Association of Genomic Domains in *BRCA1* and *BRCA2* with Prostate Cancer Risk and Aggressiveness

Vivek Patel[1], Evan L. Busch[2,3], Tara M. Friebel[2,4], Angel Cronin[4], Goska Leslie[5], Lesley McGuffog[5], Julian Adlard[6], Simona Agata[7], Bjarni A. Agnarsson[8,9], Munaza Ahmed[10], Kristiina Aittomäki[11], Elisa Alducci[7], Irene L. Andrulis[12,13], Adalgeir Arason[8,14], Norbert Arnold[15], Grazia Artioli[16], Brita Arver[17], Bernd Auber[18],Jacopo Azzollini[19], Judith Balmaña[20], Rosa B. Barkardottir[8,14], Daniel R. Barnes[5], Alicia Barroso[21], Daniel Barrowdale[5], Muriel Belotti[22], Javier Benitez[23,24], Birgitte Bertelsen[25], Marinus J. Blok[26], Istvan Bodrogi[27], Valérie Bonadona[28], Bernardo Bonanni[29], Davide Bondavalli[29], Susan Boonen[30], Julika Borde[31-33], Ake Borg[34], Angela R. Bradbury[35], Angela Brady[36], Carole Brewer[37], Joan Brunet[38],Bruno Buecher[22], Saundra S. Buys[39], Santiago Cabezas[40], Trinidad Caldés[41], Almuth Caliebe[42], Maria A. Caligo[43], Mariarosaria Calvello[29], Ian Campbell[44,45], Ileana Carnevali[46], Estela Carrasco[20], Tsun L. Chan[47,48], Annie TW Chu[47], Wendy K. Chung[49], Kathleen B.M. Claes[50], GEMO Study Collaborators[22], EMBRACE Collaborators[5], Jackie Cook[51], Laura Cortesi[52], Fergus J. Couch[53], Mary B. Daly[54], Giuseppe Damante[55],Esther Darder[38], Rosemarie Davidson[56], Miguel de la Hoya[41], Lara Della Puppa[57], Joe Dennis[5], Orland Diez[58], Yuan Chun Ding[59], Nina Ditsch[60], Susan M. Domchek[35], Alan Donaldson[61], Bernd Dworniczak[62], Douglas F. Easton[5,63], Diana M. Eccles[64], Ros Eeles[65], Hans Ehrencrona[66], Bent Ejlertsen[67], Christoph Engel[68,69], D. Gareth Evans[70,71], Laurence Faivre[72], Ulrike Faust[73], Lidia Feliubadalo[74], Lenka Foretova[75], Florentia Fostira[76], George Fountzilas[77], Debra Frost[5] Vanesa Garcia-Barberan[41], Pilar Garre[41], Marion Gauthier-Villars[22], Lajos Geczy[27], Andrea Gehrig[78], Anne-Marie Gerdes[79], Paul Gesta[80], Giuseppe Giannini[81], Gord Glendon[12], Andrew K. Godwin[82], David E. Goldgar[83], Mark H. Greene[84], Angelica Gutierrez-Barrera[85], Eric Hahnen[32,33], Ute Hamann[86], Jan Hauke[31-33], Natalie Herold[31-33], Frans B.L. Hogervorst[87], Ellen Honisch[88], John L. Hopper[89], Peter J. Hulick[90,91], KConFab Investigators[44,45], HEBON

Investigators[92], Louise Izatt[93], Agnes Jager[94], Paul James[45,95], Ramunas Janavicius[96], Uffe Birk Jensen[97], Thomas Dyrso Jensen[98], Oskar Th. Johannsson[99], Esther M. John[100], Vijai Joseph[101], Eunyoung Kang[102], Karin Kast[103], Johanna I. Kiiski[104], Sung-Won Kim[105], Zisun Kim[106], Kwangpil Ko[107], Irene Konstantopoulou[76], Gero Kramer[108], Lotte Krogh[109], Torben A. Kruse[109], Ava Kwong[47,110,111], Mirjam Larsen[31-33], Christine Lasset[28], Charlotte Lautrup[112], Conxi Lazaro[74], Jihyoun Lee[113], Jong Won Lee[114], Min Hyuk Lee[113], Johannes Lemke[115], Fabienne Lesueur[22,116-118,] Annelie Liljegren[17], Annika Lindblom[119,120], Patricia Llovet[41], Adria Lopez-Fernández[20], Irene Lopez-Perolio[41], Victor Lorca[41], Jennifer T. Loud[84], Edmond S.K. Ma[47,48], Phuong L. Mai[121], Siranoush Manoukian[19], Véronique Mari[122], Lynn Martin[123], Laura Matricardi[7], Noura Mebirouk[22,116-118], Veronica Medici[52], Hanne E.J. Meijers-Heijboer[124], Alfons Meindl[60], Arjen R. Mensenkamp[125], Clare Miller[126], Denise Molina Gomes[127], Marco Montagna[7], Thea M. Mooij[128], Lidia Moserle[7], Emmanuelle Mouret-Fourme[22], Anna Marie Mulligan[129,130], Katherine L. Nathanson[35], Marie Navratilova[75], Heli Nevanlinna[104], Dieter Niederacher[88], Finn C. Nielsen[25], Liene Nikitina-Zake[131], Kenneth Offit[101,132], Edith Olah[133], Olufunmilayo I. Olopade[134], Kai-ren Ong[135], Ana Osorio[23,24], Claus-Eric Ott[136], Domenico Palli[137], Sue K. Park[138-140], Michael T. Parsons[141], Inge Sokilde Pedersen[142], Bernard Peissel[19], Ana Peixoto[143], Pedro Perez-Segura[40], Paolo Peterlongo[144], Annabeth H. Petersen[98], Mary E. Porteous[145], Miquel Angel Pujana[146], Paolo Radice[147], Juliane Ramser[148], Johanna Rantala[149], Muhammad U. Rashid[86,150], Kerstin Rhiem[31-33], Piera Rizzolo[81], Mark Robson[132], Matti A. Rookus[128], Caroline Maria Rossing[25], Kathryn J. Ruddy[151], Catarina Santos[143], Claire Saule[22], Rosa Scarpitta[152], Rita K. Schmutzler[32,33], Helene Schuster[153], Leigha Senter[154], Caroline MD Seynaeve[94], Payal D. Shah[35],' Priyanka Sharma[155], VY Shin[110], Valentina Silvestri[81], Jacques Simard[156], Christian F. Singer[157], Anne-Bine Skytte[97], Katie Snape[158], Angela R. Solano[159], Penny Soucy[156], Melissa C. Southey[160,161], Amanda B. Spurdle[141], Linda Steele[59], Doris Steinemann[162], Dominique Stoppa-Lyonnet[22,163,164], Agostina Stradella[165], Lone Sunde[97], Christian Sutter[166], Yen Yen Tan[167], Manuel R. Teixeira[143,168], Soo H. Teo[169,170], Mads Thomassen[109], Maria Grazia Tibiletti[46], Marc Tischkowitz[171,172], Silvia Tognazzo[7],

Amanda E. Toland[173], Stefania Tommasi[174], Diana Torres[86,175], Angela Toss[52], Alison H. Trainer[95], Nadine Tung[176], Christi J. van Asperen[177], Frederieke H. van der Baan[128], Lizet E. van der Kolk[87], Rob B. van der Luijt[178], Liselotte P van Hest[179], Liliana Varesco[180], Raymonda Varon-Mateeva[136], Alessandra Viel[57], Jeroen Vierstrate[50], Roberta Villa[19], Anna von Wachenfeldt[17], Philipp Wagner[181], Shan Wang-Gohrke[182], Barbara Wappenschmidt[32,33], Jeffrey N. Weitzel[183], Greet Wieme[50], Siddhartha Yadav[151], Drakoulis Yannoukakos[76], Sook-Yee Yoon[184], Cristina Zanzottera[19], Kristin K. Zorn[121], Anthony D'Amico[1], Matthew Freedman[4], Mark Pomerantz[4], Georgia Chenevix-Trench[141], Antonis C. Antoniou[5], Susan L. Neuhausen[59], Laura Ottini[81], Henriette Roed Nielsen[109], Timothy R. Rebbeck[2,4]*

1. Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital.
2. Harvard T.H. Chan School of Public Health. 02115, USA: Boston, MA.
3. Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School. 02115, USA: Boston, MA.
4. Dana-Farber Cancer Institute. 02215, USA: Boston, MA.
5. Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge. CB1 8RN, UK: Cambridge.
6. Yorkshire Regional Genetics Service, in Chapel Allerton Hospital. LS7 4SA, UK: Leeds.
7. Immunology and Molecular Oncology Unit, in Veneto Institute of Oncology IOV - IRCCS. 35128, Italy: Padua.
8. Department of Pathology, in Landspitali University Hospital. 101, Iceland: Reykjavik.
9. School of Medicine, in University of Iceland. 101, Iceland: Reykjavik.
10. North East Thames Regional Genetics Service, in Great Ormond Street Hospital for Children NHS Trust. WC1N 3JH, UK: London.

11. Department of Clinical Genetics, Helsinki University Hospital, University of Helsinki. 00290, Finland: Helsinki.
12. Fred A. Litwin Center for Cancer Genetics, Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital. M5G 1X5, Canada: Toronto, ON.
13. Department of Molecular Genetics, in University of Toronto. M5S 1A8, Canada: Toronto, ON.
14. BMC (Biomedical Centre), Faculty of Medicine, University of Iceland. 101, Iceland: Reykjavik.
15. Department of Gynaecology and Obstetrics, University Hospital of Schleswig-Holstein, Campus Kiel, Christian-Albrechts University Kiel. 24118, Germany: Kiel.
16. ULSS 3 Serenissima, in U.O.C. Oncologia ed Ematologia Oncologica. 30035, Italy: Mirano (VE).
17. Department of Oncology, in Karolinska Institutet. 171 76, Sweden: Stockholm.
18. Institute of Human Genetics, in Hannover Medical School. 30625, Germany: Hannover.
19. Unit of Medical Genetics, Department of Medical Oncology and Hematology,Fondazione IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico) Istituto Nazionale dei Tumori di Milano. 20133, Italy: Milan.
20. High Risk and Cancer Prevention Group, Vall d'Hebron Institute of Oncology, University Hospital Vall d'Hebron. 08035, Spain: Barcelona.
21. Human Genetics Group, in Spanish National Cancer Research Centre (CNIO). 28029, Spain: Madrid.
22. Service de Génétique, in Institut Curie. 75005, France: Paris.
23. Human Cancer Genetics Programme, in Spanish National Cancer Research Centre (CNIO). 28029, Spain: Madrid.
24. Biomedical Network on Rare Diseases (CIBERER). 28029, Spain: Madrid.

25. Center for Genomic Medicine, Rigshospitalet, Copenhagen University Hospital. DK-2100, Denmark: Copenhagen.
26. Department of Clinical Genetics, in Maastricht University Medical Center. 6229 HX, The Netherlands: Maastricht.
27. Department of Chemotherapy, in National Institute of Oncology. H-1525, Hungary: Budapest.
28. Unité de Prévention et d'Epidémiologie Génétique, in Centre Léon Bérard. 69373, France: Lyon.
29. Division of Cancer Prevention and Genetics, in "IEO, European Institute of Oncology IRCCS". 20141, Italy: Milan.
30. Department of Clinical Genetics, in Zealand University Hospital. Denmark: Roskilde.
31. Center for Integrated Oncology (CIO), in University Hospital of Cologne. 50937, Germany: Cologne.
32. Center for Molecular Medicine Cologne (CMMC), in University of Cologne. 50931, Germany: Cologne.
33. Center for Hereditary Breast and Ovarian Cancer, in University Hospital of Cologne. 50937, Germany: Cologne.
34. Department of Oncology, in Lund University and Skåne University Hospital. 222 41, Sweden: Lund.
35. "Department of Medicine, Abramson Cancer Center,Perelman School of Medicine at the University of Pennsylvania. 19104, USA: Philadelphia, PA.
36. North West Thames Regional Genetics Service, Kennedy Galton Centre, The North West London Hospitals NHS Trust. HA1 3UJ, UK: Middlesex.
37. Department of Clinical Genetics, in Royal Devon & Exeter Hospital. EX2 5DW, UK: Exeter.

38. Genetic Counseling Unit, Hereditary Cancer Program, IDIBGI (Institut d'Investigació Biomèdica de Girona), Catalan Institute of Oncology, CIBERONC. 17007, Spain: Girona.
39. Department of Medicine, in Huntsman Cancer Institute. 84112, USA: Salt Lake City, UT.
40. Department of Oncology, Hospital Clinico San Carlos, IdISSC. 28040, Spain: Madrid.
41. "Medical Oncology Department, Hospital Clínico San Carlos", in "Instituto de Investigación Sanitaria San Carlos (IdISSC), Centro Investigación Biomédica en Red de Cáncer (CIBERONC)". 28040, Spain: Madrid.
42. Institute of Human Genetics, University Hospital of Schleswig-Holstein, Campus Kiel, Christian-Albrechts University Kiel. 24118, Germany: Kiel.
43. Section of Molecular Genetics, Dept. of Laboratory Medicine, in University Hospital of Pisa. Italy: Pisa.
44. Peter MacCallum Cancer Center. 3000, Australia: Melbourne, Victoria.
45. Sir Peter MacCallum Department of Oncology, The University of Melbourne. 3000, Australia: Melbourne, Victoria.
46. UO Anatomia Patologica, in Ospedale di Circolo-Università dell'Insubria. 21100, Italy: Varese.
47. Hong Kong Hereditary Breast Cancer Family Registry, in Cancer Genetics Centre. Hong Kong: Happy Valley.
48. Department of Pathology, in Hong Kong Sanatorium and Hospital. Hong Kong: Happy Valley.
49. Departments of Pediatrics and Medicine, in Columbia University. 10032, USA: "New York, NY".
50. Centre for Medical Genetics, in Ghent University. 9000, Belgium: Gent.
51. Sheffield Clinical Genetics Service, in Sheffield Children’s Hospital. S10 2TH, UK: Sheffield.

52. Department of Oncology and Haematology, in University of Modena and Reggio Emilia. 41121, Italy: Modena.
53. Department of Laboratory Medicine and Pathology, in Mayo Clinic. 55905, USA: Rochester, MN".
54. Department of Clinical Genetics, in Fox Chase Cancer Center. 19111, USA: Philadelphia, PA.
55. Department of Medical and Biological Sciences, in University of Udine. 33100, Italy: Udine.
56. Department of Clinical Genetics, in South Glasgow University Hospitals. G51 4TF, UK: Glasgow.
57. Division of Functional onco-genomics and genetics, in Centro di Riferimento Oncologico di Aviano (CRO), IRCCS. 33081, Italy: Aviano.
58. Oncogenetics Group, Clinical and Molecular Genetics Area, in Vall d'Hebron Institute of Oncology (VHIO), University Hospital, Vall d'Hebron. 08035, Spain: Barcelona.
59. Department of Population Sciences, in Beckman Research Institute of City of Hope. 91010, USA: Duarte, CA.
60. Department of Gynecology and Obstetrics, in Ludwig Maximilian University of Munich. 80336, Germany: Munich.
61. Clinical Genetics Department, in St Michael's Hospital. BS2 8EG, UK: Bristol.
62. Institute of Human Genetics, in University of Münster. 48149, Germany: Münster.
63. Centre for Cancer Genetic Epidemiology, Department of Oncolog, in University of Cambridge. CB1 8RN, UK: Cambridge.
64. Cancer Sciences Academic Unit, Faculty of Medicine, in University of Southampton. SO17 1BJ, UK: Southampton.
65. Oncogenetics Team, in The Institute of Cancer Research and Royal Marsden NHS Foundation Trust. SM2 5NG, UK: Sutton.

66. Department of Clinical Genetics, in Lund University Hospital. 222 42, Sweden: Lund.

67. Department of Oncology, in "Rigshospitalet, Copenhagen University Hospital". DK-2100, Denmark: Copenhagen.

68. Institute for Medical Informatics, Statistics and Epidemiology, in University of Leipzig. 04107, Germany: Leipzig.

69. LIFE - Leipzig Research Centre for Civilization Diseases, in University of Leipzig. 04103, Germany: Leipzig.

70. Division of Evolution and Genomic Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, in University of Manchester, Manchester Academic Health Science Centre. M13 9WL, UK: Manchester.

71. Manchester Centre for Genomic Medicine, in "St Mary’s Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre. M13 9WL, UK: Manchester.

72. Unité d'oncogénétique, Centre de Lutte Contre le Cancer, in Centre Georges-François Leclerc. 21000, France: Dijon.

73. Institute of Medical Genetics and Applied Genomics, in University of Tübingen. 72074, Germany: Tübingen.

74. Molecular Diagnostic Unit, Hereditary Cancer Program, in "IDIBELL (Bellvitge Biomedical Research Institute),Catalan Institute of Oncology, CIBERONC. 08908, Spain: Barcelona.

75. Department of Cancer Epidemiology and Genetics, in Masaryk Memorial Cancer Institute. 65653, Czech Republic: Brno.

76. Molecular Diagnostics Laboratory, INRASTES", in National Centre for Scientific Research 'Demokritos'. 15310, Greece: Athens.

77. Second Department of Medical Oncology, EUROMEDICA General Clinic of Thessaloniki", in Aristotle University of Thessaloniki School of Medicine. 54124, Greece: Thessalon?ki.

78. Centre of Familial Breast and Ovarian Cancer, Department of Medical Genetics, Institute of Human Genetics", in University Würzburg. 97070, Germany: Würzburg.

79. Department of Clinical Genetics, in Rigshospitalet. DK-2100, Denmark: Copenhagen.

80. Service Régional Oncogénétique Poitou-Charentes, in CH Niort. 79021, France: Niort.

81. Department of Molecular Medicine, in University La Sapienza. 00161, Italy: Rome.

82. Department of Pathology and Laboratory Medicine, in Kansas University Medical Center. 66160, USA: Kansas City, KS.

83. Department of Dermatology, in Huntsman Cancer Institute, University of Utah School of Medicine. 84112, USA: "Salt Lake City, UT".

84. Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, in National Cancer Institute. 20850-9772, USA: "Bethesda, MD".

85. Department of Breast Medical Oncology and Clinical Genetics Program, in University of Texas MD Anderson Cancer Center. 77030, USA: Houston, TX.

86. Molecular Genetics of Breast Cancer, in German Cancer Research Center (DKFZ). 69120, Germany: Heidelberg.

87. Family Cancer Clinic, in The Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital. 1066 CX, The Netherlands: Amsterdam.

88. Department of Gynecology and Obstetrics, in "University Hospital Düsseldorf, Heinrich-Heine University Düsseldorf". 40225, Germany: Düsseldorf.

89. Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, in The University of Melbourne. 3010, Australia: Melbourne, Victoria.

90. Center for Medical Genetics, in NorthShore University HealthSystem. 60201, USA: Evanston, IL.

91. The University of Chicago Pritzker School of Medicine. 60637, USA: Chicago, IL.
92. The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON), in Coordinating center: The Netherlands Cancer Institute. 1066 CX, The Netherlands: Amsterdam.
93. Clinical Genetics, in Guy's and St Thomas' NHS Foundation Trust. SE1 9RT, UK: London.
94. Department of Medical Oncology, Family Cancer Clinic, in Erasmus MC Cancer Institute. 3015 CN, The Netherlands: Rotterdam.
95. Parkville Familial Cancer Centre, in Peter MacCallum Cancer Center. 3000, Australia: Melbourne, Victoria.
96. Hematology, oncology and transfusion medicine center, Dept. of Molecular and Regenerative Medicine, in Vilnius University Hospital Santariskiu Clinics. Lithuania: Vilnius.
97. Department of Clinical Genetics, in Aarhus University Hospital. 8200, Denmark: Aarhus N.
98. Department of Clinical Genetics, in Vejle Hospital. 7100, Denmark: Vejle.
99. Department of Oncology, in Landspitali University Hospital. 101, Iceland: Reykjavik.
100. Department of Medicine, Division of Oncology, in Stanford Cancer Institute, Stanford University School of Medicine. 94304, USA: Stanford, CA.
101. Clinical Genetics Research Lab, Department of Cancer Biology and Genetics, in Memorial Sloan-Kettering Cancer Center. 10065, USA: New York, NY.
102. Department of Surgery, in Seoul National University Bundang Hospital. 13260, Korea: Seongnam.
103. Department of Gynecology and Obstetrics, in Technical University of Dresden. 01307, Germany: Dresden.

104. Department of Obstetrics and Gynecology, Helsinki University Hospital, in University of Helsinki. 00290, Finland: Helsinki.
105. Department of Surgery, in Daerim Saint Mary's Hospital. 07442, Korea: Seoul.
106. Department of Surgery, in Soonchunhyang University Hospital Bucheon Hospital. 14584, Korea: Bucheon.
107. Department of Preventive Medicine, in Gacheon University College of Medicine. 21565, Republic of Korea: Incheon.
108. Department of Urology, in Medical University of Vienna. 1090, Austria: Vienna.
109. Department of Clinical Genetics, in Odense University Hospital. 5000, Denmark: Odence C.
110. Department of Surgery, in The University of Hong Kong. Hong Kong: Pok Fu Lam.
111. Department of Surgery, in Hong Kong Sanatorium and Hospital. Hong Kong: Happy Valley.
112. Department of Clinical Genetics, in Aalborg University Hospital. 9100, Denmark: Aalborg.
113. Department of Surgery, in Soonchunhyang University College of Medicine and Soonchunhyang University Hospital. 04401, Korea: Seoul.
114. Department of Surgery, in Ulsan University College of Medicine and Asan Medical Center. 05505, Korea: Seoul.
115. Institute of Human Genetics, in University Hospital Leipzig. 04103, Germany: Leipzig.
116. Genetic Epidemiology of Cancer team, in Inserm U900. 75005, France: Paris.
117. Institut Curie. 75005, France: Paris.
118. Mines ParisTech. 77305, France: Fontainebleau.
119. Department of Molecular Medicine and Surgery, in Karolinska Institutet. 171 76, Sweden: Stockholm.

120. Department of Clinical Genetics, in Karolinska University Hospital. 171 76, Sweden: Stockholm.
121. Magee-Womens Hospital, University of Pittsburgh School of Medicine. 15213, USA: Pittsburgh, PA.
122. Département d'Hématologie-Oncologie Médicale, in Centre Antoine Lacassagne. 06100, France: Nice.
123. Institute of Cancer and Genomic Sciences, in University of Birmingham. B15 2TT, UK: Birmingham.
124. Department of Clinical Genetics, in VU University Medical Center. 1105 AZ, The Netherlands: Amsterdam.
125. Department of Human Genetics, in Radboud University Medical Center. 6525 GA, The Netherlands: Nijmegen.
126. Department of Clinical Genetics, in Alder Hey Hospital. L12 2AP, UK: Liverpool.
127. Service de Biologie de la reproduction, Cytogénétique et Génétique Médicale, in CHI Poissy - Saint Germain. 78303, France: Poissy.
128. Department of Epidemiology, in The Netherlands Cancer Institute. 1066 CX, The Netherlands: Amsterdam.
129. Department of Laboratory Medicine and Pathobiology, in University of Toronto. M5S 1A8, Canada: "Toronto, ON".
130. Laboratory Medicine Program, in University Health Network. M5G 2C4, Canada: Toronto, ON.
131. Latvian Biomedical Research and Study Centre. Latvia: Riga.
132. Clinical Genetics Service, Department of Medicine, in Memorial Sloan-Kettering Cancer Center. 10065, USA: New York, N".
133. Department of Molecular Genetics, in National Institute of Oncology. 1122, Hungary: Budapest.

134. Center for Clinical Cancer Genetics, in The University of Chicago. 60637, USA: Chicago, IL.

135. West Midlands Regional Genetics Service, in Birmingham Women's Hospital Healthcare NHS Trust. B15 2TG, UK: Birmingham.

136. Institute of Human Genetics, in "Campus Virchov Klinikum, Charite". 13353, Germany: Berlin.

137. Cancer Risk Factors and Life-Style Epidemiology Unit, in Institute for Cancer Research, Prevention and Clinical Network (ISPRO). Italy: Florence.

138. Department of Preventive Medicine, in Seoul National University College of Medicine. 03080, Korea: Seoul.

139. Department of Biomedical Sciences, in Seoul National University Graduate School. 03080, Korea: Seoul.

140. Cancer Research Institute, in Seoul National University. 03080, Korea: Seoul.

141. Department of Genetics and Computational Biology, in QIMR Berghofer Medical Research Institute. 4006, Australia: "Brisbane, Queensland".

142. Section of Molecular Diagnostics, Clinical Biochemistry, in Aalborg University Hospital. 9000, Denmark: Aalborg.

143. Department of Genetics, in Portuguese Oncology Institute. 4220-072, Portugal: Porto.

144. Genome Diagnostics Program, in IFOM - the FIRC (Italian Foundation for Cancer Research) Institute of Molecular Oncology. 20139, Italy: Milan.

145. South East of Scotland Regional Genetics Service, in Western General Hospital. EH4 2XU, UK: Edinburgh.

146. Translational Research Laboratory, in "IDIBELL (Bellvitge Biomedical Research Institute),Catalan Institute of Oncology, CIBERONC". 08908, Spain: Barcelona.

147. Unit of Molecular Bases of Genetic Risk and Genetic Testing, Department of Research, in Fondazione IRCCS (Istituto Di Ricovero e Cura a Carattere Scientifico) Istituto Nazionale dei Tumori (INT). 20133, Italy: Milan.
148. Division of Gynaecology and Obstetrics, in Klinikum rechts der Isar der Technischen Universität München. 80333, Germany: Munich.
149. Clinical Genetics, in Karolinska Institutet. 171 76, Sweden: Stockholm.
150. Department of Basic Sciences, in Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH & RC). 54000, Pakistan: Lahore.
151. Department of Oncology, in Mayo Clinic. 55905, USA: "Rochester, MN".
152. Section of Genetic Oncology, Dept. of Laboratory Medicine, in University and University Hospital of Pisa. 56126, Italy: Pisa.
153. Oncogénétique - Prévention - Dépistage, in Centre Paul Strauss. 67065, France: Strasbourg.
154. Clinical Cancer Genetics Program, Division of Human Genetics, Department of Internal Medicine, The Comprehensive Cancer Center, in The Ohio State University. 43210, USA: Columbus, OH.
155. Department of Internal Medicine, Division of Oncology, in University of Kansas Medical Center. 66205, USA: Westwood, KS.
156. Genomics Center, in Centre Hospitalier Universitaire de Québec – Université Laval, Research Cente". G1V 4G2, Canada: Québec City, QC.
157. Dept of OB/GYN and Comprehensive Cancer Center, in Medical University of Vienna. 1090, Austria: Vienna.
158. Medical Genetics Unit, in "St George's, University of London". SW17 0RE, UK: London.
159. INBIOMED, Faculty of Medicine/ CONICET and CEMIC, Department of Clinical Chemistry, Medical Direction, in University of Buenos Aires. C1121ABG, Argentina: Buenos Aires.

160. Precision Medicine, School of Clinical Sciences at Monash Health, in Monash University. 3168, Australia: Clayton, Victoria.
161. Department of Clinical Pathology, in The University of Melbourne. 3010, Australia: Melbourne, Victoria.
162. Institute of Cell and Molecular Pathology, in Hannover Medical School. 30625, Germany: Hannover.
163. Department of Tumour Biology, in INSERM U830. 75005, France: Paris.
164. Université Paris Descartes. 75006, France: Paris.
165. Genetic Counseling Unit, Hereditary Cancer Program, in IDIBELL (Bellvitge Biomedical Research Institute),Catalan Institute of Oncology, CIBERONC. 08908, Spain: Barcelona.
166. Institute of Human Genetics, in University Hospital Heidelberg. 69120, Germany: Heidelberg.
167. Dept of OB/GYN, in Medical University of Vienna. 1090, Austria: Vienna.
168. Biomedical Sciences Institute (ICBAS), in University of Porto. 4050-013, Portugal: Porto.
169. Cancer Research Malaysia. 47500, Malaysia: Subang Jaya, Selangor.
170. Breast Cancer Research Unit, Cancer Research Institute, in University Malaya Medical Centre. 59100, Malaysia: Kuala Lumpur.
171. Program in Cancer Genetics, Departments of Human Genetics and Oncology, in McGill University. H4A 3J1, Canada: Montréal, QC.
172. Department of Medical Genetics, in University of Cambridge. CB2 0QQ, UK: Cambridge.
173. Department of Cancer Biology and Genetics, in The Ohio State University. 43210, USA: Columbus, OH.
174. Istituto Nazionale Tumori 'Giovanni Paolo II'. 70124, Italy: Bari.
175. Institute of Human Genetics, in Pontificia Universidad Javeriana. Colombia: Bogota.
176. Department of Medical Oncology, in Beth Israel Deaconess Medical Center. 02215, USA: Boston, MA.

177. Department of Clinical Genetics, in Leiden University Medical Center. 2333 ZA, The Netherlands: Leiden.
178. Department of Medical Genetics, in University Medical Center. 3594 CX, The Netherlands: Utrecht.
179. Clinical Genetics, in Amsterdam UMC, Vrije Universiteit Amsterdam. 1007 MB, The Netherlands: Amsterdam.
180. Unit of Hereditary Cancer, Department of Epidemiology, Prevention and Special Functions, in IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico) AOU San Martino - IST Istituto Nazionale per la Ricerca sul Cancro. 16132, Italy: Genoa.
181. Department of Women's Health, in Tubingen University Hospital. 72076, Germany: Tubingen.
182. Department of Gynaecology and Obstetrics, in University Hospital Ulm. 89075, Germany: Ulm.
183. Clinical Cancer Genetics, in City of Hope. 91010, USA: Duarte, CA.
184. Cancer Research Initiatives Foundation, in Sime Darby Medical Centre. 47500, Malaysia: Subang Jaya, Selangor.

*Address for Correspondence:

Timothy R. Rebbeck, PhD

Dana Farber Cancer Institute, 1101 Dana Building, 450 Brookline Ave

Boston, MA 02215

Tel: 617-632-6128

Email: Timothy_Rebbeck@dfci.harvard.edu

Running title: *BRCA2* Prostate Cancer Cluster Region

Key words: *BRCA1*, *BRCA2*, Prostate Cancer, Pathogenic sequence variant location, Risk estimation

Financial support and conflict of interest statements are included at the end of the manuscript.

Word Count: 3,094

Author Contributions:

All authors assisted in the writing and editing of the manuscript.

All authors read and approved the submitted version of the manuscript.

All authors have agreed to be personally accountable for the author's own contribution and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the authors was not personally involved, are appropriately investigated, resolved and the resolution documented in the literature.

Vivek Patel[1], Evan Busch[2,3], Tara M. Friebel[2,4], Angel Cronin[4], Antonis C. Antoniou[5], and Timothy Rebbeck were primarily responsible for the statistical analyses.

Tara M. Friebel[2,4], Antonis C. Antoniou[5], Goska Leslie[5] and Lesley McGuffog[5] were primarily responsible for managing and cleaning the research database.

Julian Adlard[6], Simona Agata[7], Bjarni A. Agnarsson[8,9], Munaza Ahmed[10], Kristiina Aittomäki[11], Elisa Alducci[7], Irene L. Andrulis[12,13], Adalgeir Arason[8,14], Norbert Arnold[15], Grazia Artioli[16], Brita Arver[17], Bernd Auber[18],Jacopo Azzollini[19], Judith Balmaña[20], Rosa B. Barkardottir[8,14], Daniel R. Barnes[5], Alicia Barroso[21], Daniel Barrowdale[5], Muriel Belotti[22], Javier Benitez[23,24], Birgitte Bertelsen[25], Marinus J. Blok[26], Istvan Bodrogi[27], Valérie Bonadona[28], Bernardo Bonanni[29], Davide Bondavalli[29], Susan Boonen[30], Julika Borde[31-33], Ake Borg[34], Angela R. Bradbury[35], Angela Brady[36], Carole Brewer[37], Joan Brunet[38],Bruno Buecher[22], Saundra S. Buys[39], Santiago Cabezas[40], Trinidad Caldés[41], Almuth Caliebe[42], Maria A. Caligo[43], Mariarosaria Calvello[29], Ian Campbell[44,45], Ileana Carnevali[46], Estela Carrasco[20], Tsun L. Chan[47,48], Annie TW Chu[47], Wendy K. Chung[49], Kathleen B.M. Claes[50], GEMO Study Collaborators[22], EMBRACE Collaborators[5],

Jackie Cook[51], Laura Cortesi[52], Fergus J. Couch[53], Mary B. Daly[54], Giuseppe Damante[55],Esther Darder[38], Rosemarie Davidson[56], Miguel de la Hoya[41], Lara Della Puppa[57], Joe Dennis[5], Orland Diez[58], Yuan Chun Ding[59], Nina Ditsch[60], Susan M. Domchek[35], Alan Donaldson[61], Bernd Dworniczak[62], Douglas F. Easton[5,63], Diana M. Eccles[64], Ros Eeles[65], Hans Ehrencrona[66], Bent Ejlertsen[67], Christoph Engel[68,69], D. Gareth Evans[70,71], Laurence Faivre[72], Ulrike Faust[73], Lidia Feliubadalo[74], Lenka Foretova[75], Florentia Fostira[76], George Fountzilas[77], Debra Frost[5] Vanesa Garcia-Barberan[41], Pilar Garre[41], Marion Gauthier-Villars[22], Lajos Geczy[27], Andrea Gehrig[78], Anne-Marie Gerdes[79], Paul Gesta[80], Giuseppe Giannini[81], Gord Glendon[12], Andrew K. Godwin[82], David E. Goldgar[83], Mark H. Greene[84], Angelica Gutierrez-Barrera[85], Eric Hahnen[32,33], Ute Hamann[86], Jan Hauke[31-33], Natalie Herold[31-33], Frans B.L. Hogervorst[87], Ellen Honisch[88], John L. Hopper[89], Peter J. Hulick[90,91], KConFab Investigators[44,45], HEBON Investigators[92], Louise Izatt[93], Agnes Jager[94], Paul James[45,95], Ramunas Janavicius[96], Uffe Birk Jensen[97], Thomas Dyrso Jensen[98], Oskar Th. Johannsson[99], Esther M. John[100], Vijai Joseph[101], Eunyoung Kang[102], Karin Kast[103], Johanna I. Kiiski[104], Sung-Won Kim[105], Zisun Kim[106], Kwangpil Ko[107], Irene Konstantopoulou[76], Gero Kramer[108], Lotte Krogh[109], Torben A. Kruse[109], Ava Kwong[47,110,111], Mirjam Larsen[31-33], Christine Lasset[28], Charlotte Lautrup[112], Conxi Lazaro[74], Jihyoun Lee[113], Jong Won Lee[114], Min Hyuk Lee[113], Johannes Lemke[115], Fabienne Lesueur[22,116-118,] Annelie Liljegren[17], Annika Lindblom[119,120], Patricia Llovet[41], Adria Lopez-Fernández[20], Irene Lopez-Perolio[41], Victor Lorca[41], Jennifer T. Loud[84], Edmond S.K. Ma[47,48], Phuong L. Mai[121], Siranoush Manoukian[19], Véronique Mari[122], Lynn Martin[123], Laura Matricardi[7], Noura Mebirouk[22,116-118], Veronica Medici[52], Hanne E.J. Meijers-Heijboer[124], Alfons Meindl[60], Arjen R. Mensenkamp[125], Clare Miller[126], Denise Molina Gomes[127], Marco Montagna[7], Thea M. Mooij[128], Lidia Moserle[7], Emmanuelle Mouret-Fourme[22], Anna Marie Mulligan[129,130], Katherine L. Nathanson[35], Marie Navratilova[75], Heli Nevanlinna[104], Dieter Niederacher[88], Finn C. Nielsen[25], Liene Nikitina-Zake[131], Kenneth Offit[101,132], Edith Olah[133], Olufunmilayo I. Olopade[134], Kai-ren Ong[135], Ana Osorio[23,24], Claus-Eric Ott[136], Domenico Palli[137], Sue K. Park[138-140], Michael T. Parsons[141], Inge Sokilde Pedersen[142], Bernard

Peissel[19], Ana Peixoto[143], Pedro Perez-Segura[40], Paolo Peterlongo[144], Annabeth H. Petersen[98], Mary E. Porteous[145], Miquel Angel Pujana[146], Paolo Radice[147], Juliane Ramser[148], Johanna Rantala[149], Muhammad U. Rashid[86,150], Kerstin Rhiem[31-33], Piera Rizzolo[81], Mark Robson[132], Matti A. Rookus[128], Caroline Maria Rossing[25], Kathryn J. Ruddy[151], Catarina Santos[143], Claire Saule[22], Rosa Scarpitta[152], Rita K. Schmutzler[32,33], Helene Schuster[153], Leigha Senter[154], Caroline MD Seynaeve[94], Payal D. Shah[35],' Priyanka Sharma[155], VY Shin[110], Valentina Silvestri[81], Jacques Simard[156], Christian F. Singer[157], Anne-Bine Skytte[97], Katie Snape[158], Angela R. Solano[159], Penny Soucy[156], Melissa C. Southey[160,161], Amanda B. Spurdle[141], Linda Steele[59], Doris Steinemann[162], Dominique Stoppa-Lyonnet[22,163,164], Agostina Stradella[165], Lone Sunde[97], Christian Sutter[166], Yen Yen Tan[167], Manuel R. Teixeira[143,168], Soo H. Teo[169,170], Mads Thomassen[109], Maria Grazia Tibiletti[46], Marc Tischkowitz[171,172], Silvia Tognazzo[7], Amanda E. Toland[173], Stefania Tommasi[174], Diana Torres[86,175], Angela Toss[52], Alison H. Trainer[95], Nadine Tung[176], Christi J. van Asperen[177], Frederieke H. van der Baan[128], Lizet E. van der Kolk[87], Rob B. van der Luijt[178], Liselotte P van Hest[179], Liliana Varesco[180], Raymonda Varon-Mateeva[136], Alessandra Viel[57], Jeroen Vierstrate[50], Roberta Villa[19], Anna von Wachenfeldt[17], Philipp Wagner[181], Shan Wang-Gohrke[182], Barbara Wappenschmidt[32,33], Jeffrey N. Weitzel[183], Greet Wieme[50], Siddhartha Yadav[151], Drakoulis Yannoukakos[76], Sook-Yee Yoon[184], Cristina Zanzottera[19], Kristin K. Zorn[121], Georgia Chenevix-Trench[141], Antonis C. Antoniou[5], Susan L. Neuhausen[59], Laura Ottini[81], Henriette Roed Nielsen[109], Timothy R. Rebbeck[2,4] were responsible for data collection, quality control, data cleaning, and validation of genotype and phenotype data used in this analysis.

Vivek Patel[1], Anthony D'Amico[1], Matthew Freedman[4], Mark Pomerantz[4], Antonis C. Antoniou[5], Susan L. Neuhausen[59], Laura Ottini[81], Henriette Roed Nielsen[109], Timothy R. Rebbeck[2,4] were responsible for the development of the research concept and design of this work and primarily responsible for the interpretation of the data.

Abstract

Pathogenic sequence variants (PSV) in BRCA1 or *BRCA2 (BRCA1/2)* are associated with increased risk and severity of prostate cancer (PCa). We evaluated whether PSVs in *BRCA1/2* were associated with risk of overall PCa or high grade (Gleason 8+) PCa using an international sample of 65 *BRCA1* and 171 *BRCA2* male PSV carriers with PCa, and 3,388 *BRCA1* and 2,880 *BRCA2* male PSV carriers without PCa. PSVs in the 3' region of *BRCA2* (c.7914+) were significantly associated with elevated risk of PCa compared with reference bin c.1001-c.7913 (HR=1.78, 95%CI: 1.25-2.52, p=0.001), as well as elevated risk of Gleason 8+ PCa (HR=3.11, 95%CI: 1.63-5.95, p=0.001). c.756-c.1000 was also associated with elevated PCa risk (HR=2.83, 95%CI: 1.71-4.68, p=0.00004) and elevated risk of Gleason 8+ PCa (HR=4.95, 95%CI: 2.12-11.54, p=0.0002). No genotype-phenotype associations were detected for PSVs in *BRCA1*. Specific *BRCA2* PSVs may be associated with PCa severity.

Introduction

Inherited pathogenic sequence variants (PSVs) in DNA repair pathway genes including *BRCA1* and *BRCA2 (BRCA1/2)* are associated with prostate cancer (PCa) risk and severity(1-15). Carriers of *BRCA2* PSVs have been reported to have increased levels of serum prostate-specific antigen (PSA) at diagnosis, increased proportion of high Gleason (7+) tumors, less favorable tumor stage, increased rates of nodal and distant metastases, and increased rate of recurrence after treatment(2,11-18). *BRCA2* PSVs confer lower overall survival and PCa specific survival(13-15). Ashkenazi Jewish carriers of *BRCA1* PSVs have been reported to have elevated rates of Gleason 7+ tumors, higher rates of recurrence, and a five-fold increase in PCa death(5,19), although the association of *BRCA1* and PCa has not been replicated in all studies(20). Distinct tumor PSV, methylation, and expression patterns have been identified in *BRCA2* compared with non-*BRCA2* mutant prostate tumors. These data suggest that *BRCA2* mutant tumors have features that are more similar to metastatic castrate resistant disease than localized PCa(21-23).

Specific genotype-phenotype correlations have been reported(24), including *BRCA1/2*-associated breast and ovarian cancers(25-27), *APC* PSVs and severity of familial adenomatous polyposis (FAP)(28,29), and *RET* PSVs in multiple endocrine neoplasia type 2 (MEN2) and Familial Medullary Thyroid Carcinoma(30). There have been suggestions in the literature that similar patterns exist for *BRCA1* or *BRCA2* and PCa. Liede et al.(31) reported that early-onset PCa (<age 65 years) was more frequent in men with *BRCA2* PSVs outside of the ovarian cancer cluster region. More recently, Roed Nielsen et al.(32), using a sample of 37 PCa cases, 19 of whom had *BRCA2* PSVs, identified a region in *BRCA2* at c.6373-c.6492 in which PSVs were associated with an increased risk of PCa.

We analyzed a large international cohort of 3,453 *BRCA1* and 3,051 *BRCA2* PSV male carriers to evaluate the distribution of germline PSVs in men diagnosed with PCa and men without prior

PCa diagnosis. We hypothesized that specific PSVs in *BRCA1* or *BRCA2* might influence development of PCa and be associated with PCa severity.

Materials and Methods

Study Sample

The Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) is an international collaboration of centers on six continents that has collected information about carriers of *BRCA1/2* PSVs(33). All carriers participated in clinical assessment and/or research studies at a participating institution after providing informed consent under protocols approved by local institutional review boards. Participants ascertainment date was defined as the time of study interview (e.g., enrollment in a research study). Forty-eight centers and multicenter consortia (**Supplementary Table 1**) in 31 countries submitted de-identified data that met the CIMBA inclusion criteria as previously described. No races/ethnicities were excluded from this study. Self-reported race/ethnicity data were collected across the various centers using either fixed categories or open-ended questions.

We analyzed only male carriers with clearly pathogenic *BRCA1/2* PSVs that occurred 3' of nucleotide position 1 (A of the ATC translation initiation codon in either *BRCA1* and *BRCA2.* This excluded 101 males who had a PSV occurring 5' translation start site. Definitions of these PSVs are shown in **Supplementary Table 2**. PSVs were defined using CIMBA criteria as follows: (1) PSVs generating a premature termination codon, except those in exon 27 at or after codon 3310 of *BRCA2*; (2) large in-frame deletions that spanned ≥1 exons; and (3) deletions of transcription regulatory regions (promoter and/or first exon) expected to cause lack of mutant allele expression(33-35). We also included missense variants considered pathogenic as determined by using multifactorial likelihood approaches(35,36). PSVs are described using the Human Genome Variation Society (HGVS) nomenclature (**Supplementary Table 2**).

Pathogenic Sequence Variant Binning

To identify segments across the intronic and exonic regions of *BRCA1* and *BRCA2* associated with different PCa risks, we created PSV bins by base pair location within each gene. These genomic sequence bins contained all PSVs regardless of category or function, except for large genomic rearrangements, which were excluded from this analysis since they may span multiple bins. Bins were constructed in two ways. First, we used an algorithm in which each bin contained approximately equal numbers of participants (including all cases and controls) with bin length defined by distance in base pairs. Thus, bin length for common PSVs (e.g., the Icelandic founder PSV c.771_775del) were small compared to bins with a wider range of PSVs. We divided the number of PSVs across the span of *BRCA1* or *BRCA2* into deciles of PSVs observed in cases and non-cases (i.e., "decile" bins). Second, we identified putative functional domains in *BRCA1* or *BRCA2* and created bins that captured these domains, as well as bins that contained no functional domain. These domains were determined by boundaries reported in the pfam database(37). The resulting bin boundaries are presented in **Supplementary Table 3** and shown graphically in **Figure 1** for *BRCA1* and **Figure 2** for *BRCA2*. We chose to use these two binning methods based on our earlier published research(24) that indicated the inferences about mutation risk association differences were similar regardless of the binning approach used. After the initial evaluation across all bins (**Supplementary Table 3**), we further collapsed bins that were inferred to have homogeneous PCa, either elevated above or not different from the reference bin.

Pathogenic Sequence Variant Type and Function

In addition to the binning analyses described above, we also considered whether the predicted type and function of heritable *BRCA1/2* PSVs in the CIMBA database were associated with PCa. The definition of these PSV types and their functions are presented in **Supplementary Table 2.** PSVs were grouped by type and function as frameshift (FS), nonsense (NS), missense (MS), and splice site (SP) (**Supplementary Table 2**). PSVs expected to generate stable or unstable, or no

proteins were designated into previously reported classes 1, 2, or 3(38-40). Missense PSVs in *BRCA1* were combined into one group that contained PSVs in the RING(41,42) and BRCT domains(43-46). We compared PSVs predicted to produce nonsense-mediated decay (NMD) vs. those that were not. PSVs predicted not to cause NMD were defined as those creating a stop codon within 50 nucleotides before or within the last exon(47). Premature termination codons comprised all PSVs leading to a truncated open reading frame.

Statistical Methods

For the first set of analyses assessing all bins across the genes, a different reference group was defined for each combination of gene (*BRCA1* or *BRCA2*) and binning scheme (decile or functional). Reference bins were chosen based on analysis of each bin's association with PCa compared with all other bins as a group and found to have the lowest hazard of PCa for each gene. The reference bins used in each analysis are shown in **Table 2**. An exploration of other reference bins did not change the inferences of this analysis (results not shown).

To estimate the relative hazards associated with each bin compared with the reference bin, we fitted Cox proportional hazards regression models separately in *BRCA1* and *BRCA2* PSV carriers. The primary outcomes of interest were diagnosis of PCa (vs. no PCa) or Gleason 8+ PCa (vs. no PCa) and Gleason $\leq$7 (vs. No PCa). Time to event was computed from birth to age at PCa diagnosis or age at ascertainment (which ever occurred first). No time or events were considered after time of ascertainment. All analyses were adjusted for confounding by race (African American vs. any other ethnicity) and birth cohort, defined as those born before or after median birth date of the total sample. We also adjusted all analyses by country of ascertainment. We computed the PCa hazard ratio for each defined bin relative to the common reference bin. To account for intra-cluster dependence due to multiple individuals from the same family, a robust sandwich variance estimate was specified in Cox proportional hazards models(48).

Hypothesis tests were judged to be statistically significant based on 2-sided tests with P-value < 0.05. All P-values were corrected for multiple hypothesis testing within each table of results by controlling the false discovery rate (FDR) using the method of Benjamini and Hochberg(49). Analyses were conducted in STATA v14, SPSS, or R version 2.7.2 (R Foundation for Statistical Computing).

Results

A total of 3,453 male *BRCA1* and 3,051 male *BRCA2 PSV* carriers were eligible for analysis. (see **Table 1)**. The median PCa diagnosis ages were 64 years in both *BRCA1* and *BRCA2* PSV carriers. Among *BRCA1/2* PSV carriers, 74% and 81%, respectively, self-reported their race as white.

BRCA1

As shown in **Table 2a**, there were no statistically significant associations between PSVs in any *BRCA1* bin and elevated PCa risk. There was also no association of *BRCA1* PSVs with Gleason 8+ disease with region (results not shown).

BRCA2

In *BRCA2*, we identified a "prostate cancer cluster region" (PCCR) in which PSVs were associated with elevated PCa risk. The risk estimates were obtained by considering all PSVs within the region of interest defined by the overlap of bins generated using the "decile" and functional binning methods described above. The PCCR included all PSVs 3' of c.7914 and associated with HR=1.78 (95%CI: 1.25-2.52, p=0.001) when compared with PSVs in the reference bin c.1001-c.7913 (**Table 2b**). In addition, we identified a region bounded by c.756 and c.1000 (**Supplementary Table 3** and **Figure 2) t**hat was associated with elevated PCa risk with HR=2.83

(95% CI: 1.71-4.68, $p=4x10^{-5}$) compared with PSVs in the reference bin c.1001-c.7913. This region contains the c.771_775del Icelandic founder PSV, which is the dominant PSV in this bin (n=92 of 117 total PSVs in this bin). Comparison of the risk in carriers of c.771_775del to the risk in carriers of PSVs in c.1001-c.7913 gave HR=3.34 (95%CI: 2.01-5.55, $p=3x10^{-6}$). Due to the small number of carriers of other PSVs in this bin (N=25), it was not possible to estimate risk of PCa for carriers of the other (non-c.771_775del) PSVs in this bin. Risk of PCa among those without a PCCR PSV was not elevated except for carriers of PSVs in bin 6 (c.5910-c.6275) (HR=2.83, 95%CI: 1.21-6.58, p=0.016) (Table 2b). Both the PCCR and region c.756-c.1000 were contained almost entirely within the previously identified breast cancer cluster regions (BCCRs)(24). Collectively, regions in which PSVs were associated with a significantly increased risk of PCa development contained the *BRCA2* helical plasma domain, the oligonucleotide/oligosaccharide-binding domain 1 (OB1), the Tower domain (OB2), and the N-terminal PALB2 binding site (**Figure 2**). Highest risk was associated with PSVs affecting OB1 and OB2 (**Figure 2**).

Risk of high-grade PCa (Gleason 8+) was even more strongly associated with PSVs in the PCCR (HR=3.11, 95% CI: 1.63-5.95, p=0.001; **Table 2c**). A similar association was also observed for PSVs in the region containing the Icelandic founder PSV, c.771_775_del (HR=4.95, 95% CI: 2.12-11.54, $p=2x10^{-4}$), and the c.771_775del PSV itself (HR=5.66, 95% CI: 2.43-13.22, $p=6x10^{-5}$) Together, these regions were associated with increased Gleason 8+ PCa risk (HR=3.80, 95% CI: 2.10-6.89, $p=1x10^{-5}$). Risk of Gleason $\leq$7 PCa was elevated for carriers of c.771_775del (HR=3.29, 95%CI: 1.38-7.83, p=0.007), but not elevated for those with PSVs in the PCCR (HR=1.56, 95%CI: 0.88-2.78, p=0.130; **Table 2c**).

To ensure that the inferred effects were not due to the common Jewish founder PSV c.5946del that was included in the reference bin, we repeated calculations after excluding carriers these

PSVs from the reference bin. After excluding these PSV carriers from the reference bin, the association with PSVs in the bin containing the c.771_775del and in the PCCR remained statistically significant (HR=3.03, 95%CI: 1.83-5.04, $p=2x10^{-5}$ and HR=1.89, 95%CI: 1.34-2.66, $p=3x10^{-4}$, respectively). Similarly, we repeated the analysis including only self-identified Caucasians. In part because of the small number of non-Caucasians in the study, the point estimates did not change to the second decimal place compared with the total sample that included non-Caucasians (results not shown). Finally, we corrected for correlation due to the presence of multiple individuals in a family. With and without this correction, no change in the inferences were observed.

Pathogenic Sequence Variant Type and Function

In addition to seeking for regional variation in PCa risk associated with PSVs across *BRCA1/2*, we also evaluated potential genotype-phenotype correlations by PSV type or function (**Table 3**). No PSV groups defined by type or function were significantly associated with prostate cancer for either *BRCA1* or *BRCA2*.

Discussion

Using a multinational data resource of ~6,500 men carrying a *BRCA1/2* PSV, we identified 2 regions in *BRCA2* (c.756-c 1000 and c.7914+) that were associated with increased risk of PCa diagnosis and of Gleason 8+ PCa. These data suggest that PSV-specific PCA-risks exist for *BRCA2* PSV carriers. This observation is consistent with earlier studies reporting a PSV-specific increase in PCa risk among *BRCA1/2* PSV carriers(31,32). However, most studies that have made these observations have estimated the prevalence of *BRCA1/2* mutations in PCa cases. Few studies have evaluated PCa incidence in mutation *BRCA1/2* carriers. Roed Nielsen et al. (32) reported an elevated PCa relative risk in *BRCA2* mutation carriers whose mutations fell in

c.6373-c.6492 with a relative risk of 3.7 for mutations within this region compared with mutations outside this region. This elevated relative risk was not observed in the larger current analysis, which included the carriers reported by Roed Nielsen. We also demonstrated a remarkable similarity between PSVs conferring increased PCa risk and those associated with increased breast cancer risk in female *BRCA2* PSV carriers(24).

BRCA2 is among the few known clinically relevant loci, in which many deleterious variants cause a highly penetrant PCa predisposition(50). Our work addressed the hypothesis that germline PSVs in *BRCA1/2* that influence development of overall PCa and PCa severity demonstrate nonrandom distribution by location and/or function of the gene. Since PCa patients with Gleason 8+ disease are far more likely than men with Gleason <8 PCa to have unfavorable clinical outcome(2,11-18), the observation that PCCR PSVs are associated with elevated Gleason score suggests that PCCR PSVs may be associated with poorer prognosis than other *BRCA2* PSVs. However, this needs to be investigated in future studies. We observe an elevated risk of both Gleason 8+ and Gleason $\leq$7 cancers, although the magnitude of association for Gleason 8+ is higher than that for Gleason $\leq$7. Thus, it is possible that the PCCR reported here is associated with PCa in general, and not only with high grade PCa. This observation requires additional research to confirm. Additionally, knowledge of the importance of DNA damage repair suggests that the mechanism of prostate carcinogenesis is broadly modified by *BRCA2*-related pathways(23). The IMPACT trial reported that PSA screening may be more informative in detecting PCa in *BRCA2* PSV carriers compared with non-carriers(51). Additional research is needed to evaluate whether the PCCR PSVs reported here also influence the results of different management strategies.

In addition to its co-location with a previously-identified breast cancer cluster region(24), PSVs in the PCCR (3' of c.7914) are focused within two of the principal DNA binding domains of the OB1 (i.e., oligonucleotide/oligosaccharide-binding domain 1; amino acids 2670 - 2796) and OB2 (i.e., Tower ssDNA and dsDNA binding domain 2; amino acids 2831 - 2872). However, the present data set does not allow us to understand the mechanism that might explain why *BRCA2* PCCR PSVs are associated with elevated PCa risks. Additional mechanistic research will be required to elucidate the biological basis for risk heterogeneity implied by the present results.

The most common PSV in the c.756-c.1000 region was the Icelandic and Finnish founder PSV, c.771_775del, which has long been known as a PCa predisposition PSV(52-54) and is associated with a rapid progression to fatal PCa(10). Thus, our results regarding the association of this founder PSV with PCa severity are consistent with this prior report. We were not able to infer if c.756-c.1000 is a second PCCR region, or if the observed effect is due solely to c.771_775del. We returned to the original data from participants with this PSV to identify any potential bias in ascertainment that may have influenced this result. Based on original records from the Icelandic clinics from which these men were ascertained, no individual was ascertained based on genetic testing of prostate cancer. The carriers of this PSV were identified through family studies of breast cancer, mainly by screening unselected breast cancer patients and then, if mutation positive, by screening their close relatives. There was no ascertainment preference for prostate cancer cases (Aðalgeir Arason, Personal communication).

Our present results complement the growing body of knowledge that cancer susceptibility PSVs demonstrate clinically relevant genotype-phenotype relationships. PSV location within *APC* is associated with polyposis severity and prevalence of extracolonic features, such as desmoid fibromas(55). Similarly, genotype-phenotype relationships have been reported for (missense) PSVs in *RET* in multiple endocrine neoplasia type 2 (MEN2) and Familial Medullary Thyroid

Carcinoma(30). These findings have shaped the Neuroendocrine Tumor Society consensus guidelines, which now suggest thyroidectomy before age five years for individuals with PSVs within these high-risk regions, providing insight into the structure and function of cancer susceptibility PSVs in these genes and guiding clinical risk assessment and management. Despite evidence of genotype-phenotype relationships at multiple loci, the characteristics and mechanistic influences on cancer risk are likely quite different for PVSs in *APC*, *RET*, *BRCA1/2,* and others.

In contrast to prior work that evaluated prevalence of PSVs in *BRCA1/2* in various PCa case series, we have leveraged a large, international multicenter consortium study of *BRCA1/2* PSV carriers, irrespective of PCa status. However, our analysis has some limitations. The CIMBA study uses a non-standardized recruitment strategy from multiple referral centers. Thus, our data may not represent either the full spectrum of PCa patients or *BRCA1/2* PSV carriers in the general population. Similarly, we were not able to assess issues of survival bias in our data that may be related to cancer screening or treatment.

While the present study identifies potentially interesting PSV-specific PCa associations, there are limitations in the data and analysis that require future validation. We used two binning approaches to identify relevant regions of *BRCA1/2* that could have different risk or penetrance effects on PCa based on our earlier research that undertook a similar analysis for breast and ovarian cancer(24). In that analysis, we determined that the combination of these two approaches were complementary and identified similar regions of interest. While this approach points toward genomic regions that may confer different PCa risks, a full understanding of the causes of the effects we report will require experimental and mechanistic studies to further define the boundaries of the relevant domains and to understand the underlying mechanisms that lead to the observations reported here. In addition, the choice of the reference bin in our analysis will

affect estimates of the hazard ratios reported here. Thus, the present report focuses on the identification of genomic regions that may confer elevated PCa risks in *BRCA2* mutation carriers, and the hazard ratio estimates presented here should be interpreted with caution and not used for clinical risk estimation purposes.

Studies in female PSV carriers using a study design similar to that used here applied analytical corrections to account for the possibility that affected individuals (particularly those affected at younger ages) are more likely to be sampled than unaffected individuals. Unlike prior breast and ovarian cancer studies in *BRCA1/2* mutation carriers, the present sample did not ascertain specific PCa cases (e.g., those diagnosed at an early age). Our median age at diagnosis is 64 years, which is similar to that reported in other non-*BRCA1/2* populations. Our case sample is substantially older than PCa cases ascertained for BRCA1/2 screening studies, which tend to have a large proportion of cases diagnosed before age 55 (56). Thus, while there is limited evidence that ascertainment of cases conferred a major bias to the present results, future research is required to determine the extent of bias in our relative risk estimates arising from these issues.

Finally, pathology review of prostate tumors was neither centralized or available for all cases. A relatively large proportion of Gleason score and tumor stage data were also missing from the present sample, since many cases were based on self-report only. Cases with missing tumor stage and grade were excluded from those analyses, so any differential reporting of tumor traits could have caused bias in those results.

The present study indicates that personalized PCa risk assessment may be a future option, as well as individualized clinical management based on the specific *BRCA2* PSV status. Additional research is required to fully understand the implication of carrying specific *BRCA2* PSVs. Further

characterization of the relationship between these PSVs and various cancer outcomes might help direct the future use of DNA repair-directed treatments and radiation therapy in men carrying these PSVs.

Acknowledgements

Funding Support

ELB was supported by grants from the National Cancer Institute (5T32CA009001, P60-CA105641). The CIMBA data management and data analysis were supported by Cancer Research – UK grants C12292/A20861, C12292/A11174. ACA is a Cancer Research -UK Senior Cancer Research Fellow. GCT and ABS are NHMRC Research Fellows. iCOGS: the European Community's Seventh Framework Programme under grant agreement n° 223175 (HEALTH-F2-2009-223175) (COGS), Cancer Research UK (C1287/A10118, C1287/A 10710, C12292/A11174, C1281/A12014, C5047/A8384, C5047/A15007, C5047/A10692, C8197/A16565), the National Institutes of Health (CA128978) and Post-Cancer GWAS initiative (1U19 CA148537, 1U19 CA148065 and 1U19 CA148112 - the GAME-ON initiative), the Department of Defence (W81XWH-10-1-0341), the Canadian Institutes of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer (CRN-87521), and the Ministry of Economic Development, Innovation and Export Trade (PSR-SIIRI-701), Komen Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research Fund. The PERSPECTIVE project was supported by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research, the Ministry of Economy, Science and Innovation through Genome Québec, and The Quebec Breast Cancer Foundation. BCFR: UM1 CA164920 from the National Cancer Institute. The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the BCFR. BFBOCC: Lithuania (BFBOCC-LT): Research Council of Lithuania grant SEN-18/2015. BIDMC: Breast Cancer Research Foundation. BMBSA: Cancer Association of South Africa (PI Elizabeth J. van Rensburg). CNIO: Spanish Ministry of Health PI16/00440 supported by FEDER funds, the Spanish Ministry of Economy and Competitiveness (MINECO) SAF2014-57680-R and the Spanish Research Network on Rare

diseases (CIBERER). COH-CCGCRN: Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under grant number R25CA112486, and RC4CA153828 (PI: J. Weitzel) from the National Cancer Institute and the Office of the Director, National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. CONSIT: Associazione Italiana Ricerca sul Cancro (AIRC; IG2014 no.15547) to P. Radice. Italian Association for Cancer Research (AIRC; grant no.16933) to L. Ottini. Associazione Italiana Ricerca sul Cancro (AIRC; IG2015 no.16732) to P. Peterlongo**.** Associazione Italiana Ricerca sul Cancro (AIRC grant IG17734) to G. Giannini**.** DEMOKRITOS: European Union (European Social Fund – ESF) and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework (NSRF) - Research Funding Program of the General Secretariat for Research & Technology: SYN11_10_19 NBCA. Investing in knowledge society through the European Social Fund. DFKZ: German Cancer Research Center. EMBRACE: Cancer Research UK Grants C1287/A10118 and C1287/A11990. Fiona Lalloo is supported by an NIHR grant to the Biomedical Research Centre, Manchester. The Investigators at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust are supported by an NIHR grant to the Biomedical Research Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust. Elizabeth Bancroft id supported by Cancer Research UK Grant C5047/A8385FCCC: The University of Kansas Cancer Center (P30 CA168524) and the Kansas Bioscience Authority Eminent Scholar Program. A.K.G. was funded by R0 1CA140323, R01 CA214545, and by the Chancellors Distinguished Chair in Biomedical Sciences Professorship. FPGMX: FISPI05/2275 and Mutua Madrileña Foundation (FMMA). GC-HBOC: German Cancer Aid (grant no 110837, Rita K. Schmutzler) and the European Regional Development Fund and Free State of Saxony, Germany (LIFE - Leipzig Research Centre for Civilization Diseases, project numbers 713-241202, 713-241202, 14505/2470, 14575/2470). GEMO: Ligue Nationale Contre le Cancer; the Association “Le cancer du sein, parlons-en!”

Award, the Canadian Institutes of Health Research for the "CIHR Team in Familial Risks of Breast Cancer" program and the French National Institute of Cancer (INCa). GEORGETOWN: the Non-Therapeutic Subject Registry Shared Resource at Georgetown University (NIH/NCI grant P30-CA051008), the Fisher Center for Hereditary Cancer and Clinical Genomics Research, and Swing Fore the Cure. G-FAST: Bruce Poppe is a senior clinical investigator of FWO. Mattias Van Heetvelde obtained funding from IWT. HCSC: Spanish Ministry of Health PI15/00059, PI16/01292, and CB-161200301 CIBERONC from ISCIII (Spain), partially supported by European Regional Development FEDER funds. HEBCS: Helsinki University Hospital Research Fund, Academy of Finland (266528), the Finnish Cancer Society and the Sigrid Juselius Foundation. HEBON: the Dutch Cancer Society grants NKI1998-1854, NKI2004-3088, NKI2007-3756, the Netherlands Organization of Scientific Research grant NWO 91109024, the Pink Ribbon grants 110005 and 2014-187.WO76, the BBMRI grant NWO 184.021.007/CP46 and the Transcan grant JTC 2012 Cancer 12-054. HEBON thanks the registration teams of Dutch Cancer Registry (IKNL; S. Siesling, J. Verloop) and the Dutch Pathology database (PALGA; L. Overbeek) for part of the data collection. HRBCP: Hong Kong Sanatorium and Hospital, Dr Ellen Li Charitable Foundation, The Kerry Group Kuok Foundation, National Institute of Health1R 03CA130065, and North California Cancer Center. HUNBOCS: Hungarian Research Grants KTIA-OTKA CK-80745 and OTKA K-112228. ICO: The authors would like to particularly acknowledge the support of the Asociación Española Contra el Cáncer (AECC), the Instituto de Salud Carlos III (organismo adscrito al Ministerio de Economía y Competitividad) and “Fondo Europeo de Desarrollo Regional (FEDER), una manera de hacer Europa” (PI10/01422, PI13/00285, PIE13/00022, PI15/00854, PI16/00563 and CIBERONC) and the Institut Català de la Salut and Autonomous Government of Catalonia (2009SGR290, 2014SGR338 and PERIS Project MedPerCan). IHCC: PBZ_KBN_122/P05/2004. ILUH: Icelandic Association “Walking for Breast Cancer Research” and by the Landspitali University Hospital Research Fund. INHERIT: Canadian Institutes of Health Research for the “CIHR Team in Familial Risks of Breast Cancer” program – grant # CRN-87521

and the Ministry of Economic Development, Innovation and Export Trade – grant # PSR-SIIRI-701. IOVHBOCS: Ministero della Salute and “5x1000” Istituto Oncologico Veneto grant. IPOBCS: Liga Portuguesa Contra o Cancro. kConFab: The National Breast Cancer Foundation, and previously by the National Health and Medical Research Council (NHMRC), the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia, and the Cancer Foundation of Western Australia. MAYO: NIH grants CA116167, CA192393 and CA176785, an NCI Specialized Program of Research Excellence (SPORE) in Breast Cancer (CA116201),and a grant from the Breast Cancer Research Foundation. MCGILL: Jewish General Hospital Weekend to End Breast Cancer, Quebec Ministry of Economic Development, Innovation and Export Trade. MSKCC: the Breast Cancer Research Foundation, the Robert and Kate Niehaus Clinical Cancer Genetics Initiative, the Andrew Sabin Research Fund and a Cancer Center Support Grant/Core Grant (P30 CA008748). NAROD: 1R01 CA149429-01. NCI: the Intramural Research Program of the US National Cancer Institute, NIH, and by support services contracts NO2-CP-11019-50, N02-CP-21013-63 and N02-CP-65504 with Westat, Inc, Rockville, MD. NICCC: Clalit Health Services in Israel, the Israel Cancer Association and the Breast Cancer Research Foundation (BCRF), NY. NNPIO: the Russian Federation for Basic Research (grants 15-04-01744, 16-54-00055 and 17-54-12007). NRG Oncology: U10 CA180868, NRG SDMC grant U10 CA180822, NRG Administrative Office and the NRG Tissue Bank (CA 27469), the NRG Statistical and Data Center (CA 37517) and the Intramural Research Program, NCI. OSUCCG: Ohio State University Comprehensive Cancer Center. PBCS: Italian Association of Cancer Research (AIRC) [IG 2013 N.14477] and Tuscany Institute for Tumors (ITT) grant 2014-2015-2016. SEABASS: Ministry of Science, Technology and Innovation, Ministry of Higher Education (UM.C/HIR/MOHE/06) and Cancer Research Initiatives Foundation. SMC: the Israeli Cancer Association. SWE-BRCA: the Swedish Cancer Society. UCHICAGO: NCI Specialized Program of Research Excellence (SPORE) in Breast Cancer (CA125183), R01 CA142996, 1U01CA161032 and by the Ralph and Marion Falk Medical Research Trust, the Entertainment

Industry Fund National Women's Cancer Research Alliance and the Breast Cancer research Foundation. OIO is an ACS Clinical Research Professor. UCLA: Jonsson Comprehensive Cancer Center Foundation; Breast Cancer Research Foundation. UCSF: UCSF Cancer Risk Program and Helen Diller Family Comprehensive Cancer Center. UKFOCR: Cancer Researc h UK. UPENN: Breast Cancer Research Foundation; Susan G. Komen Foundation for the cure, Basser Center for BRCA. UPITT/MWH: Hackers for Hope Pittsburgh. VFCTG: Victorian Cancer Agency, Cancer Australia, National Breast Cancer Foundation. WCP: Dr Karlan is funded by the American Cancer Society Early Detection Professorship (SIOP-06-258-01-COUN) and the National Center for Advancing Translational Sciences (NCATS), Grant UL1TR000124. S. Gutiérrez-Enríquez is supported by the Miguel Servet Progam (CP10/00617).

Acknowledgements

All the families and clinicians who contribute to the studies; Sue Healey, in particular taking on the task of PSV classification with the late Olga Sinilnikova; Maggie Angelakos, Judi Maskiell, Gillian Dite, Helen Tsimiklis; members and participants in the New York site of the Breast Cancer Family Registry; members and participants in the Ontario Familial Breast Cancer Registry; Vilius Rudaitis and Laimonas Griškevičius; Drs Janis Eglitis, Anna Krilova and Aivars Stengrevics; Rosario Alonso and Guillermo Pita; Milena Mariani, Daniela Zaffaroni, Monica Barile, Irene Feroce, Riccardo Dolcetti, Laura Papi, Gabriele Lorenzo Capone, Viviana Gismondi, Daniela Furlan, Antonella Savarese, Aline Martayan, Brunella Pilato; the personnel of the Cogentech Cancer Genetic Test Laboratory, Milan, Italy. Ms. JoEllen Weaver and Dr. Betsy Bove; Marta Santamariña, Ana Blanco, Miguel Aguado, Uxía Esperón and Belinda Rodríguez; IFE - Leipzig Research Centre for Civilization Diseases (Markus Loeffler, Joachim Thiery, Matthias Nüchter, Ronny Baber); We thank all participants, clinicians, family doctors, researchers, and technicians for their contributions and commitment to the DKFZ study and the collaborating groups in Lahore, Pakistan (Muhammad U. Rashid, Noor Muhammad, Sidra Gull, Seerat Bajwa, Faiz Ali Khan,

Humaira Naeemi, Saima Faisal, Asif Loya, Mohammed Aasim Yusuf) and Bogota, Colombia (Ignacio Briceno, Fabian Gil). Genetic Modifiers of Cancer Risk in BRCA1/2 Mutation Carriers (GEMO) study is a study from the National Cancer Genetics Network UNICANCER Genetic Group, France. We wish to pay a tribute to Olga M. Sinilnikova, who initiated and coordinated GEMO until she sadly passed away on the 30th June 2014. The team in Lyon (Olga Sinilnikova, Mélanie Léoné, Laure Barjhoux, Carole Verny-Pierre, Sylvie Mazoyer, Francesca Damiola, Valérie Sornin) managed the GEMO samples until the biological resource centre was transferred to Paris in December 2015 (. We want to thank all the GEMO collaborating groups for their contribution to this study: Coordinating Centre, Service de Génétique, Institut Curie, Paris, France: Ophélie Bertrand, Anne-Marie Birot, Sandrine Caputo, Anaïs Dupré, Emmanuelle Fourme, Lisa Golmard, Claude Houdayer, Marine Le Mentec, Virginie Moncoutier, Antoine de Pauw, Dominique yen yand Inserm U900, Institut Curie, Paris, France: Fabienne Lesueur, Noura Mebirouk.Contributing Centres : Unité Mixte de Génétique Constitutionnelle des Cancers Fréquents, Hospices Civils de Lyon - Centre Léon Bérard, Lyon, France: Nadia Boutry-Kryza, Alain Calender, Sophie Giraud, Mélanie Léone. Institut Gustave Roussy, Villejuif, France: Brigitte Bressac-de-Paillerets, Olivier Caron, Marine Guillaud-Bataille. Centre Jean Perrin, Clermont–Ferrand, France: Yves-Jean Bignon, Nancy Uhrhammer. Centre François Baclesse, Caen, France: Pascaline Berthet, Laurent Castera, Dominique Vaur. Institut Paoli Calmettes, Marseille, France: Violaine Bourdon, Catherine Noguès, Tetsuro Noguchi, Cornel Popovici, Audrey Remenieras, Hagay Sobol. CHU Arnaud-de-Villeneuve, Montpellier, France: Isabelle Coupier, Pascal Pujol. Centre Oscar Lambret, Lille, France: Claude Adenis, Aurélie Dumont, Françoise Révillion. Centre Paul Strauss, Strasbourg, France: Danièle Muller. Institut Bergonié, Bordeaux, France: Emmanuelle Barouk-Simonet, Françoise Bonnet, Virginie Bubien, Michel Longy, Nicolas Sevenet, Institut Claudius Regaud, Toulouse, France: Laurence Gladieff, Rosine Guimbaud, Viviane Feillel, Christine Toulas. CHU Grenoble, France: Hélène Dreyfus, Christine Dominique Leroux, Magalie Peysselon, Rebischung. CHU Dijon, France: Amandine Baurand, Geoffrey

Bertolone, Fanny Coron, Caroline Jacquot, Sarab Lizard. CHU St-Etienne, France: Caroline Kientz, Marine Lebrun, Fabienne Prieur. Hôtel Dieu Centre Hospitalier, Chambéry, France: Sandra Fert Ferrer. Centre Antoine Lacassagne, Nice, France: Véronique Mari. CHU Limoges, France: Laurence Vénat-Bouvet. CHU Nantes, France: Stéphane Bézieau, Capucine Delnatte. CHU Bretonneau, Tours and Centre Hospitalier de Bourges France: Isabelle Mortemousque. Groupe Hospitalier Pitié-Salpétrière, Paris, France: Chrystelle Colas, Florence Coulet, Florent Soubrier, Mathilde Warcoin. CHU Vandoeuvre-les-Nancy, France: Myriam Bronner, Johanna Sokolowska. CHU Besançon, France: Marie-Agnès Collonge-Rame, Alexandre Damette. CHU Poitiers, Centre Hospitalier d'Angoulême and Centre Hospitalier de Niort, France: Hakima Lallaoui. CHU Nîmes Carémeau, France : Jean Chiesa. CHI Poissy, France: Denise Molina-Gomes. CHU Angers, France : Olivier Ingster; Ilse Coene en Brecht Crombez; Ilse Coene and Brecht Crombez; Alicia Tosar and Paula Diaque; Sofia Khan, Taru A. Muranen, Carl Blomqvist, Irja Erkkilä and Virpi Palola; The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON) consists of the following Collaborating Centers: Coordinating center: Netherlands Cancer Institute, Amsterdam, NL: F.E. van Leeuwen, S. Verhoef, M.K. Schmidt, N.S. Russell, D.J. Jenner; Erasmus Medical Center, Rotterdam, NL: J.M. Collée, A.M.W. van den Ouweland, M.J. Hooning, C.H.M. van Deurzen, I.M. Obdeijn; Leiden University Medical Center, NL: J.T. Wijnen, R.A.E.M. Tollenaar, P. Devilee, T.C.T.E.F. van Cronenburg; Radboud University Nijmegen Medical Center, NL: C.M. Kets; University Medical Center Utrecht, NL: M.G.E.M. Ausems, C.C. van der Pol; Amsterdam Medical Center, NL: C.M. Aalfs, T.A.M. van Os; VU University Medical Center, Amsterdam, NL: J.J.P. Gille, Q. Waisfisz,; ; University Medical Center Groningen, NL: J.C. Oosterwijk, A.H. van der Hout, M.J. Mourits, G.H. de Bock; The Netherlands Foundation for the detection of hereditary tumours, Leiden, NL: H.F. Vasen; The Netherlands Comprehensive Cancer Organization (IKNL): S. Siesling, J.Verloop; The Dutch Pathology Registry (PALGA): L.I.H. Overbeek; Hong Kong Sanatorium and Hospital; the Hungarian Breast and Ovarian Cancer Study Group members (Janos Papp, Aniko Bozsik, Timea Pocza, Zoltan

Matrai, Miklos Kasler, Judit Franko, Maria Balogh, Gabriella Domokos, Judit Ferenczi, Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary) and the clinicians and patients for their contributions to this study; the Oncogenetics Group (VHIO) and the High Risk and Cancer Prevention Unit of the University Hospital Vall d'Hebron, and the Cellex Foundation for providing research facilities and equipment; the ICO Hereditary Cancer Program team led by Dr. Gabriel Capella; the ICO Hereditary Cancer Program team led by Dr. Gabriel Capella; Dr Martine Dumont for sample management and skillful assistance; Pedro Pinto; members of the Center of Molecular Diagnosis, Oncogenetics Department and Molecular Oncology Research Center of Barretos Cancer Hospital; Heather Thorne, Eveline Niedermayr, all the kConFab research nurses and staff, the heads and staff of the Family Cancer Clinics, and the Clinical Follow Up Study (which has received funding from the NHMRC, the National Breast Cancer Foundation, Cancer Australia, and the National Institute of Health (USA)) for their contributions to this resource, and the many families who contribute to kConFab; the KOBRA Study Group; Csilla Szabo (National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA Eva Machackova (Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute and MF MU, Brno, Czech Republic); and Michal Zikan, Petr Pohlreich and Zdenek Kleibl (Oncogynecologic Center and Department of Biochemistry and Experimental Oncology, First Faculty of Medicine, Charles University, Prague, Czech Republic); Anne Lincoln, Lauren Jacobs; the NICCC National Familial Cancer Consultation Service team led by Sara Dishon, the lab team led by Dr. Flavio Lejbkowicz, and the research field operations team led by Dr. Mila Pinchev; the investigators of the Australia New Zealand NRG Oncology group; members and participants in the Ontario Cancer Genetics Network; Kevin Sweet, Caroline Craven, Julia Cooper, and Michelle O'Conor; Yip Cheng Har, Nur Aishah Mohd Taib, Phuah Sze Yee, Norhashimah Hassan and all the research nurses, research assistants and doctors involved in the MyBrCa Study for assistance in patient recruitment, data collection and sample preparation, Philip Iau, Sng Jen-Hwei and Sharifah Nor Akmal for contributing samples

from the Singapore Breast Cancer Study and the HUKM-HKL Study respectively; the Meirav Comprehensive breast cancer center team at the Sheba Medical Center; Christina Selkirk; Håkan Olsson, Helena Jernström, Karin Henriksson, Katja Harbst, Maria Soller, Ulf Kristoffersson; from Gothenburg Sahlgrenska University Hospital: Anna Öfverholm, Margareta Nordling, Per Karlsson, Zakaria Einbeigi; from Stockholm and Karolinska University Hospital: Gisela Barbany Bustinza; from Umeå University Hospital: Beatrice Melin, Christina Edwinsdotter Ardnor, Monica Emanuelsson; from Uppsala University: Maritta Hellström Pigg, Richard Rosenquist; from Linköping University Hospital: Marie Stenmark-Askmalm, Sigrun Liedgren; Cecilia Zvocec, Qun Niu; Joyce Seldon and Lorna Kwan; Dr. Robert Nussbaum, Beth Crawford, Kate Loranger, Julie Mak, Nicola Stewart, Robin Lee, Amie Blanco and Peggy Conrad and Salina Chan; Simon Gayther, Susan Ramus, Paul Pharoah, Carole Pye, Patricia Harrington and Eva Wozniak; Geoffrey Lindeman, Marion Harris, Martin Delatycki, Sarah Sawyer, Rebecca Driessen, and Ella Thompson for performing all DNA amplification.

References

1. Giusti RM, Rutter JL, Duray PH, Freedman LS, Konichezky M, Fisher-Fischbein J*, et al.* A twofold increase in BRCA mutation related prostate cancer among Ashkenazi Israelis is not associated with distinctive histopathology. J Med Genet **2003**;40:787-92
2. Gallagher DJ, Gaudet MM, Pal P, Kirchhoff T, Balistreri L, Vora K*, et al.* Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clin Cancer Res **2010**;16:2115-21
3. Kirchhoff T, Kauff ND, Mitra N, Nafa K, Huang H, Palmer C*, et al.* BRCA mutations and risk of prostate cancer in Ashkenazi Jews. Clin Cancer Res **2004**;10:2918-21
4. Agalliu I, Kwon EM, Salinas CA, Koopmeiners JS, Ostrander EA, Stanford JL. Genetic variation in DNA repair genes and prostate cancer risk: results from a population-based study. Cancer Causes Control **2010**;21:289-300
5. Agalliu I, Gern R, Leanza S, Burk RD. Associations of high-grade prostate cancer with BRCA1 and BRCA2 founder mutations. Clin Cancer Res **2009**;15:1112-20
6. Agalliu I, Karlins E, Kwon EM, Iwasaki LM, Diamond A, Ostrander EA*, et al.* Rare germline mutations in the BRCA2 gene are associated with early-onset prostate cancer. Br J Cancer **2007**;97:826-31
7. Agalliu I, Kwon EM, Zadory D, McIntosh L, Thompson J, Stanford JL*, et al.* Germline mutations in the BRCA2 gene and susceptibility to hereditary prostate cancer. Clin Cancer Res **2007**;13:839-43
8. Eerola H, Heikkila P, Tamminen A, Aittomaki K, Blomqvist C, Nevanlinna H. Histopathological features of breast tumours in BRCA1, BRCA2 and mutation-negative breast cancer families. Breast Cancer Res **2005**;7:R93-100
9. Cybulski C, Wokołorczyk D, Kluźniak W, Kashyap A, Gołąb A, Słojewski M*, et al.* A personalised approach to prostate cancer screening based on genotyping of risk founder alleles. Br J Cancer **2013**;108:2601-9
10. Tryggvadottir L, Vidarsdottir L, Thorgeirsson T, Jonasson JG, Olafsdottir EJ, Olafsdottir GH*, et al.* Prostate cancer progression and survival in BRCA2 mutation carriers. J Natl Cancer Inst **2007**;99:929-35
11. Kote-Jarai Z, Leongamornlert D, Saunders E, Tymrakiewicz M, Castro E, Mahmud N*, et al.* BRCA2 is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients. Br J Cancer **2011**;105:1230-4
12. Leongamornlert D, Mahmud N, Tymrakiewicz M, Saunders E, Dadaev T, Castro E*, et al.* Germline BRCA1 mutations increase prostate cancer risk. Br J Cancer **2012**;106:1697-701
13. Castro E, Goh C, Olmos D, Saunders E, Leongamornlert D, Tymrakiewicz M*, et al.* Germline BRCA Mutations Are Associated With Higher Risk of Nodal Involvement, Distant Metastasis, and Poor Survival Outcomes in Prostate Cancer. J Clin Oncol **2013**
14. Thorne H, Willems AJ, Niedermayr E, Hoh IM, Li J, Clouston D*, et al.* Decreased prostate cancer-specific survival of men with BRCA2 mutations from multiple breast cancer families. Cancer Prev Res (Phila) **2011**;4:1002-10
15. Gleicher S, Kauffman EC, Kotula L, Bratslavsky G, Vourganti S. Implications of High Rates of Metastatic Prostate Cancer in BRCA2 Mutation Carriers. Prostate **2016**;76:1135-45
16. Thompson D, Easton D. Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. Am J Hum Genet **2001**;68:410-9

17. Walker R, Louis A, Berlin A, Horsburgh S, Bristow RG, Trachtenberg J. Prostate cancer screening characteristics in men with BRCA1/2 mutations attending a high-risk prevention clinic. Can Urol Assoc J **2014**;8:E783-8
18. Maier C, Herkommer K, Luedeke M, Rinckleb A, Schrader M, Vogel W. Subgroups of familial and aggressive prostate cancer with considerable frequencies of BRCA2 mutations. Prostate **2014**;74:1444-51
19. Laitman Y, Keinan Boker L, Liphsitz I, Weissglas-Volkov D, Litz-Philipsborn S, Schayek H*, et al.* Cancer risks in Jewish male BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat **2015**;150:631-5
20. Streff H, Profato J, Ye Y, Nebgen D, Peterson SK, Singletary C*, et al.* Cancer Incidence in First- and Second-Degree Relatives of BRCA1 and BRCA2 Mutation Carriers. Oncologist **2016**;21:869-74
21. Taylor RA, Fraser M, Livingstone J, Espiritu SM, Thorne H, Huang V*, et al.* Germline BRCA2 mutations drive prostate cancers with distinct evolutionary trajectories. Nat Commun **2017**;8:13671
22. Armenia J, Wankowicz SAM, Liu D, Gao J, Kundra R, Reznik E*, et al.* The long tail of oncogenic drivers in prostate cancer. Nat Genet **2018**
23. Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM*, et al.* Integrative clinical genomics of advanced prostate cancer. Cell **2015**;161:1215-28
24. Rebbeck TR, Mitra N, Wan F, Sinilnikova OM, Healey S, McGuffog L*, et al.* Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. JAMA **2015**;313:1347-61
25. Gayther SA, Warren W, Mazoyer S, Russell PA, Harrington PA, Chiano M*, et al.* Germline mutations of the BRCA1 gene in breast and ovarian cancer families provide evidence for a genotype-phenotype correlation. Nature Genetics **1995**;11:428-33
26. Gayther SA, Mangion J, Russell P, Seal S, Barfoot R, Ponder BA*, et al.* Variation of risks of breast and ovarian cancer associated with different germline mutations of the BRCA2 gene. Nat Genet **1997**;15:103-5
27. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ*, et al.* Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA **2017**;317:2402-16
28. Rowan AJ, Lamlum H, Ilyas M, Wheeler J, Straub J, Papadopoulou A*, et al.* APC mutations in sporadic colorectal tumors: A mutational "hotspot" and interdependence of the "two hits". Proc Natl Acad Sci U S A **2000**;97:3352-7
29. Amos-Landgraf JM, Kwong LN, Kendziorski CM, Reichelderfer M, Torrealba J, Weichert J*, et al.* A target-selected Apc-mutant rat kindred enhances the modeling of familial human colon cancer. Proc Natl Acad Sci U S A **2007**;104:4036-41
30. Krampitz GW, Norton JA. RET gene mutations (genotype and phenotype) of multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma. Cancer **2014**;120:1920-31
31. Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. J Clin Oncol **2004**;22:735-42
32. Roed Nielsen H, Petersen J, Therkildsen C, Skytte AB, Nilbert M. Increased risk of male cancer and identification of a potential prostate cancer cluster region in BRCA2. Acta Oncol **2016**;55:38-44
33. Chenevix-Trench G, Milne RL, Antoniou AC, Couch FJ, Easton DF, Goldgar DE*, et al.* An international initiative to identify genetic modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: the Consortium of Investigators of Modifiers of BRCA1 and BRCA2 (CIMBA). Breast Cancer Res **2007**;9:104

34. Claes K, Vandesompele J, Poppe B, Dahan K, Coene I, De Paepe A*, et al.* Pathological splice mutations outside the invariant AG/GT splice sites of BRCA1 exon 5 increase alternative transcript levels in the 5' end of the BRCA1 gene. Oncogene **2002**;21:4171-5
35. Goldgar DE, Easton DF, Deffenbaugh AM, Monteiro AN, Tavtigian SV, Couch FJ. Integrated evaluation of DNA sequence variants of unknown clinical significance: application to BRCA1 and BRCA2. Am J Hum Genet **2004**;75:535-44
36. Bernstein JL, Teraoka S, Southey MC, Jenkins MA, Andrulis IL, Knight JA*, et al.* Population-based estimates of breast cancer risks associated with ATM gene variants c.7271T>G and c.1066-6T>G (IVS10-6T>G) from the Breast Cancer Family Registry. Hum Mutat **2006**;27:1122-8
37. PFam v.31.0. 2017.
38. Perrin-Vidoz L, Sinilnikova OM, Stoppa-Lyonnet D, Lenoir GM, Mazoyer S. The nonsense-mediated mRNA decay pathway triggers degradation of most BRCA1 mRNAs bearing premature termination codons. Human Molecular Genetics **2002**;11:2805-14
39. Mikaelsdottir EK, Valgeirsdottir S, Eyfjord JE, Rafnar T. The Icelandic founder mutation BRCA2 999del5: analysis of expression. Breast Cancer Res **2004**;6:R284-90
40. Buisson M, Anczukow O, Zetoune AB, Ware MD, Mazoyer S. The 185delAG mutation (c.68_69delAG) in the BRCA1 gene triggers translation reinitiation at a downstream AUG codon. Hum Mutat **2006**;27:1024-9
41. Brzovic PS, Rajagopal P, Hoyt DW, King MC, Klevit RE. Structure of a BRCA1-BARD1 heterodimeric RING-RING complex. Nat Struct Biol **2001**;8:833-7
42. Bienstock RJ, Darden T, Wiseman R, Pedersen L, Barrett JC. Molecular modeling of the amino-terminal zinc ring domain of BRCA1. Cancer Res **1996**;56:2539-45
43. Wu LC, Wang ZW, Tsan JT, Spillman MA, Phung A, Xu XL*, et al.* Identification of a RING protein that can interact in vivo with the BRCA1 gene product. Nat Genet **1996**;14:430-40
44. Bork P, Hofmann K, Bucher P, Neuwald AF, Altschul SF, Koonin EV. A superfamily of conserved domains in DNA damage-responsive cell cycle checkpoint proteins. FASEB J **1997**;11:68-76
45. Williams RS, Green R, Glover JN. Crystal structure of the BRCT repeat region from the breast cancer-associated protein BRCA1. Nat Struct Biol **2001**;8:838-42
46. Huyton T, Bates PA, Zhang X, Sternberg MJ, Freemont PS. The BRCA1 C-terminal domain: structure and function. Mutat Res **2000**;460:319-32
47. Palacios IM. Nonsense-mediated mRNA decay: from mechanistic insights to impacts on human health. Brief Funct Genomics **2013**;12:25-36
48. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. JASA **1989**;84:1074-8
49. Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. J R Stat Soc B **1995**;57:289-300
50. Giri VN, Knudsen KE, Kelly WK, Abida W, Andriole GL, Bangma CH*, et al.* Role of Genetic Testing for Inherited Prostate Cancer Risk: Philadelphia Prostate Cancer Consensus Conference 2017. J Clin Oncol **2017**:JCO2017741173
51. Bancroft EK, Page EC, Castro E, Lilja H, Vickers A, Sjoberg D*, et al.* Targeted prostate cancer screening in BRCA1 and BRCA2 mutation carriers: results from the initial screening round of the IMPACT study. Eur Urol **2014**;66:489-99
52. Sigurdsson S, Thorlacius S, Tomasson J, Tryggvadottir L, Benediktsdottir K, Eyfjord JE*, et al.* BRCA2 mutation in Icelandic prostate cancer patients. Journal of Molecular Medicine **1997**;75:758-61
53. Gudmundsson J, Johannesdottir G, Bergthorsson JT, Arason A, Ingvarsson S, Egilsson V*, et al.* Different tumor types from BRCA2 carriers show wild-type chromosome deletions on 13q12-q13. Cancer Res **1995**;55:4830-2

54. Barkardottir RB, Sarantaus L, Arason A, Vehmanen P, Bendahl PO, Kainu T*, et al.* Haplotype analysis in Icelandic and Finnish BRCA2 999del5 breast cancer families. Eur J Hum Genet **2001**;9:773-9
55. Nieuwenhuis MH, Vasen HF. Correlations between mutation site in APC and phenotype of familial adenomatous polyposis (FAP): a review of the literature. Crit Rev Oncol Hematol **2007**;61:153-61
56. Cavanagh H, Rogers KM. The role of BRCA1 and BRCA2 mutations in prostate, pancreatic and stomach cancers. Hered Cancer Clin Pract **2015**;13:16

Table 1: Characteristics of Study Participants

		Carriers of PSV in *BRCA1*		Carriers of PSV in *BRCA2*	
		N	%	N	%
	Total	3,453		3,051	
Region	Asia	76	2.2	90	2.9
	Australia	386	11.2	292	9.6
	Europe	2,287	66.2	2,165	71.0
	North America	662	19.2	497	16.3
	South America	42	1.2	7	0.2
Self-Identified Race/Ethnicity	Caucasian	2,557	74.1	2,455	80.5
	African American	20	0.6	14	0.5
	Asian	76	2.2	101	3.3
	Hispanic	54	1.6	16	0.5
	Jewish	124	3.6	94	3.1
	Other	45	1.3	10	0.3
	Unknown	575	16.7	358	11.7
Ascertainment	Clinic-based	3,352	97.1	2,969	97.3
	Population-based	101	2.9	82	2.7
PCa	Yes	65	1.9	171	5.5
	No	3,388	98.1	2,880	94.4
Gleason Score	≤6	16	24.6	32	18.7
	7	9	13.8	30	17.5
	8	3	4.6	16	3.1
	9	7	10.8	26	15.2
	10	0	0.0	5	2.9
	Missing	30	46.2	62	36.2
M Stage	M0	18	27.7	33	19.3
	M1	2	3.1	14	8.2
	MX	8	12.3	28	16.4
	Missing	37	56.9	96	56.1
Other Cancer Diagnosis	Yes	332	9.6	657	21.5
	No	3,121	90.4	2,389	78.5

	N	Median	Range	N	Median	Range
Age at Ascertainment (yrs)	3,453	50	18-91	3,051	51	18-101
Time to PCa or Censoring (yrs)	3,453	50	18-91	3,051	54	18-101
Age at PCa Diagnosis (yrs)	65	64	30-85	171	64	29-87
Age at Other Cancer Diagnosis (yrs)	332	59	19-88	657	60	21-88

Table 2: Association Analyses of Prostate Cancer by bin for *BRCA1* and *BRCA2* PSVs

BRCA1 – All Prostate Cancer

Grouping	Bin	Nucleotide Range	PC+	PC-	HR	95% CI	p-value
***BRCA1* Decile**	1	≤c.81	11	339	1.06	0.36-3.13	0.917
	2	c.82-c.302	5	325	REF		
	3	c.303 – c.1504	4	331	0.82	0.23-2.92	0.761
	4	c.1505 – c.2475	8	431	1.09	0.34-3.43	0.888
	5	c.2476 – c.3319	3	274	0.33	0.15-2.60	0.526
	6	c.3320 – c.3710	5	308	1.32	0.36-4.89	0.677
	7	c.3711 – c.4065	9	318	1.96	0.65-5.86	0.230
	8	c.4066 – c.5030	1	333	0.16	0.02-1.27	0.084
	9	c.5031 – c.5266	13	425	1.68	0.58-4.84	0.339
	10	c.5267+	2	231	0.49	0.10-2.49	0.389
***BRCA1* Functional**	1	≤c.181	13	515	0.72	0.34-1.53	0.396
	2	c.182-c.1287	6	433	0.83	0.32-2.20	0.713
	3	c.1288-c.2475	9	478	0.93	0.37-2.36	0.887
	4	c.2476-c.3607	5	487	0.58	0.19-1.75	0.333
	5	c.3608-c.4183	12	462	1.19	0.54-2.64	0.671
	6	c.4184-c.5194	5	485	0.38	0.12-1.25	0.112
	7	c.5195+	11	455	REF		

BRCA2 – All Prostate Cancer

Grouping	Bin	Nucleotide Range	PC+	PC-	HR	95% CI	p-value
Decile	1	≤c.755	12	296	1.71	0.66-4.46	0.268
	2	c.756-c.1813	25	277	3.38	1.24-9.19	0.017
	3	c.1814-c.3530	6	293	REF		
	4	c.3531-c.4965	13	296	2.00	0.69-5.76	0.202
	5	c.4966-c.5909	13	307	2.14	0.66-7.00	0.207
	6	c.5910-c.6275	30	334	2.83	1.21-6.58	0.016
	7	c.6276-c.7007	12	214	2.69	0.89-8.13	0.079
	8	c.7008-c.7913	10	285	2.12	0.60-7.42	0.240
	9	c.7914-c.8953	26	281	3.32	1.28-8.65	0.014
	10	c.8954+	23	274	4.26	1.60-11.37	0.004
Functional	1	≤c.1000	27	398	1.39	0.74-2.64	0.307
	2	c.1001-c.3005	14	397	0.80	0.39-1.63	0.535
	3	c.3006-c.5172	16	408	REF		
	4	c.5173-c.6255	32	498	1.01	0.53-1.93	0.967
	5	c.6256-c.7436	24	400	1.44	0.74-2.82	0.286
	6	c.7437-c.8616	28	390	1.68	0.91-3.13	0.100

Grouping	Bin	Nucleotide Range	PC+	PC-	HR	95% CI	p-value
	7	c.8617+	29	366	1.64	0.90-3.01	0.106
Elevated vs. No Elevated PCa Risk	1	≤c.755	12	296	0.73	0.40-1.31	0.288
	2*	c.756-c.1000	15	102	2.83	1.71-4.68	$4x10^{-5}$
	3	c.1001-c.7913	94	1904	REF		
	PCCR	c.7914+	49	555	1.78	1.25-2.52	0.001
Elevated vs. No Elevated PCa Risk	No Elevated PCa Risk	≤c.755, c.1001-c.7913	106	2,200	REF		
	Elevated PCa Risk	c.756-c.1000, c.7914+	65	657	2.02	1.48-2.77	$9x10^{-6}$

BRCA2 –Prostate Cancer by Gleason Grade

Gleason 8+	Bin	Nucleotide Range	PC+	PC-	HR	95% CI	p-value
Bins with Elevated Risk	1	≤c.755	2	299	0.53	0.12-2.32	0.399
	2	c.756-c.1000	6	108	4.95	2.12-11.54	$2x10^{-4}$
	3	c.1001-c.7913	19	1940	REF		
	PCCR	c.7914+	18	572	3.11	1.63-5.95	0.001
Bins with Elevated Risk	No Elevated PCa Risk	≤c.755, c.1001-c.7913	21	2239	REF		
	Elevated PCa Risk	c.756-c.1000, c.7914+	24	680	3.80	2.10-6.89	$1x10^{-5}$
Gleason ≤7							
Bins with Elevated Risk	1	≤c.755	3	298	0.47	0.14-1.57	0.221
	2*	c.756-c.1000	6	108	3.29	1.38-7.83	0.007
	3	c.1001-c.7913	36	1923	REF		
	PCCR	c.7914+	17	573	1.56	0.88-2.78	0.130
Bins with Elevated Risk	No Elevated PCa Risk	≤c.755, c.1001-c.7913	39	2221	REF		
	Elevated PCa Risk	c.756-c.1000, c.7914+	23	681	1.89	1.14-3.14	0.014

*Bin containing Icelandic Founder PSV c.771_775del

Table 3: Association of Pathogenic Sequence Variant (PSV) Type or Function with risk of prostate cancer. Hazard Ratios (HRs) represent the comparison of PSVs with a certain type or function designation vs. all other PSVs. HRs are adjusted for year of birth cohort, race, and country of ascertainment.

			BRCA1 mutation carriers		*BRCA2* mutation carriers			
PSV type	N	PCa	HR (95% CI)	p-value	N	PCa	HR (95% CI)	p-value
Premature Truncating Codon	2,720	54 (2.0%)	1.04 (0.47-2.28)	0.931	2,699	151 (5.6%)	0.90 (0.40-2.04)	0.805
Nonsense-Mediated Decay	1,996	31 (1.6%)	0.65 (0.38-1.11)	0.117	2,692	150 (5.6%)	0.86 (0.41-1.82)	0.698
Class 1	2,489	48 (1.9%)	0.80 (0.44-1.47)	0.474	2,712	151 (5.6%)	0.81 (0.37-1.78)	0.596
Deletion	279	5 (1.8%)	0.79 (0.32-1.95)	0.606	57	5 (8.8)	1.25 (0.51-3.08)	0.469
Frameshift	1,845	43 (2.3%)	1.66 (0.99-2.77)	0.055	2,040	115 (5.6%)	1.01 (0.74-1.41)	0.910
Insertion	61	0	*	*	21	0	*	*
Missense	283	3 (1.1%)	0.66 (0.21-2.11)	0.488	60	4 (7%)	1.08 (0.37-3.17)	0.886
Nonsense	679	9 (1.3%)	0.68 (0.34-1.36)	0.271	591	32 (5.4%)	0.94 (0.64-1.39)	0.740
Splicing	306	5 (1.6%)	0.94 (0.39-2.30)	0.896	282	15 (5.3%)	1.00 (0.57-1.76)	0.994

*Could not be estimated.

Figure Legends

Figure 1: *BRCA1* Pathogenic Sequence Variant Distribution

The x-axis displays the amino acid sequence of the *BRCA1* gene. The violet markers indicate the position of PSVs found in the *BRCA1* PSV carriers. The vertical position of the markers on the y-axis indicates the frequency of the PSV found in the cohort. Additionally, the blue and tan bars with corresponding axis markers delineate the bins of the *BRCA1* PSVs that were created using the "decile" binning strategy and the "functional" binning strategy. Orange and light blue bars indicate the position of breast and ovarian cancer cluster regions, respectively, as identified in the CIMBA breast cancer cohort (Rebbeck et al. *JAMA* 2015). Lastly, known functional domains within the *BRCA1* gene are highlighted.

A. Distribution of total *BRCA1* PSVs in carriers, B. Distribution of *BRCA1* PSVs in carriers who did not develop prostate cancer, C. Distribution of *BRCA1* PSVs in carriers who developed prostate cancer.

Figure 2. *BRCA2* Pathogenic Sequence Variant Distribution

The x-axis displays the amino acid sequence of the *BRCA2* gene. The violet markers indicate the position of PSVs found in the *BRCA2* PSV carriers. The vertical position of the markers on the y-axis indicates the frequency of the PSV found in the cohort. Additionally, the blue and tan bars with corresponding axis markers delineate the bins of the *BRCA2* PSVs that were created using the "decile" binning strategy and the "functional" binning strategy. Orange and light blue bars indicate the position of breast and ovarian cancer cluster regions, respectively, as identified in the CIMBA breast cancer cohort (Rebbeck et al. *JAMA* 2015). Lastly, known functional domains within the *BRCA2* gene are highlighted.

A. Distribution of total *BRCA2* PSVs in carriers, B. Distribution of *BRCA2* PSVs in carriers who did not develop prostate cancer, C. Distribution of *BRCA2* PSVs in carriers who developed prostate cancer.

Supplementary Tables

Supplementary Table 1: *BRCA1/2* PSV Carriers by Center

Supplementary Table 2: Observed *BRCA1/2* PSVs by Type and Function

Supplementary Table 3: Bins defined by PSV location for *BRCA1* and *BRCA2*

Figure 1

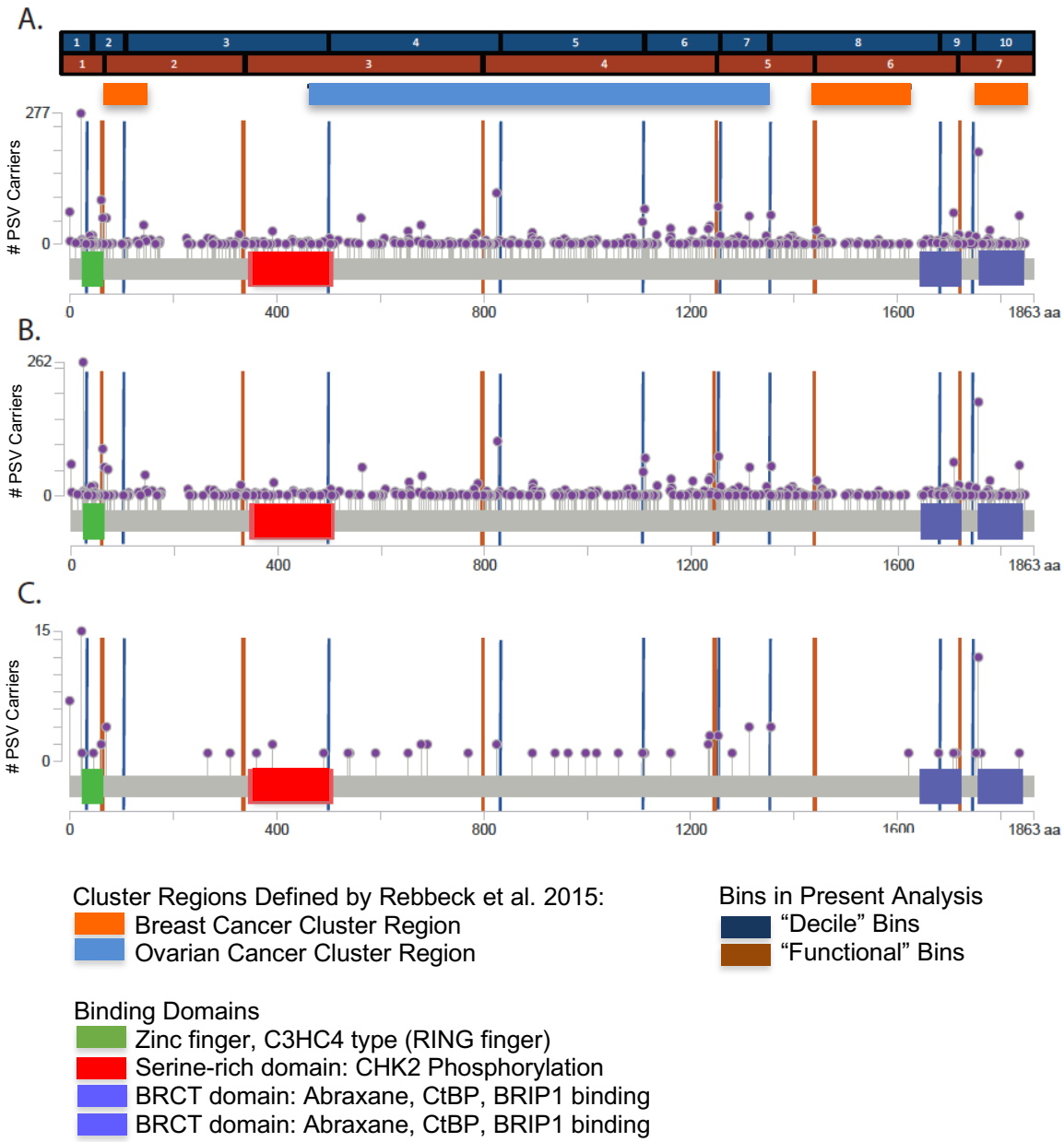
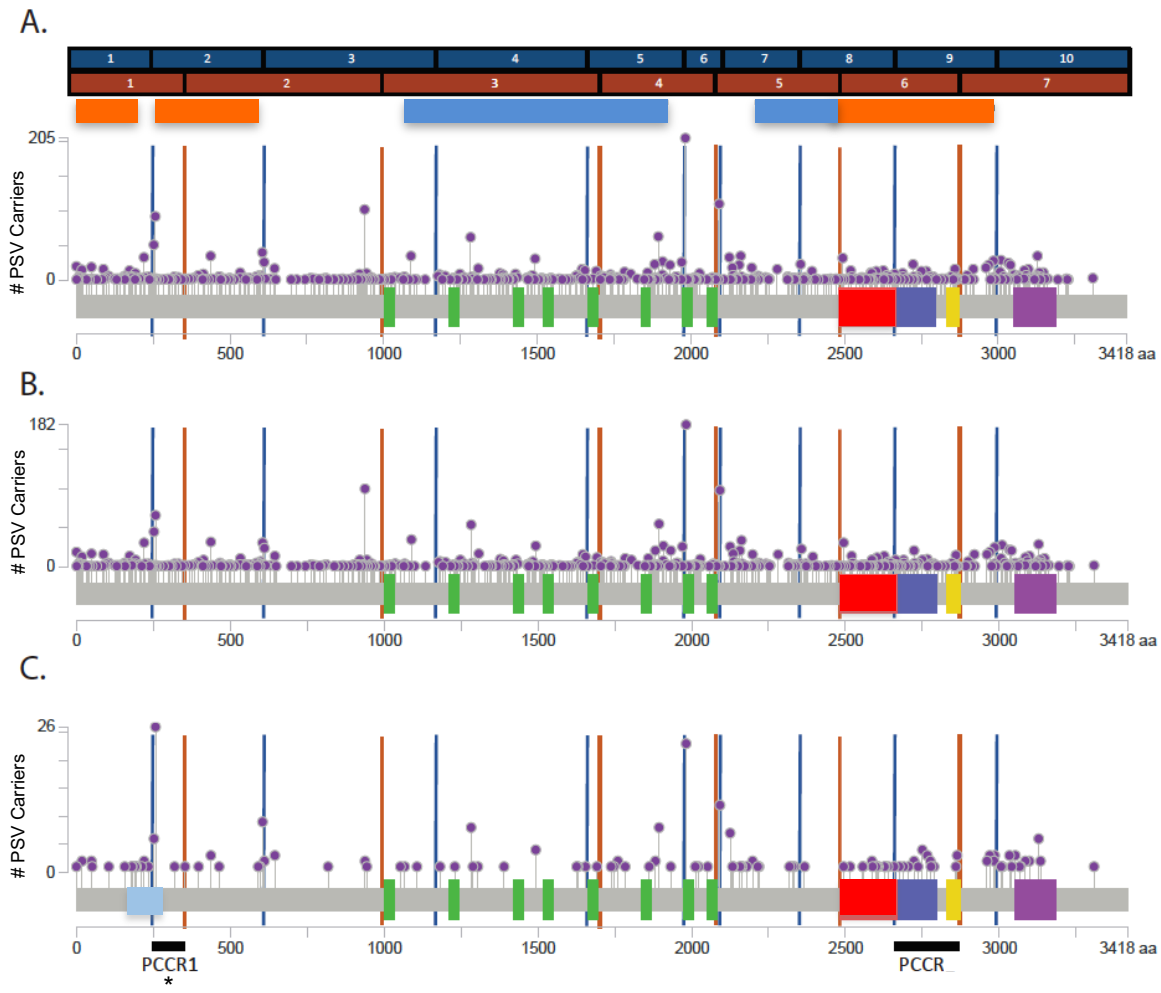

A.
1
2
3
4
5
6
7
8
9
10
277
PSV Carriers
0
0
400
800
1200
1600
1863 aa
B.
262
PSV Carriers
0
0
400
800
1200
1600
1863 aa
C.
15
PSV Carriers
0
0
400
800
1200
1600
1863 aa
Cluster Regions Defined by Rebbeck et al. 2015:
Breast Cancer Cluster Region
Ovarian Cancer Cluster Region
Bins in Present Analysis
"Decile" Bins
"Functional" Bins
Binding Domains
Zinc finger, C3HC4 type (RING finger)
Serine-rich domain: CHK2 Phosphorylation
BRCT domain: Abraxane, CtBP, BRIP1 binding
BRCT domain: Abraxane, CtBP, BRIP1 binding

Figure 2


A.
1 2 3 4 5 6 7 8 9 10
1 2 3 4 5 6 7
205
PSV Carriers
0
0 500 1000 1500 2000 2500 3000 3418 aa
B.
182
PSV Carriers
0
0 500 1000 1500 2000 2500 3000 3418 aa
C.
26
PSV Carriers
0
0 500 1000 1500 2000 2500 3000 3418 aa
PCCR1
*
PCCR
Cluster Regions Defined by Rebbeck et al. 2015
Breast Cancer Cluster Region
Ovarian Cancer Cluster Region
Bins in Present Analysis
"Decile" Bins
"Functional" Bins
Binding Domains
PALB2 Binding
BRC repeats
Helical domain
OB1 oligonucleotide/oligosaccharide-binding, domain 1
OB2 Tower ssDNA and dsDNA binding domain 2
OB3 oligonucleotide/oligosaccharide-binding, domain 3
* Region Containing
Icelandic Founder PSV