characteristics and treatment. The adjusted HR per unit SD of PRS313 was 1.01 (95%CI: 0.98-1.05) for OS, 1.02 (95%CI: 0.98-1.07) for BCSS and 1.03 (95%CI: 0.99-1.07) for DMFI (Table 3 and Figure 2). Of note, the association with PRS313 that was seen in the unadjusted analysis disappeared after adjusting for ER status and grade only (BCSS, 1.01 [95%CI: 0.98-1.04]). The estimates for individual clinical-pathological characteristics from the complete case analyses are provided in the Supplementary Appendix (Supplementary Table S1-3). The HR estimates in MINDACT were close to 1, and consistent with the estimates in BCAC, but with very wide 95%CIs.

Furthermore, results of the analyses in 12,528 women of Asian ancestry with 1,323 deaths (316 known breast cancers deaths) included in BCAC, with a median follow-up for overall survival of 4.2 years, were consistent with those of women of European ancestry in BCAC and MINDACT (Table 3 and Figure 2). The adjusted HR per unit SD of PRS313 was 0.96 (95%CI: 0.87-1.07) for OS; BCSS, 0.93 (95%CI: 0.75-1.17), and DMFI 0.98 (95%CI: 0.87-1.10).

We also evaluated the associations between subtype-specific PRS and breast cancer-specific survival in women of European ancestry (Supplementary Table S4). For BCSS the HR estimates for ER-positive PRS313 were similar to the PRS313 for overall breast cancer, but the association disappeared when analyses were restricted to ER-positive patients. There was no evidence of association between the ER-negative PRS313 and BCSS, either in all patients nor in ER-negative patients. The association between PRS313 and BCSS was also evaluated in subgroups based on clinical-pathological characteristics (Supplementary Table S5). There were no subgroups of patients with a higher probability of breast cancer related death per unit SD increase in PRS313.

**DISCUSSION**

The observed association between the PRS313 and the lower probability of distant metastasis or (breast cancer related) death in the unadjusted analysis disappeared after adjustment for clinical-pathological characteristics. In line with this observation, an increase in PRS313 was associated both with more favorable clinical-pathological characteristics and with a low risk 70-gene signature. The simplest interpretation of these results is that clinical-pathological characteristics, particularly ER-status and grade, act as intermediates on the causal pathway from germline PRS313 to outcomes of breast cancer.

Three studies, each including between 5,000 and 9,000 patients, have previously investigated the association of PRSs consisting of smaller SNP sets (ranging from 77 to 162 SNPs) with clinical-pathological characteristics and clinical outcomes after breast cancer; all in women of European descent.28–30 These PRSs were found to be associated with favorable tumor characteristics; smaller, lower grade and hormone receptor positive tumors. No associations with survival outcomes were observed for any of these PRSs, with HRs per unit SD ranging from 0.91 to 1.02, and all 95% CI including 1.00.28–30 Furthermore, Li et al have shown that patients with a higher PRS are more likely to be found as a screen-detected cancer, which is in line with the findings that an increase in PRS is associated with more favorable clinical-pathological characteristics.28,30,31 Screen-detection itself has been shown to be a prognostic factor for good prognosis, independent of clinical-pathological characteristics.32,33

The 313 SNP PRS is currently the most comprehensively validated PRS of breast cancer risk prediction. In the largest cohort to date, in accordance with previous studies, we observed that higher PRS313 was associated with favorable tumor characteristics. Every SD increase in PRS was associated with lower grade, ER- and PR-positive tumors. We also found associations with smaller size and HER2-negative tumors, but these associations were weaker. In our study, we observed no association between the PRS313 and overall survival (HR per unit SD increase in PRS; 1.01 (95%CI: 0.98-1.05)), breast cancer-specific survival (HR; 1.02 (95%CI: 0.98-1.07)) or distant metastasis free interval (HR; 1.03 (95%CI: 0.99-1.07)) in the adjusted models. Of note, the favorable association that was seen in the unadjusted analysis already disappeared after only adjusting for ER status and grade. Our results, together with those previously reported, demonstrate that a higher PRS, and thus higher breast cancer risk, does not imply a poorer outcome amongst those women that develop breast cancer. The PRS313 does not have independent prognostic value in addition to clinical-pathological characteristics, and has no role in the clinical management of primary breast cancer at time of diagnosis. It is important to emphasize, however, that the absolute mortality from breast cancer will still be higher among women with a higher PRS, because more of them will develop breast cancer and die from the disease. To illustrate this: multiplying the OR per unit SD increase in PRS for breast cancer risk (OR 1.61) with the HR per unit SD increase in PRS for breast cancer-specific survival (HR 0.96) gives an approximate estimate for the relative risk of breast cancer mortality per unit SD of the PRS of 1.55. This is an important message to convey when counseling women about the PRS, and as PRS313 mostly predicts the development of ER-positive breast cancer, it could be used to identify women eligible for endocrine risk reduction.

A limitation of this study is that the analyses were mostly limited to patients of European ancestry, and similar analyses in patients of non-European ancestry are therefore needed. However, an analysis in a subgroup of women of Asian ancestry showed HR estimates that were consistent with those of women of European ancestry.27 Prediction of breast cancer risk with PRS313 is better for ER-positive disease than for ER-negative disease, despite using subtype specific PRSs (ER-positive and ER-negative), likely due to the inclusion of more ER-positive cases in most GWAS and consequently a higher identification of loci that are specifically associated with ER-positive breast cancer than with ER-negative breast cancer.7,12 There was substantial missing information in BCAC for some variables; however, similar results were seen in a complete case sensitivity analysis. Furthermore, data on cause of death were missing or incomplete in some studies in BCAC, possibly underestimating the number of breast cancer deaths in BCAC; however, the outcomes of the association between PRS313 and the three survival endpoints were consistent. The average duration of follow-up of approximately 8 years precludes strong conclusions on late recurrences and long-term outcomes of breast cancer. The association between PRS313 and the 70-gene signature could only be evaluated in a relatively small subgroup of 683 patients from the MINDACT study, leading to uncertain HR estimates with wide 95% CI. Nevertheless, the estimates were in the expected direction, given the association of PRS313 with favorable clinical-pathological characteristics.

Several ongoing studies are evaluating the effectiveness of using comprehensive risk prediction models, including the PRS and other breast cancer risk factors, to adapt the age at initiation and frequency of breast cancer screening according to risk. 15–19 However, our findings that the PRS313 is associated with favorable tumor characteristics imply that improvements in cancer detection may not translate straightforwardly into improvements in breast cancer mortality. The results from these analyses will be important for modelling the effectiveness of different stratified screening approaches, especially since there is also an association between higher PRS and screen-detected cancers. Randomized trials (such as MyPeBS and WISDOM) powered to measure overall down-staging at time of diagnosis, are necessary to demonstrate the (cost-)effectiveness of risk-stratified screening.16,34,35

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**AUTHOR CONTRIBUTIONS**

**Conception and design:** Marjanka K. Schmidt, Josephine M.N. Lopes Cardozo, Laura J. van ’t Veer, Douglas F. Easton, Per Hall **Provision of study materials or patients:** All authors **Collection and assembly of data:** Manjeet Bolla, Renske Keeman, Coralie Poncet, Jean Wang and all authors for individual study data **Data analysis and interpretation:** Josephine M.N. Lopes Cardozo, Marjanka K. Schmidt **Manuscript writing:** Josephine M.N. Lopes Cardozo, Irene L. Andrulis, Stig E. Bojesen, Thilo Dörk, Douglas F. Easton, Diana M. Eccles, Peter A. Fasching, Per Hall, Maartje J. Hooning, Renske Keeman, Heli Nevanlinna, Paul D.P. Pharoah, Emiel J.T. Rutgers, Laura J. van ‘t Veer, Marjanka K. Schmidt  
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**CONFLICT OF INTERESTS DISCLOSURES**

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**DATA SHARING STATEMENT:**

BCAC: Data of the Breast Cancer Association Consortium may be requested for non-profit research through an application procedure with the Breast Cancer Association Consortium.

MINDACT: The MINDACT dataset with patient characteristics and clinical outcomes was made available by the EORTC (https://www.eortc.org/data-sharing/). Following a successful data request procedure, the EORTC can share all or a selection of the clinical-pathological and/or full-transcriptome data for translational research.

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Each study included in this analysis was approved by its institutional ethics review board, and all participants provided written informed consent.

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**Figure 1** Association between PRS313 and clinical-pathological characteristics in BCAC and MINDACT

See Table 2 for exact numeric estimates.  
Univariable (multinomial/binary) logistic regression models with clinical-pathological characteristics as the dependent variable and PRS313 as the independent variable and for BCAC with country as co-variable.  
ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; PRS, polygenic risk score; SD, standard deviation

**Figure 2** Association between PRS313 and overall survival, breast cancer specific survival and distant metastasis free interval in BCAC and MINDACT

See Table 3 for exact numeric estimates.  
Cox regression models, unadjusted analysis was stratified for country in BCAC.  
\*Additionally adjusted for age (continuous), tumor size, lymph node status, grade, ER, PR and HER2 status.  
\*\*Additionally adjusted for age (continuous), tumor size, lymph node status, grade, ER, PR, HER2 status, chemotherapy and endocrine therapy.  
For analysis using BCAC data, follow-up was right censored at 15 years and patients with stage 4 disease were excluded from the analysis.  
BCSS, breast cancer-specific survival; DMFI, distant metastasis-free interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OS, overall survival; PR, progesterone receptor; PRS, polygenic risk score; SD, standard deviation.

**Table 1** Patient, tumor and treatment characteristics of women diagnosed with invasive breast cancer included in BCAC and MINDACT

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic** | | **BCAC - European**  **(N=98,397)**  No. (% including missing)  [% excluding missing] | **MINDACT (N=683)**  No. (%) | **BCAC - Asian**  **(N=12,920)**  No. (% including missing)  [% excluding missing] |
| **Years of diagnosis (median)** | | 1947-2018 (2004) | 2007-2011 | 1967-2016 (2006) |
| **Age (mean, SD)** | | 57.1 ± 12.1 | 54.4 ±9.2 | 50.9 ± 11.1 |
| **Age** | |  |  |  |
|  | <40 | 8,182 (8) | 43 (6) | 1,937 (15) |
|  | >=40-50 | 19,180 (20) | 190 (28) | 4,290 (33) |
|  | >=50-60 | 27,485 (28) | 225 (33) | 3,876 (30) |
|  | >=60 | 43,550 (44) | 225 (33) | 2,817 (22) |
| **Tumor stage** | |  |  |  |
|  | Stage I | 26,302 (27)[45] |  | 3,707 (29)[36] |
|  | Stage II | 25,494 (26)[44] |  | 4,683 (36)[46] |
|  | Stage III | 5,504 (6)[9] |  | 1,578 (12)[15] |
|  | Stage IV | 1,101 (1)[2] |  | 283 (2)[3] |
|  | Missing/ Unknown | 39,669 (41)[0] | 683 (100) | 2,669 (21)[0] |
| **Tumor size** | |  |  |  |
|  | T1 (≤2cm) | 46,123 (47)[64] | 484 (71) | 4,132 (32)[51] |
|  | T2 (2-5 cm) | 22,522 (23)[31] | 194 (28) | 3,328 (26)[41] |
|  | T3 (>5 cm) | 3,261 (3)[5] | 5 (1) | 654 (5)[8] |
|  | Missing/ Unknown | 26,491 (27)[0] |  | 4,806 (37)[0] |
| **Lymph node status** | |  |  |  |
|  | Negative | 49,348 (50)[63] | 521 (76) | 5,751 (44)[60] |
|  | Positive | 29,335 (30)[37] | 162 (24) | 3,827 (30)[40] |
|  | Missing/ Unknown | 19,714 (20)[0] |  | 3,342 (26)[0] |
| **Grade** | |  |  |  |
|  | 1 | 15,778 (16)[20] | 151 (22) | 1,165 (9)[13] |
|  | 2 | 37,654 (38)[48] | 300 (44) | 3,890 (30)[43] |
|  | 3 | 24,666 (25)[32] | 215 (32) | 3,960 (31)[44] |
|  | Missing/ Unknown | 20,299 (21)[0] | 17 (2) | 3,905 (30)[0] |
| **Tumor histology** | |  |  |  |
|  | Ductal | 62,644 (64)[73] | 559 (82) | 8,514 (66)[90] |
|  | Lobular | 12,451 (13)[14] | 85 (12) | 338 (3)[3] |
|  | Mixed (ductolobular) | 4,386 (4)[5] | 30 (4) | 82 (1)[1] |
|  | Other | 6,731 (7)[8] | 9 (1) | 568 (4)[6] |
|  | Unknown | 12,185 (12)[0] |  | 3,418 (26)[0] |
| **ER status** | |  |  |  |
|  | Positive | 67,248 (68)[81] | 579 (85) | 8,326 (65)[69] |
|  | Negative | 15,502 (16)[19] | 104 (15) | 3,792 (29)[31] |
|  | Missing/ Unknown | 15,647 (16)[0] |  | 802 (6)[0] |
| **PR status** | |  |  |  |
|  | Positive | 49,634 (50)[69] | 462 (71) | 7,244 (56)[63] |
|  | Negative | 22,637 (23)[31] | 187 (29) | 4,169 (32)[37] |
|  | Missing/ Unknown | 26,126 (27)[0] |  | 1,507 (12)[0] |
| **HER2 status** | |  |  |  |
|  | Positive | 8,723 (9)[16] | 68 (10) | 3,310 (26)[38] |
|  | Negative | 45,072 (46)[84] | 614 (90) | 5,454 (42)[62] |
|  | Missing/ Unknown | 44,602 (45)[0] |  | 4,156 (32)[0] |
| **70-gene signature** | |  |  |  |
|  | Low risk |  | 403 (59) |  |
|  | High risk |  | 280 (41) |  |
|  | Missing/ Unknown | 98,397 (100) |  | 12,920 (100) |
| **Chemotherapy** | |  |  |  |
|  | No | 29,148 (30)[52] | 367 (54) | 2,673 (21)[25] |
|  | Yes | 26,914 (27)[48] | 315 (46) | 8,089 (63)[75] |
|  | Missing/ Unknown | 42,335 (43)[0] | 1 (0.1) | 2,158 (17)[0] |
| **Endocrine therapy** | |  |  |  |
|  | No | 14,186 (14)[28] | 199 (29) | 2,622 (20)[30] |
|  | Yes | 36,416 (37)[72] | 480 (71) | 6,214 (48)[70] |
|  | Missing/ Unknown | 47,795 (49)[0] |  | 4,085 (32)[0] |
| **Trastuzumab** | |  |  |  |
|  | No | 24,635 (25)[93] | 632 (92) | 3,526 (27)[88] |
|  | Yes | 1,919 (2)[7] | 47 (7) | 503 (4)[12] |
|  | Missing/ Unknown | 71,843 (73)[0] | 4 (1) | 8,891 (69)[0] |
| **PRS313 (mean, range)** | | -0.15 (-4.56 – 4.08) | -0.15 (-3.54 – 2.94) | 0.65 (-3.86 – 4.27) |

ER, Estrogen receptor; HER2, Human epidermal growth factor receptor 2; PR, Progesterone receptor; PRS, polygenic risk score; SD, standard deviation.

**Table 2** Association between PRS313 and clinical-pathological characteristics in BCAC and MINDACT

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | BCAC - European (N=98,397) | | | MINDACT (N=683) | | | BCAC - Asian (N=12,920) | | |
|  |  | **Unadjusted OR per Unit SD of PRS313a** | **95% CI** | ***P*** | **Unadjusted OR per Unit SD of PRS313a** | **95% CI** | ***P*** | **Unadjusted OR per Unit SD of PRS313a** | **95% CI** | ***P*** |
| Age at diagnosis | |  |  |  |  |  |  |  |  |  |
|  | <40 | 1.11 | 1.08-1.14 | <.0001 | 0.90 | 0.65-1.25 | .52 | 1.04 | 0.97-1.11 | .28 |
|  | ≥40-50 | 1.12 | 1.10-1.14 | <.0001 | 1.05 | 0.86-1.27 | .65 | 1.05 | 1.00-1.11 | .06 |
|  | ≥50-60 | 1.07 | 1.05-1.09 | <.0001 | 1.12 | 0.93-1.35 | .24 | 0.99 | 0.94-1.04 | .69 |
|  | ≥60 | Reference |  |  | Reference |  |  | Reference |  |  |
| Tumor stage |  |  |  |  |  |  |  |  |  |  |
|  | Stage I-III | Reference |  |  | - |  |  | Reference |  |  |
|  | Stage IV | 1.01 | 0.96-1.08 | .63 | - |  |  | 1.04 | 0.92-1.19 | .52 |
| Tumor size, cm |  |  |  |  |  |  |  |  |  |  |
|  | ≤2 | Reference |  |  | Reference |  |  | Reference |  |  |
|  | 2-5 | 0.97 | 0.96-0.99 | .002 | 1.01 | 0.86-1.19 | .91 | 0.98 | 0.93-1.03 | .41 |
|  | >5 | 1.02 | 0.98-1.06 | .28 | 1.37 | 0.58-3.27 | .47 | 1.00 | 0.91-1.10 | .96 |
| Lymph node status | |  |  |  |  |  |  |  |  |  |
|  | Negative | Reference |  |  | Reference |  |  | Reference |  |  |
|  | Positive | 1.02 | 1.01-1.04 | .003 | 1.07 | 0.89-1.27 | .48 | 1.01 | 0.96-1.05 | .77 |
| Tumor histology | |  |  |  |  |  |  |  |  |  |
|  | Ductal | Reference |  |  | Reference |  |  | Reference |  |  |
|  | Lobular | 1.06 | 1.04-1.08 | <.0001 | 1.34 | 1.06-1.68 | .013 | 1.05 | 0.94-1.19 | .39 |
|  | Other | 0.97 | 0.95-0.99 | .015 | 1.07 | 0.55-2.07 | .85 | 0.98 | 0.88-1.07 | .62 |
|  | Mixed | 1.08 | 1.05-1.12 | <.0001 | 0.83 | 0.57-1.21 | .33 | 0.99 | 0.78-1.25 | .91 |
|  | Unknown | 1.03 | 1.00-1.05 | .017 |  |  |  | 1.00 | 0.94-1.06 | .89 |
| Grade |  |  |  |  |  |  |  |  |  |  |
|  | 1 | Reference |  |  | Reference |  |  | Reference |  |  |
|  | 2 | 0.98 | 0.96-1.00 | .054 | 1.10 | 0.90-1.33 | .37 | 1.01 | 0.94-1.08 | .84 |
|  | 3 | 0.85 | 0.83-0.86 | <.0001 | 0.80 | 0.65-0.99 | .041 | 0.94 | 0.87-1.01 | .08 |
| ER status |  |  |  |  |  |  |  |  |  |  |
|  | Negative | 0.80 | 0.79-0.82 | <.0001 | 0.80 | 0.65-0.99 | .038 | 0.86 | 0.82-0.89 | <.0001 |
|  | Positive | Reference |  |  | Reference |  |  | Reference |  |  |
| PR status |  |  |  |  |  |  |  |  |  |  |
|  | Negative | 0.85 | 0.83-0.86 | <.0001 | 0.84 | 0.71-1.00 | .047 | 0.89 | 0.86-0.94 | <.0001 |
|  | Positive | Reference |  |  | Reference |  |  | Reference |  |  |
| HER2 status |  |  |  |  |  |  |  |  |  |  |
|  | Negative | Reference |  |  | Reference |  |  | Reference |  |  |
|  | Positive | 0.97 | 0.94-0.99 | .003 | 1.02 | 0.80-1.31 | .87 | 0.99 | 0.95-1.04 | .75 |
| 70-gene signature | |  |  |  |  |  |  |  |  |  |
|  | Low risk | **-** |  |  | Reference |  |  | - |  |  |
|  | High risk | **-** |  |  | 0.86 | 0.74-1.01 | .064 | - |  |  |

aUnivariable (multinomial/binary) logistic regression models with clinical-pathological characteristics as the dependent variable and PRS313 as the independent variable and for BCAC with country as co-variable.  
CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; PR, progesterone receptor; PRS, polygenic risk score; SD, standard deviation

**Table 3** Association between PRS313 and overall survival, breast cancer-specific survival and distant metastasis-free interval in BCAC and MINDACT

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Endpoint | No. of patientsa | No. of eventsa | Unadjusted HR per Unit SD of PRS313b | 95% CI | *P* | Adjusted HR per Unit SD of PRS313c | 95% CI | *P* | Adjusted HR per Unit SD of PRS313d | 95% CI | *P* |
| OS |  |  |  |  |  |  |  |  |  |  |  |
| BCAC - European | 95,955 | 16,582 | 0.96 | 0.94-0.97 | <.0001 | 1.00 | 0.97-1.02 | .88 | 1.01 | 0.98-1.05 | .46 |
| MINDACT | 683 | 61 | 0.91 | 0.71-1.17 | .45 | 0.90 | 0.69-1.17 | .42 | 0.91 | 0.69-1.18 | .91 |
| BCAC - Asian | 12,528 | 1,323 | 0.97 | 0.91-1.02 | .24 | 0.97 | 0.88-1.07 | .53 | 0.96 | 0.87-1.07 | .48 |
| BCSS |  |  |  |  |  |  |  |  |  |  |  |
| BCAC - European | 95,955 | 7,635 | 0.96 | 0.94-0.98 | .001 | 1.00 | 0.96-1.03 | .83 | 1.02 | 0.98-1.07 | .39 |
| MINDACT | 683 | 31 | 1.10 | 0.77-1.56 | .60 | 1.02 | 0.70-1.49 | .93 | 1.01 | 0.69-1.49 | .95 |
| BCAC - Asian | 12,528 | 316 | 1.05 | 0.93-1.19 | .40 | 0.93 | 0.74-1.16 | .50 | 0.93 | 0.75-1.17 | .55 |
| DMFI |  |  |  |  |  |  |  |  |  |  |  |
| BCAC - European | 95,587 | 8,931 | 0.98 | 0.96-1.00 | .050 | 1.00 | 0.97-1.04 | .79 | 1.03 | 0.99-1.07 | .12 |
| MINDACT | 683 | 60 | 1.03 | 0.80-1.33 | .82 | 0.95 | 0.72-1.25 | .72 | 0.94 | 0.72-1.24 | .68 |
| BCAC - Asian | 12,361 | 775 | 1.02 | 0.94-1.10 | .64 | 0.96 | 0.86-1.07 | .44 | 0.98 | 0.87-1.10 | .74 |

a Number of patients (and events) included in the univariable analysis. Cases with missing values were not included in the multivariable analyses.  
b Cox regression models: unadjusted analysis was stratified for country in BCAC.   
c Additionally adjusted for age (continuous), tumor size, lymph node status, grade, ER, PR and HER2 status. d Additionally adjusted for age (continuous), tumor size, lymph node status, grade, ER, PR, HER2 status, chemotherapy and endocrine therapy.  
For analysis using BCAC data, follow-up was right censored at 15 years and patients with stage 4 disease were excluded from the analysis.  
For BCAC – European, the estimates for individual clinical-pathological characteristics from the complete case analyses are provided in the Supplementary Appendix (Supplementary Table S1-3).  
BCSS, breast cancer-specific survival; CI, confidence interval; DMFI, distant metastasis-free interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; PR, progesterone receptor; PRS, polygenic risk score; SD, standard deviation.