

OPEN

Two truncating variants in *FANCC* and breast cancer risk

Thilo Dörk<sup>1</sup>, Paolo Peterlongo<sup>2</sup>, Arto Mannermaa<sup>3,4,5</sup>, Manjeet K. Bolla<sup>6</sup>, Qin Wang<sup>6</sup>, Joe Dennis<sup>6</sup>, Thomas Ahearn<sup>7</sup>, Irene L. Andrulis<sup>8,9</sup>, Hoda Anton-Culver<sup>10</sup>, Volker Arndt<sup>11</sup>, Kristan J. Aronson<sup>12</sup>, Annelie Augustinsson<sup>13</sup>, Laura E. Beane Freeman<sup>7</sup>, Matthias W. Beckmann<sup>14</sup>, Alicia Beeghly-Fadiel<sup>15</sup>, Sabine Behrens<sup>16</sup>, Marina Bermisheva<sup>17</sup>, Carl Blomqvist<sup>18,19</sup>, Natalia V. Bogdanova<sup>1,20,21</sup>, Stig E. Bojesen<sup>22,23,24</sup>, Hiltrud Brauch<sup>25,27,156</sup>, Hermann Brenner<sup>11,27,28</sup>, Barbara Burwinkel<sup>29,30</sup>, Federico Canzian<sup>31</sup>, Tsun L. Chan<sup>32,33</sup>, Jenny Chang-Claude<sup>16,34</sup>, Stephen J. Chanock<sup>7</sup>, Ji-Yeob Choi<sup>35,36</sup>, Hans Christiansen<sup>20</sup>, Christine L. Clarke<sup>37</sup>, Fergus J. Couch<sup>38</sup>, Kamila Czene<sup>39</sup>, Mary B. Daly<sup>40</sup>, Isabel dos-Santos-Silva<sup>41</sup>, Miriam Dwek<sup>42</sup>, Diana M. Eccles<sup>43</sup>, Arif B. Ekici<sup>44</sup>, Mikael Eriksson<sup>39</sup>, D. Gareth Evans<sup>45,46</sup>, Peter A. Fasching<sup>14,47</sup>, Jonine Figueroa<sup>7,48,49</sup>, Henrik Flyger<sup>50</sup>, Lin Fritschi<sup>51</sup>, Marike Gabrielson<sup>39</sup>, Manuela Gago-Dominguez<sup>52,53</sup>, Chi Gao<sup>54,55</sup>, Susan M. Gapstur<sup>56</sup>, Montserrat Garcia-Closas<sup>7,57</sup>, José A. Garcia-Sáenz<sup>58</sup>, Mia M. Gaudet<sup>56</sup>, Graham G. Giles<sup>59,60,61</sup>, Mark S. Goldberg<sup>62,63</sup>, David E. Goldgar<sup>64</sup>, Pascal Guénel<sup>65</sup>, Lothar Haeberle<sup>66</sup>, Christopher A. Haiman<sup>67</sup>, Niclas Håkansson<sup>68</sup>, Per Hall<sup>39,69</sup>, Ute Hamann<sup>70</sup>, Mikael Hartman<sup>71,72</sup>, Jan Hauke<sup>73,74,75</sup>, Alexander Hein<sup>14</sup>, Peter Hillemanns<sup>1</sup>, Frans B. L. Hogervorst<sup>76</sup>, Maartje J. Hooning<sup>77</sup>, John L. Hopper<sup>60</sup>, Tony Howell<sup>78</sup>, Dezheng Huo<sup>79</sup>, Hidemi Ito<sup>80,81</sup>, Motoki Iwasaki<sup>82</sup>, Anna Jakubowska<sup>83,84</sup>, Wolfgang Janni<sup>85</sup>, Esther M. John<sup>86</sup>, Audrey Jung<sup>16</sup>, Rudolf Kaaks<sup>16</sup>, Daehee Kang<sup>35,36,87</sup>, Pooja Middha Kapoor<sup>16,88</sup>, Elza Khusnutdinova<sup>17,89</sup>, Sung-Won Kim<sup>90</sup>, Cari M. Kitahara<sup>91</sup>, Stella Koutros<sup>7</sup>, Peter Kraft<sup>54,55</sup>, Vessela N. Kristensen<sup>92,93</sup>, Ava Kwong<sup>32,94,95</sup>, Diether Lambrechts<sup>96,97</sup>, Loic Le Marchand<sup>98</sup>, Jingmei Li<sup>99</sup>, Sara Lindström<sup>100,101</sup>, Martha Linet<sup>91</sup>, Wing-Yee Lo<sup>25,26</sup>, Jirong Long<sup>15</sup>, Artitaya Lophatananon<sup>103</sup>, Jan Lubinski<sup>83</sup>, Mehdi Manoochehri<sup>70</sup>, Siranoush Manoukian<sup>104</sup>, Sara Margolin<sup>69,105</sup>, Elena Martinez<sup>53,106</sup>, Keitaro Matsuo<sup>80,81</sup>, Dimitris Mavroudis<sup>107</sup>, Alfons Meindl<sup>108</sup>, Usha Menon<sup>109</sup>, Roger L. Milne<sup>59,60,110</sup>, Nur Aishah Mohd Taib<sup>111</sup>, Kenneth Muir<sup>102,103</sup>, Anna Marie Mulligan<sup>112,113</sup>, Susan L. Neuhausen<sup>114</sup>, Heli Nevanlinna<sup>115</sup>, Patrick Neven<sup>116</sup>, William G. Newman<sup>45,46</sup>, Kenneth Offit<sup>117,118</sup>, Olufunmilayo I. Olopade<sup>79</sup>, Andrew F. Olshan<sup>119</sup>, Janet E. Olson<sup>120</sup>, Håkan Olsson<sup>13</sup>, Sue K. Park<sup>35,36,87</sup>, Tjong-Won Park-Simon<sup>1</sup>, Julian Peto<sup>41</sup>, Dijana Plaseska-Karanfilska<sup>121</sup>, Esther Pohl-Rescigno<sup>73,74,75</sup>, Nadege Presneau<sup>42</sup>, Brigitte Rack<sup>85</sup>, Paolo Radice<sup>122</sup>, Muhammad U. Rashid<sup>70,123</sup>, Gad Rennert<sup>124</sup>, Hedy S. Rennert<sup>124</sup>, Atocha Romero<sup>125</sup>, Matthias Ruebner<sup>66</sup>, Emmanouil Saloustros<sup>126</sup>, Marjanka K. Schmidt<sup>127,128</sup>, Rita K. Schmutzler<sup>73,74,75</sup>, Michael O. Schneider<sup>66</sup>, Minouk J. Schoemaker<sup>129</sup>, Christopher Scott<sup>120</sup>, Chen-Yang Shen<sup>130,131</sup>, Xiao-Ou Shu<sup>15</sup>, Jacques Simard<sup>132</sup>, Susan Slager<sup>120</sup>, Snezhana Smichkoska<sup>133</sup>, Melissa C. Southey<sup>110,134</sup>, John J. Spinelli<sup>135,136</sup>, Jennifer Stone<sup>60,137</sup>, Harald Surowy<sup>29,30</sup>, Anthony J. Swerdlow<sup>129,138</sup>, Rulla M. Tamimi<sup>54,55,139</sup>, William J. Tapper<sup>140</sup>, Soo H. Teo<sup>111,141</sup>, Mary Beth Terry<sup>142</sup>, Amanda E. Toland<sup>143</sup>, Rob A. E. M. Tollenaar<sup>144</sup>, Diana Torres<sup>70,145</sup>, Gabriela Torres-Mejía<sup>146</sup>, Melissa A. Troester<sup>119</sup>, Thérèse Truong<sup>65</sup>, Shoichiro Tsugane<sup>147</sup>, Michael Untch<sup>148</sup>, Celine M. Vachon<sup>149</sup>, Ans M. W. van den Ouweland<sup>150</sup>, Elke M. van Veen<sup>45,46</sup>, Joseph Vijai<sup>117,118</sup>, Camilla Wendt<sup>105</sup>, Alicja Wolk<sup>68,151</sup>, Jyh-Cherng Yu<sup>152</sup>, Wei Zheng<sup>15</sup>, Argyrios Ziogas<sup>10</sup>, Elad Ziv<sup>153</sup>, ABCTB Investigators\*, NBCS Collaborators\*, Alison M. Dunning<sup>165</sup>, Paul D. P. Pharoah<sup>6,165</sup>, Detlev Schindler<sup>166</sup>, Peter Devilee<sup>167,168</sup> & Douglas F. Easton<sup>6,165</sup>

Received: 13 March 2019

Accepted: 9 August 2019

Published online: 29 August 2019

<sup>1</sup>Gynaecology Research Unit, Hannover Medical School, Hannover, Germany. <sup>2</sup>Genome Diagnostics Program, IFOM - the FIRC Institute of Molecular Oncology, Milan, Italy. <sup>3</sup>Translational Cancer Research Area, University of Eastern Finland, Kuopio, Finland. <sup>4</sup>Institute of Clinical Medicine, Pathology and Forensic Medicine, University of Eastern Finland, Kuopio, Finland. <sup>5</sup>Imaging Center, Department of Clinical Pathology, Kuopio University Hospital, Kuopio, Finland. <sup>6</sup>Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. <sup>7</sup>Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA. <sup>8</sup>Fred A. Litwin Center for Cancer Genetics, Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto, ON, Canada. <sup>9</sup>Department of Molecular Genetics, University of Toronto, Toronto, ON, Canada. <sup>10</sup>Department of Epidemiology, Genetic Epidemiology Research Institute, University of California Irvine, Irvine, CA, USA. <sup>11</sup>Division of Clinical Epidemiology and Aging Research, C070, German Cancer Research Center (DKFZ), Heidelberg, Germany. <sup>12</sup>Department of Public Health Sciences, and Cancer Research Institute, Queen's University, Kingston, ON, Canada. <sup>13</sup>Department of Cancer Epidemiology, Clinical Sciences, Lund University, Lund, Sweden. <sup>14</sup>Department of Gynecology and Obstetrics, Comprehensive Cancer Center ER-EMN, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany. <sup>15</sup>Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA. <sup>16</sup>Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany. <sup>17</sup>Institute of Biochemistry and Genetics of the Ufa Federal Research Centre of the Russian Academy of Sciences, Ufa, Russia. <sup>18</sup>Department of Oncology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland. <sup>19</sup>Department of Oncology, Örebro University Hospital, Örebro, Sweden. <sup>20</sup>Department of Radiation Oncology, Hannover Medical School, Hannover, Germany. <sup>21</sup>N.N. Alexandrov Research Institute of Oncology and Medical Radiology, Minsk, Belarus. <sup>22</sup>Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark. <sup>23</sup>Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark. <sup>24</sup>Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. <sup>25</sup>Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany. <sup>26</sup>University of Tübingen, Tübingen, Germany. <sup>27</sup>German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany. <sup>28</sup>Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany. <sup>29</sup>Molecular Epidemiology Group, C080, German Cancer Research Center (DKFZ), Heidelberg, Germany. <sup>30</sup>Molecular Biology of Breast Cancer, University Womens Clinic Heidelberg, University of Heidelberg, Heidelberg, Germany. <sup>31</sup>Genomic Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany. <sup>32</sup>Hong Kong Hereditary Breast Cancer Family Registry, Cancer Genetics Centre, Happy Valley, Hong Kong. <sup>33</sup>Department of Pathology, Hong Kong Sanatorium and Hospital, Happy Valley, Hong Kong. <sup>34</sup>Cancer Epidemiology Group, University Cancer Center Hamburg (UCCH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany. <sup>35</sup>Department of Biomedical Sciences, Seoul National University Graduate School, Seoul, Korea. <sup>36</sup>Cancer Research Institute, Seoul National University, Seoul, Korea. <sup>37</sup>Westmead Institute for Medical Research, University of Sydney, Sydney, New South Wales, Australia. <sup>38</sup>Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA. <sup>39</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. <sup>40</sup>Department of Clinical Genetics, Fox Chase Cancer Center, Philadelphia, PA, USA. <sup>41</sup>Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK. <sup>42</sup>Department of Biomedical Sciences, Faculty of Science and Technology, University of Westminster, London, UK. <sup>43</sup>Cancer Sciences Academic Unit, Faculty of Medicine, University of Southampton, Southampton, UK. <sup>44</sup>Institute of Human Genetics, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany. <sup>45</sup>Division of Evolution and Genomic Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK. <sup>46</sup>Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK. <sup>47</sup>David Geffen School of Medicine, Department of Medicine Division of Hematology and Oncology, University of California at Los Angeles, Los Angeles, CA, USA. <sup>48</sup>Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh Medical School, Edinburgh, UK. <sup>49</sup>Cancer Research UK Edinburgh Centre, Edinburgh, UK. <sup>50</sup>Department of Breast Surgery, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark. <sup>51</sup>School of Public Health, Curtin University, Perth, Western Australia, Australia. <sup>52</sup>Genomic Medicine Group, Galician Foundation of Genomic Medicine, Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Complejo Hospitalario Universitario de Santiago, SERGAS, Santiago de Compostela, Spain. <sup>53</sup>Moore's Cancer Center, University of California San Diego, La Jolla, CA, USA. <sup>54</sup>Program in Genetic Epidemiology and Statistical Genetics, Harvard T.H. Chan School of Public Health, Boston, MA, USA. <sup>55</sup>Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA. <sup>56</sup>Behavioral and Epidemiology Research Group, American Cancer Society, Atlanta, GA, USA. <sup>57</sup>Division of Genetics and Epidemiology, Institute of Cancer Research, London, UK. <sup>58</sup>Medical Oncology Department, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria San Carlos (IdISSC), Centro Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain. <sup>59</sup>Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Victoria, Australia. <sup>60</sup>Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia. <sup>61</sup>Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia. <sup>62</sup>Department of Medicine, McGill University, Montréal, QC, Canada. <sup>63</sup>Division of Clinical Epidemiology, Royal Victoria Hospital, McGill University, Montréal, QC, Canada. <sup>64</sup>Department of Dermatology, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT, USA. <sup>65</sup>Cancer & Environment Group, Center for Research in Epidemiology and Population Health (CESP), INSERM, University Paris-Sud, University Paris-Saclay, Villejuif, France. <sup>66</sup>Department of Gynaecology and Obstetrics, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany. <sup>67</sup>Department of Preventive Medicine, Keck School of Medicine, University of

Southern California, Los Angeles, CA, USA. <sup>68</sup>Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. <sup>69</sup>Department of Oncology, Södersjukhuset, Stockholm, Sweden. <sup>70</sup>Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany. <sup>71</sup>Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore. <sup>72</sup>Department of Surgery, National University Health System, Singapore, Singapore. <sup>73</sup>Center for Familial Breast and Ovarian Cancer, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. <sup>74</sup>Center for Molecular Medicine Cologne (CMMC), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. <sup>75</sup>Center for Integrated Oncology (CIO), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. <sup>76</sup>Family Cancer Clinic, The Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital, Amsterdam, The Netherlands. <sup>77</sup>Department of Medical Oncology, Family Cancer Clinic, Erasmus MC Cancer Institute, Rotterdam, The Netherlands. <sup>78</sup>Division of Cancer Sciences, University of Manchester, Manchester, UK. <sup>79</sup>Center for Clinical Cancer Genetics, The University of Chicago, Chicago, IL, USA. <sup>80</sup>Division of Cancer Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan. <sup>81</sup>Division of Cancer Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan. <sup>82</sup>Division of Epidemiology, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan. <sup>83</sup>Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland. <sup>84</sup>Independent Laboratory of Molecular Biology and Genetic Diagnostics, Pomeranian Medical University, Szczecin, Poland. <sup>85</sup>Department of Gynaecology and Obstetrics, University Hospital Ulm, Ulm, Germany. <sup>86</sup>Department of Medicine, Division of Oncology, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA, USA. <sup>87</sup>Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea. <sup>88</sup>Faculty of Medicine, University of Heidelberg, Heidelberg, Germany. <sup>89</sup>Department of Genetics and Fundamental Medicine, Bashkir State University, Ufa, Russia. <sup>90</sup>Department of Surgery, Daerim Saint Mary's Hospital, Seoul, Korea. <sup>91</sup>Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA. <sup>92</sup>Department of Cancer Genetics, Institute for Cancer Research, Oslo University Hospital-Radiumhospitalet, Oslo, Norway. <sup>93</sup>Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway. <sup>94</sup>Department of Surgery, The University of Hong Kong, Pok Fu Lam, Hong Kong. <sup>95</sup>Department of Surgery, Hong Kong Sanatorium and Hospital, Happy Valley, Hong Kong. <sup>96</sup>VIB Center for Cancer Biology, VIB, Leuven, Belgium. <sup>97</sup>Laboratory for Translational Genetics, Department of Human Genetics, University of Leuven, Leuven, Belgium. <sup>98</sup>Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI, USA. <sup>99</sup>Human Genetics Division, Genome Institute of Singapore, Singapore, Singapore. <sup>100</sup>Department of Epidemiology, University of Washington School of Public Health, Seattle, WA, USA. <sup>101</sup>Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA. <sup>102</sup>Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK. <sup>103</sup>Division of Population Health, Health Services Research and Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK. <sup>104</sup>Unit of Medical Genetics, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy. <sup>105</sup>Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden. <sup>106</sup>Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, USA. <sup>107</sup>Department of Medical Oncology, University Hospital of Heraklion, Heraklion, Greece. <sup>108</sup>Department of Gynecology and Obstetrics, Ludwig Maximilian University of Munich, Munich, Germany. <sup>109</sup>MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, University College London, London, UK. <sup>110</sup>Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia. <sup>111</sup>Breast Cancer Research Unit, UM Cancer Research Institute, University of Malaya Medical Centre, Kuala Lumpur, Malaysia. <sup>112</sup>Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada. <sup>113</sup>Laboratory Medicine Program, University Health Network, Toronto, ON, Canada. <sup>114</sup>Department of Population Sciences, Beckman Research Institute of City of Hope, Duarte, CA, USA. <sup>115</sup>Department of Obstetrics and Gynecology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland. <sup>116</sup>Leuven Multidisciplinary Breast Center, Department of Oncology, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium. <sup>117</sup>Clinical Genetics Research Lab, Department of Cancer Biology and Genetics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. <sup>118</sup>Clinical Genetics Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. <sup>119</sup>Department of Epidemiology, Gillings School of Global Public Health and UNC Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. <sup>120</sup>Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA. <sup>121</sup>Research Centre for Genetic Engineering and Biotechnology 'Georgi D. Efremov', Macedonian Academy of Sciences and Arts, Skopje, Republic of Macedonia. <sup>122</sup>Unit of Molecular Bases of Genetic Risk and Genetic Testing, Department of Research, Fondazione IRCCS Istituto Nazionale dei Tumori (INT), Milan, Italy. <sup>123</sup>Department of Basic Sciences, Shaikat Khanum Memorial Cancer Hospital and Research Centre (SKMCH & RC), Lahore, Pakistan. <sup>124</sup>Clalit National Cancer Control Center, Carmel Medical Center and Technion Faculty of Medicine, Haifa, Israel. <sup>125</sup>Medical Oncology Department, Hospital Universitario Puerta de Hierro, Madrid, Spain. <sup>126</sup>Department of Oncology, University Hospital of Larissa, Larissa, Greece. <sup>127</sup>Division of Molecular Pathology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands. <sup>128</sup>Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital, Amsterdam, The Netherlands. <sup>129</sup>Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK. <sup>130</sup>Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan. <sup>131</sup>School of Public Health, China Medical University, Taichung, Taiwan. <sup>132</sup>Genomics Center, Centre Hospitalier Universitaire de Québec – Université Laval Research Center, Québec City, QC, Canada. <sup>133</sup>Ss. Cyril and Methodius University in Skopje, Medical Faculty, University Clinic of Radiotherapy and Oncology, Skopje, Republic of Macedonia. <sup>134</sup>Department of Clinical Pathology, The University of Melbourne, Melbourne, Victoria, Australia. <sup>135</sup>Population Oncology, BC Cancer, Vancouver, BC, Canada. <sup>136</sup>School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada. <sup>137</sup>The Curtin UWA Centre for Genetic Origins of Health and Disease, Curtin University and University of Western Australia, Perth, Western Australia, Australia. <sup>138</sup>Division of Breast Cancer Research, The Institute of Cancer Research, London, UK. <sup>139</sup>Channing Division of Network Medicine, Department of

Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. <sup>140</sup>Faculty of Medicine, University of Southampton, Southampton, UK. <sup>141</sup>Cancer Research Malaysia, Subang Jaya, Selangor, Malaysia. <sup>142</sup>Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA. <sup>143</sup>Department of Cancer Biology and Genetics, The Ohio State University, Columbus, OH, USA. <sup>144</sup>Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands. <sup>145</sup>Institute of Human Genetics, Pontificia Universidad Javeriana, Bogota, Colombia. <sup>146</sup>Center for Population Health Research, National Institute of Public Health, Mexico, Mexico. <sup>147</sup>Center for Public Health Sciences, National Cancer Center, Tokyo, Japan. <sup>148</sup>Department of Gynecology and Obstetrics, Helios Clinics Berlin-Buch, Berlin, Germany. <sup>149</sup>Department of Health Science Research, Division of Epidemiology, Mayo Clinic, Rochester, MN, USA. <sup>150</sup>Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands. <sup>151</sup>Department of Surgical Sciences, Uppsala University, Uppsala, Sweden. <sup>152</sup>Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan. <sup>153</sup>Department of Medicine, Institute for Human Genetics, UCSF Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA. <sup>154</sup>Westmead Institute for Medical Research, University of Sydney, Sydney, New South Wales, Australia. <sup>155</sup>Department of Research, Vestre Viken Hospital, Drammen, Norway. <sup>156</sup>iFIT Cluster of Excellence, University of Tübingen, Tübingen, Germany. <sup>157</sup>Section for Breast- and Endocrine Surgery, Department of Cancer, Division of Surgery, Cancer and Transplantation Medicine, Oslo University Hospital-Ullevål, Oslo, Norway. <sup>158</sup>Department of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway. <sup>159</sup>Department of Pathology, Akershus University Hospital, Lørenskog, Norway. <sup>160</sup>Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway. <sup>161</sup>Department of Oncology, Division of Surgery, Cancer and Transplantation Medicine, Oslo University Hospital-Radiumhospitalet, Oslo, Norway. <sup>162</sup>National Advisory Unit on Late Effects after Cancer Treatment, Oslo University Hospital-Radiumhospitalet, Oslo, Norway. <sup>163</sup>Department of Oncology, Akershus University Hospital, Lørenskog, Norway. <sup>164</sup>Breast Cancer Research Consortium, Oslo University Hospital, Oslo, Norway. <sup>165</sup>Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK. <sup>166</sup>Institute of Human Genetics, Biocenter, University of Würzburg, Würzburg, Germany. <sup>167</sup>Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands. <sup>168</sup>Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands. \*A comprehensive list of consortium members appears at the end of the paper. Correspondence and requests for materials should be addressed to T.D. (email: [doerk.thilo@mh-hannover.de](mailto:doerk.thilo@mh-hannover.de))

**Fanconi anemia (FA) is a genetically heterogeneous disorder with 22 disease-causing genes reported to date. In some FA genes, monoallelic mutations have been found to be associated with breast cancer risk, while the risk associations of others remain unknown. The gene for FA type C, *FANCC*, has been proposed as a breast cancer susceptibility gene based on epidemiological and sequencing studies. We used the Oncoarray project to genotype two truncating *FANCC* variants (p.R185X and p.R548X) in 64,760 breast cancer cases and 49,793 controls of European descent. *FANCC* mutations were observed in 25 cases (14 with p.R185X, 11 with p.R548X) and 26 controls (18 with p.R185X, 8 with p.R548X). There was no evidence of an association with the risk of breast cancer, neither overall (odds ratio 0.77, 95%CI 0.44–1.33,  $p = 0.4$ ) nor by histology, hormone receptor status, age or family history. We conclude that the breast cancer risk association of these two *FANCC* variants, if any, is much smaller than for *BRCA1*, *BRCA2* or *PALB2* mutations. If this applies to all truncating variants in *FANCC* it would suggest there are differences between FA genes in their roles on breast cancer risk and demonstrates the merit of large consortia for clarifying risk associations of rare variants.**

Fanconi Anemia (FA) is a rare recessively inherited disorder characterized by congenital malformations, progressive bone marrow failure and predisposition to cancer. Twenty-two different FA causative genes have now been identified whose products act in concert to mediate DNA interstrand crosslink repair<sup>1–3</sup>. At least seven of them (*BRCA2/FANCD2*, *PALB2/FANCN*, *RAD51C/FANCO*, *RAD51/FANCR*, *BRCA1/FANCS*, *XRCC2/FANCU*, and *RFWD3/FANCW*) are involved in different stages of homology-directed recombinational DNA repair (HRR), a pathway for error-free maintenance of the genome during replication and after DNA damage. A number of FA genes (including *BRCA1/FANCS*, *BRCA2/FANCD1* and *PALB2/FANCN*) have been shown to be breast cancer susceptibility genes<sup>3</sup>. The products of *BRCA1*, *BRCA2*, and *PALB2* are central to early stages of HRR. Further interactors in this pathway, in particular *BRIP1/FANCI*, mainly have been linked to ovarian cancer risk<sup>4,5</sup>. It is less known to what extent other FA gene products may play a role in the inherited component of breast cancer susceptibility. Few of these other FA genes have been tested for mutations in relatively small breast cancer case-control studies, thus far<sup>6–9</sup>.

Early studies suggested that blood relatives of FA patients show an increased risk of breast cancer, although these findings have not been corroborated in a replication study and could not assess distinct FA complementation groups due to lack of genetic information at that time<sup>10–13</sup>. After FA was stratified into subsets defined by complementation assays, an increased risk of breast cancer was attributed to heterozygous carriers of *FANCC* mutations<sup>13</sup>. Historically, this was the first of the FA genes to be identified and accounts for 8–15% of FA cases<sup>14–16</sup>. More recently, *FANCC* has been suggested as a candidate breast cancer susceptibility gene in an exome sequencing study of 33 familial breast cancer cases and extension to another 438 cases<sup>17</sup>. However, the evidence for an association between *FANCC* and breast cancer risk is limited by the low prevalence of mutations<sup>17,18</sup>, and much larger numbers of individuals are needed to provide sufficient power to detect associations of plausible magnitude<sup>19</sup>.



Mutation	Cases	Controls	Odds Ratio (95% CI)	p
p.R158X	14/64,778	18/49,810	0.64 (0.32; 1.29)	0.215
p.R548X	11/64,788	8/49,816	1.03 (0.41; 2.56)	0.942
All <i>FANCC</i>	25/64,760	26/49,793	0.77 (0.44; 1.33)	0.345

**Table 1.** Overall analysis of *FANCC* variants p.R158X and p.R548X. Association analyses of *FANCC* variants p.R158X and p.R548X with overall breast cancer risk. Results are given as odds ratios (OR) with 95% confidence interval (CI) and p-value (p).

In the present study, we genotyped two truncating variants of *FANCC* (p.R158X and p.R548X) using the Oncoarray (see Methods) in 64,760 female breast cancer cases and 49,793 female population controls of European descent. Both mutations are disease-causing in European FA patients and are recurrent in the FA mutation database<sup>20</sup>.

## Results

We identified the truncating *FANCC* variants p.R158X (rs121917783) and p.R548X (rs104886457) in 40 of 153,899 individuals and 20 of 153,904 individuals, respectively. All mutation carriers were heterozygotes. Carrier distributions per study and intensity cluster plots for Europeans (which included the majority of mutation carriers) are shown in Supplementary Table 1 and Supplementary Fig. 1, respectively. Since the majority of carriers were women of European ancestry, we restricted the subsequent case-control association analysis to participants from this population. Logistic regression analyses were adjusted for study and 15 principal components<sup>21</sup>.

In Europeans, the two *FANCC* variants were observed in 25/64,760 cases (14 with p.R158X, 11 with p.R548X) and in 26/49,793 controls (18 with p.R158X, 8 with p.R548X). There was no evidence of association between the *FANCC* variants and breast cancer risk, either for carriers of both variants combined (OR 0.77, 95%CI 0.44–1.33,  $p = 0.35$ ), or for either variant individually (Table 1). Similarly, we found no evidence for an association with estrogen receptor (ER)-negative (OR 0.91, 0.35–2.37) or ER-positive (OR 0.67, 0.37–1.28) disease, nor for subsets of disease defined by age at diagnosis (<50 years), bilaterality, family history, histological morphology, grade or nodal status (Table 2).

For comparison, we also analysed the *PALB2/FANCN*\*p.R414X truncating variant that was genotyped in parallel on the same array. This variant was detected in 22/64,780 cases and 3/49,825 controls and was significantly associated with risk of breast cancer (OR 5.89, 95%CI 1.76–19.74,  $p = 0.004$ ). The variant carriers were markedly enriched among cases with ER-negative tumours ( $p = 9.4 \times 10^{-6}$ ;  $p_{\text{diff}} = 0.0006$  in a log-likelihood ratio test) and specifically triple-negative breast tumours ( $p = 3.8 \times 10^{-7}$ ;  $p_{\text{diff}} = 0.0001$ ). The p.R414X truncating variant was also associated with ductal morphology, a positive first-degree family history of breast cancer, early age at diagnosis (<50 years), and low-differentiated tumours (grade 3) (Suppl. Table 1). Hence, by contrast with the two tested *FANCC* variants, p.R158X and p.R548X, the *FANCN/PALB2* variant p.R414X was strongly associated with overall and with ER-negative disease under the same genotyping and analysis conditions.

## Discussion

Functional defects of DNA repair are a hallmark of genomic instability syndromes as well as of carcinogenesis. FA is a genome instability and cancer prone disorder that has been investigated for breast cancer predisposition in homozygotes and heterozygotes for more than three decades<sup>11,12</sup>. Monoallelic mutations in five FA genes (*BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, *BRIP1*) have now been confirmed to predispose to breast or ovarian cancer while biallelic mutations in these genes cause FA<sup>3</sup>. However, the role of the FA genes most commonly mutated, *FANCA* and *FANCC*, in the risk of developing breast cancer has remained uncertain. Epidemiological and segregation studies have provided some evidence of an increased breast cancer risk for grandmothers of FA patients, particularly those who carry the *FANCC* mutation<sup>13</sup>.

A previous sequencing study of Australian multiple-case breast cancer families had identified truncating variants in *FANCC* in 3 of 438 multiple-case breast cancer families but in none of 464 healthy controls, suggestive of a predisposing role for *FANCC* variants in breast cancer<sup>17</sup>. One of these variants, p.R158X, was also screened in our study. p.R158X was first reported shortly after the identification of the *FANCC* gene, and thus is one of the earliest recognized FA-causing mutations. Although representing an apparent nonsense mutation in exon 6, it also results in exon 6 being spliced out of a proportion of transcripts, suggesting this variant may alter splice site selection, with the aberrant transcript retaining the reading frame<sup>22</sup>. p.R548X, also an early-detected *FANCC* truncating variant<sup>23</sup>, is an authentic stop mutation in exon 14, and although in the last exon, it proved to be clearly pathogenic for FA<sup>24</sup>.

The fact that these two disease-causing variants have been frequently observed in European patients with FA<sup>20</sup> prompted us to investigate their association with breast cancer in a large case-control study. However, we did not observe a significant difference between their frequency among breast cancer cases and controls. The upper 95% confidence limit was 1.33, thus excluding a two-fold or greater increase in risk found for moderate- or high-penetrance alleles in predisposition genes such as *CHEK2* and *ATM*. Moreover, we found no evidence of association in subgroups defined by earlier age at onset, a positive family history of breast cancer, bilateral occurrence, or defined tumor parameters (histology, grade or hormone receptor status). However, confidence intervals for those estimates for subsets were wider as numbers were small – in particular we could not rule out a 2-fold increased risk for ER-negative or triple-negative breast cancer.

In contrast, we observed a clear association between the *PALB2/FANCN* variant p.R414X and breast cancer risk. *PALB2* is an established breast cancer susceptibility gene, and the investigated mutation p.R414X<sup>25</sup> occurred

Stratum	Cases	Odds Ratio (95% CI)	p
ER-negative	5/10,124	0.91 (0.35; 2.37)	0.845
ER-positive	14/40,855	0.67 (0.37; 1.28)	0.223
TNBC	2/4,126	0.89 (0.21; 3.77)	0.877
Ductal	6/36,695	0.33 (0.13; 0.80)	0.014
Lobular	4/6,842	1.27 (0.43; 3.69)	0.665
High grade	3/14,582	0.39 (0.12; 1.31)	0.129
Node-positive	1/15,937	0.14 (0.02; 1.00)	0.050
Familial	7/9,720	1.01 (0.43; 2.35)	0.988
Premenopausal	12/22,232	1.09 (0.55; 2.16)	0.814
Bilateral	0/2,741	—	0.645

**Table 2.** Analysis of *FANCC* variants (p.R158X and p.R548X combined) by tumour subtype. Association analyses of *FANCC* variants p.R158X and p.R548X with breast cancer risk for subgroups. Results are given as odds ratios (OR) with 95% confidence interval (CI) and p-value (p). Cases in subgroups were compared to the frequency 26/ 49,793 for all controls (derived from Table 1). Familial cases were defined as those with a first-degree family history of breast cancer; premenopausal cases were those with age at diagnosis <50 years. ER, estrogen-receptor; TNBC, triple-negative breast cancer.

at a similar frequency to the tested *FANCC* mutations. The observed six-fold enrichment of p.R414X in breast cancer patients is in line with previous findings for other *PALB2* founder mutations<sup>26–28</sup> and in the upper range of the overall mutational effect size in *PALB2* case-control sequencing studies<sup>29,30</sup>. We confirmed stronger associations with ER-negative breast cancer, with familial breast cancer and with a high tumor grade<sup>31</sup>. While genotyping arrays such as the Oncoarray are primarily used for evaluating common variants, these data confirm that the array provides a robust platform for evaluating even very rare alleles.

Although *PALB2* and *FANCC* are both FA genes, their products exert different roles in the recognition and repair of DNA damage. *FANCC* is a component of the FA core complex which is thought to recognize an inter-strand crosslink. *FANCL*, an E3 ubiquitin ligase in the core complex, ubiquitinates *FANCI* and *FANCD2*. After many nuclease and translesion polymerase steps, a DNA double stranded intermediate is formed and its repair requires proteins from the homology-directed repair pathway, including *FANCD1/BRCA2* and *FANCN/PALB2*. While truncating variants in *BRCA2* and *PALB2* confer a substantial risk of breast cancer, our study suggests that truncating *FANCC* variants do not confer a comparable risk. It is possible that members of the FA core complex that act upstream of HRR are less relevant for breast cancer due to their more specialized function in the repair of crosslinks while *BRCA1*, *BRCA2*, and *PALB2* function more globally at DNA double-strand breaks. On the other hand, there is some evidence that truncating mutations in another gene involved in the early detection of intra-strand crosslinks, *FANCM*, are associated with both breast and ovarian cancer risk<sup>32–34</sup>, though *FANCM* is part of an anchor complex rather than the FA core complex and is not considered a classical FA gene<sup>35,36</sup>. It is also possible that the two prototype *FANCC* truncating variants analysed here, despite being FA-causing, have reduced penetrance for breast cancer due to some residual function, and other particular *FANCC* variants may confer a more substantial risk. More work will be required to clarify the role of each FA core complex member for breast cancer susceptibility.

In conclusion, our study findings suggest important differences between FA genes, indicating that truncating variants in *FANCC* do not confer a high overall risk of breast cancer unlike *PALB2*, *BRCA1* and *BRCA2*. Our study does not exclude a role of monoallelic *FANCC* variants as low-penetrance alleles for breast cancer or as a genetic risk factor for certain breast cancer subgroups. Very large datasets, such as those generated through the BCAC, are critical to evaluate such rare mutations.

## Methods

**Patients.** A total of 87 studies from the Breast Cancer Association Consortium (BCAC), of which 78 were case-control studies (some nested within prospective cohort studies) and 9 were case-only studies, contributed data as summarized in Supplementary Table 1. All studies provided data on disease status and age at diagnosis/observation, and the majority provided information on clinico-pathological and epidemiological factors, which have been curated and incorporated into the BCAC database (version 6). All participating studies were approved by their appropriate ethics review boards and all subjects provided informed consent. A list of the ethics review boards by study is provided in Supplementary Table 3.

**Genotyping.** The Illumina OncoArray design and genotyping procedure have been described previously<sup>21,37</sup>. In brief, approximately 72,000 variants were selected, among others, for inclusion on the array specifically for their potential relevance to breast cancer, based on prior evidence of association with overall or subtype-specific disease, with breast density or with breast tissue specific gene expression. After genotype calling and quality control of the cluster file, variants with a call rate <95% in any consortium, not in Hardy-Weinberg equilibrium ( $P < 10^{-7}$  in controls or  $P < 10^{-12}$  in cases) or with concordance <98% among 5,280 duplicate pairs were excluded. We also excluded samples with extreme heterozygosity (>4.89 standard deviations [SD] from the mean for the respective ethnicity). The final dataset, before restriction based on ethnicity, consisted of 153,673 samples of which 89,733 were cases and 63,940 were controls.

**Statistical analyses.** Per-allele odds ratios and 95% confidence intervals were generated using logistic regression with adjustment for principal components and study. Principal component analysis was performed using data for 33,661 uncorrelated SNPs (which included 2,318 markers of continental ancestry) with a MAF  $\geq$  0.05 and maximum correlation of 0.1, using purpose-written PCCalc software (written by Jonathan Tyrer and available at <http://ccge.medschl.cam.ac.uk/software/pccalc/>).

We also estimated subtype-specific per-allele ORs after restricting the cases by hormone receptor and/or HER2/neu status, by tumor grade, by ductal or lobular morphology, by nodal status, by bilateral occurrence of the tumor, by early diagnosis (<50 years), and by first-degree family history of breast cancer, using available BCAC data for the cases. Since we analysed 3 variants across 10 subgroups, a two-sided p-value  $\leq$  0.016 for the overall analyses and a two-sided p-value  $\leq$  0.0016 for the subgroup analyses were considered nominally significant.

**Ethical approval.** All experimental protocols were approved by the respective ethical institutions of participating BCAC centers. The study was carried out in accordance with the Declaration of Helsinki, and informed consent was obtained from all study participants.

## Data Availability

The genotyping results from the Oncoarray are available in the dbGAP repository. The *FANCC* variants analysed in the current study are deposited in the NCBI SNP database as rs121917783 and rs104886457. The datasets analysed during the current study are available from the corresponding author upon reasonable request and with permission of the Data Access Committee of the Breast Cancer Association Consortium.

## References

1. Ceccaldi, R., Sarangi, P. & D'Andrea, A. D. The Fanconi anaemia pathway: new players and new functions. *Nat. Rev. Mol. Cell Biol.* **17**, 337–349 (2016).
2. Knies, K. *et al.* Biallelic mutations in the ubiquitin ligase RFD3 cause Fanconi anemia. *J. Clin. Invest.* **127**, 3013–3027 (2017).
3. Nalepa, G. & Clapp, D. W. Fanconi anaemia and cancer: an intricate relationship. *Nat. Rev. Cancer* **18**, 168–185 (2018).
4. Ramus, S. J. *et al.* Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. *J. Natl. Cancer Inst.* **107**, 11 (2015).
5. Easton, D. F. *et al.* No evidence that protein truncating variants in BRIP1 are associated with breast cancer risk: implications for gene panel testing. *J. Med. Genet.* **53**, 298–309 (2016).
6. García, M. J. *et al.* Mutational analysis of FANCL, FANCM and the recently identified FANCI suggests that among the 13 known Fanconi Anemia genes, only FANCD1/BRCA2 plays a major role in high-risk breast cancer predisposition. *Carcinogenesis* **30**, 1898–1902 (2009).
7. Bakker, J. L. *et al.* Analysis of the novel fanconi anemia gene SLX4/FANCP in familial breast cancer cases. *Hum. Mutat.* **34**, 70–73 (2013).
8. Osorio, A. *et al.* Evaluation of rare variants in the new fanconi anemia gene ERCC4 (FANCC) as familial breast/ovarian cancer susceptibility alleles. *Hum. Mutat.* **34**, 1615–1618 (2013).
9. Lhota, F. *et al.* Hereditary truncating mutations of DNA repair and other genes in BRCA1/BRCA2/PALB2-negatively tested breast cancer patients. *Clin. Genet.* **90**, 324–333 (2016).
10. Swift, M. Fanconi's anaemia in the genetics of neoplasia. *Nature* **230**, 370–373 (1971).
11. Swift, M., Caldwell, R. J. & Chase, C. Reassessment of cancer predisposition of Fanconi anemia heterozygotes. *J. Natl. Cancer Inst.* **65**, 863–867 (1980).
12. Jacobs, P. & Karabus, C. Fanconi's anemia. A family study with 20-year follow-up including associated breast pathology. *Cancer* **54**, 1850–1853 (1984).
13. Berwick, M. *et al.* Genetic heterogeneity among Fanconi anemia heterozygotes and risk of cancer. *Cancer Res.* **67**, 9591–9596 (2007).
14. Strathdee, C. A. *et al.* Cloning of cDNAs for Fanconi's anaemia by functional complementation. *Nature* **356**, 763–767 (1992).
15. Gibson, R. A. *et al.* Genetic mapping of the FACC gene and linkage analysis in Fanconi anaemia families. *J. Med. Genet.* **31**, 868–871 (1994).
16. Verlander, P. C. *et al.* Mutation analysis of the Fanconi anemia gene FACC. *Am. J. Hum. Genet.* **54**, 595–601 (1994).
17. Thompson, E. R. *et al.* Exome sequencing identifies rare deleterious mutations in DNA repair genes FANCC and BLM as potential breast cancer susceptibility alleles. *PLoS Genet.* **8**, e1002894 (2012).
18. Seal, S. *et al.* Evaluation of Fanconi Anemia genes in familial breast cancer predisposition. *Cancer Res.* **63**, 8596–8599 (2003).
19. Ellis, N. A. & Offit, K. Heterozygous mutations in DNA repair genes and hereditary breast cancer: a question of power. *PLoS Genet.* **8**, e1003008 (2012).
20. Fanconi anemia mutation database, <http://www2.rockefeller.edu/fanconi/>.
21. Michailidou, K. *et al.* Association analysis identifies 65 new breast cancer risk loci. *Nature* **551**, 92–94 (2017).
22. Gibson, R. A. *et al.* A nonsense mutation and exon skipping in the Fanconi anaemia group C gene. *Hum Mol Genet.* **2**, 797–799 (1993).
23. Murer-Orlando, M., Llerena, J. C. Jr. & Birjandi, F. FACC gene mutations and early prenatal diagnosis of Fanconi's anaemia. *Lancet.* p. 686 (1993).
24. Lo ten Foe, J. R. *et al.* Sequence variations in the Fanconi anaemia gene, FACC: pathogenicity of 1806insA and R548X and recognition of D195V as a polymorphic variant. *Hum Genet.* **98**, 522–523 (1996).
25. Bogdanova, N. *et al.* PALB2 mutations in German and Russian patients with bilateral breast cancer. *Breast Cancer Res. Treat.* **126**, 545–550 (2011).
26. Erkkö, H. *et al.* A recurrent mutation in PALB2 in Finnish cancer families. *Nature* **446**, 316–319 (2007).
27. Southey, M. C. *et al.* A PALB2 mutation associated with high risk of breast cancer. *Breast Cancer Res.* **12**, R109 (2010).
28. Noskowitz, M. *et al.* Prevalence of PALB2 mutation c.509\_510delGA in unselected breast cancer patients from Central and Eastern Europe. *Fam. Cancer* **13**, 137–142 (2014).
29. Rahman, N. *et al.* PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. *Nat. Genet.* **39**, 165–167 (2007).
30. Tischkowitz, M. *et al.* Rare germline mutations in PALB2 and breast cancer risk: a population-based study. *Hum. Mutat.* **33**, 674–680 (2012).
31. Heikkinen, T. *et al.* The breast cancer susceptibility mutation PALB2 1592delT is associated with an aggressive tumor phenotype. *Clin. Cancer Res.* **15**, 3214–3222 (2009).
32. Kiiski, J. I. *et al.* Exome sequencing identifies FANCM as a susceptibility gene for triple-negative breast cancer. *Proc. Natl. Acad. Sci. USA* **111**, 15172–15177 (2014).
33. Peterlongo, P. *et al.* FANCM c.5791C>T nonsense mutation (rs144567652) induces exon skipping, affects DNA repair activity and is a familial breast cancer risk factor. *Hum. Mol. Genet.* **24**, 5345–5355 (2015).

34. Dicks, E. *et al.* Germline whole exome sequencing and large-scale replication identifies *FANCM* as a likely high grade serous ovarian cancer susceptibility gene. *Oncotarget* **8**, 50930–50940 (2017).
35. Catucci, I. *et al.* Individuals with *FANCM* biallelic mutations do not develop Fanconi anemia, but show risk for breast cancer, chemotherapy toxicity and may display chromosome fragility. *Genet. Med.* **20**, 452–457 (2018).
36. Bogliolo, M. *et al.* Biallelic truncating *FANCM* mutations cause early-onset cancer but not Fanconi anemia. *Genet. Med.* **20**, 458–463 (2018).
37. Milne, R. L. *et al.* Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer. *Nat. Genet.* **49**, 1767–1778 (2017).

## Acknowledgements

We thank all the individuals who took part in these studies and all the researchers, clinicians, technicians and administrative staff who have enabled this work to be carried out. We acknowledge all contributors to the COGS and OncoArray study design, chip design, genotyping, and genotype analyses. ABCFS thank Maggie Angelakos, Judi Maskiell, Gillian Dite. ABCS thanks the Blood bank Sanquin, The Netherlands. ABCTB Investigators: C.L.C., Rosemary Balleine, Robert Baxter, Stephen Braye, Jane Carpenter, Jane Dahlstrom, John Forbes, Soon Lee, Deborah Marsh, Adrienne Morey, Nirmala Pathmanathan, Rodney Scott, Allan Spigelman, Nicholas Wilcken, Desmond Yip. Samples are made available to researchers on a non-exclusive basis. The ACP study wishes to thank the participants in the Thai Breast Cancer study. Special Thanks also go to the Thai Ministry of Public Health (MOPH), doctors and nurses who helped with the data collection process. Finally, the study would like to thank Dr Prat Boonyawongviroj, the former Permanent Secretary of MOPH and Dr Pornthep Siriwanarungsan, the Department Director-General of Disease Control who have supported the study throughout. BBCS thanks Eileen Williams, Elaine Ryder-Mills, Kara Sargus. BCEES thanks Allyson Thomson, Christobel Saunders, Terry Slevin, BreastScreen Western Australia, Elizabeth Wylie, Rachel Lloyd. The BCINIS study would not have been possible without the contributions of Dr. K. Landsman, Dr. N. Gronich, Dr. A. Flugelman, Dr. W. Saliba, Dr. E. Liani, Dr. I. Cohen, Dr. S. Kalet, Dr. V. Friedman, Dr. O. Barnett of the NICCC in Haifa, and all the contributing family medicine, surgery, pathology and oncology teams in all medical institutes in Northern Israel. The BREGAN study would not have been possible without the contributions of the following: Jose Esteban Castelao, Angel Carracedo, Victor Muñoz Garzón, Alejandro Novo Domínguez, Sara Miranda Ponte, Carmen Redondo Marey, Maite Peña Fernández, Manuel Enguix Castelo, Maria Torres, Manuel Calaza (BREGAN), José Antúnez, Máximo Fraga and the staff of the Department of Pathology and Biobank of the University Hospital Complex of Santiago-CHUS, Instituto de Investigación Sanitaria de Santiago, IDIS, Xerencia de Xestión Integrada de Santiago-SERGAS; Joaquín González-Carreró and the staff of the Department of Pathology and Biobank of University Hospital Complex of Vigo, Instituto de Investigación Biomedica Galicia Sur, SERGAS, Vigo, Spain. BSUCH thanks Peter Bugert, Medical Faculty Mannheim. The CAMA study would like to recognize CONACyT for the financial support provided for this work and all physicians responsible for the project in the different participating hospitals: Dr. Germán Castelazo (IMSS, Ciudad de México, DF), Dr. Sinhué Barroso Bravo (IMSS, Ciudad de México, DF), Dr. Fernando Mainero Ratchelous (IMSS, Ciudad de México, DF), Dr. Joaquín Zarco Méndez (ISSSTE, Ciudad de México, DF), Dr. Edelmiro Pérez Rodríguez (Hospital Universitario, Monterrey, Nuevo León), Dr. Jesús Pablo Esparza Cano (IMSS, Monterrey, Nuevo León), Dr. Heriberto Fabela (IMSS, Monterrey, Nuevo León), Dr. Fausto Hernández Morales (ISSSTE, Veracruz, Veracruz), Dr. Pedro Coronel Brizio (CECAN SS, Xalapa, Veracruz) and Dr. Vicente A. Saldaña Quiroz (IMSS, Veracruz, Veracruz). CBCS thanks study participants, co-investigators, collaborators and staff of the Canadian Breast Cancer Study, and project coordinators Agnes Lai and Celine Morissette. CCGP thanks Styliani Apostolaki, Anna Margiolaki, Georgios Nintos, Maria Perraki, Georgia Saloustrou, Georgia Sevastaki, Konstantinos Pompodakis. CGPS thanks staff and participants of the Copenhagen General Population Study. For the excellent technical assistance: Dorthe Uldall Andersen, Maria Birna Arnadottir, Anne Bank, Dorte Kjeldgård Hansen. The Danish Cancer Biobank is acknowledged for providing infrastructure for the collection of blood samples for the cases. COLBCCC thanks all patients, the physicians Justo G. Olaya, Mauricio Tawil, Lilian Torregrosa, Elias Quintero, Sebastian Quintero, Claudia Ramirez, José J. Caicedo, and Jose F. Robledo, the researchers Ignacio Briceno, Fabian Gil, Angela Umana, Angela Beltran and Viviana Ariza, and the technician Michael Gilbert for their contributions and commitment to this study. Investigators from the CPSII cohort thank the participants and Study Management Group for their invaluable contributions to this research. They also acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention National Program of Cancer Registries, as well as cancer registries supported by the National Cancer Institute Surveillance Epidemiology and End Results program. CTS Investigators include Leslie Bernstein, S.L.N., James Lacey, Sophia Wang, and Huiyan Ma at the Beckman Research Institute of City of Hope, Jessica Clague DeHart at the School of Community and Global Health Claremont Graduate University, Dennis Deapen, Rich Pinder, and Eunjung Lee at the University of Southern California, Pam Horn-Ross, Christina Clarke Dur and David Nelson at the Cancer Prevention Institute of California, Peggy Reynolds, at the Department of Epidemiology and Biostatistics, University of California San Francisco, H.A-C, A.Z., and Hannah Park at the University of California Irvine, and Fred Schumacher at Case Western University. DIETCOMPLYF thanks the patients, nurses and clinical staff involved in the study. We thank the participants and the investigators of EPIC (European Prospective Investigation into Cancer and Nutrition). ESTHER thanks Hartwig Ziegler, Sonja Wolf, Volker Hermann, Christa Stegmaier, Katja Butterbach. FHRISK thanks NIHR for funding. GC-HBOC thanks Stefanie Engert, Heide Hellebrand, Sandra Kröber and LIFE - Leipzig Research Centre for Civilization Diseases (Markus Loeffler, Joachim Thiery, Matthias Nüchter, Ronny Baber). The GENICA Network: Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, and University of Tübingen, Germany [H.B., W-Y.L.], German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ) [H.B.], Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy - EXC 2180 - 390900677, Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany [Yon-Dschun Ko, Christian



Baisch], Institute of Pathology, University of Bonn, Germany [Hans-Peter Fischer], Molecular Genetics of Breast Cancer, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany [UH], Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, Germany [Thomas Brüning, Beate Pesch, Sylvia Rabstein, Anne Lotz]; and Institute of Occupational Medicine and Maritime Medicine, University Medical Center Hamburg-Eppendorf, Germany [Volker Harth]. HABCS thanks Michael Bremer and Johann H. Karstens. HEBCS thanks Sofia Khan, Johanna Kiiski, Kristiina Aittomäki, Rainer Fagerholm, Kirsimari Aaltonen, Karl von Smitten, Irja Erkkilä. HKBCS thanks Hong Kong Sanatorium and Hospital, Dr Ellen Li Charitable Foundation, The Kerry Group Kuok Foundation, National Institute of Health 1R03CA130065 and the North California Cancer Center for support. HMBCS thanks Johann H. Karstens. HUBCS thanks Shamil Gantsev. KARMA thanks the Swedish Medical Research Counsel. KBCP thanks Eija Myöhänen, Helena Kemiläinen. We thank all investigators of the KOHBRA (Korean Hereditary Breast Cancer) Study. LMBC thanks Gilian Peuteman, Thomas Van Brussel, EvyVanderheyden and Kathleen Corthouts. MABCS thanks Milena Jakimovska (RCGEB “Georgi D. Efremov”), Emilija Lazarova (University Clinic of Radiotherapy and Oncology), Katerina Kubelka-Sabit, Mitko Karadjozov (Adzibadem-Sistina Hospital), Andrej Arsovski and Liljana Stojanovska (Re-Medika Hospital) for their contributions and commitment to this study. MARIE thanks Petra Seibold, Dieter Flesch-Janys, Judith Heinz, Nadia Obi, Alina Vrieling, Sabine Behrens, Ursula Eilber, Muhabbet Celik, Til Olchers and Stefan Nickels. MBCSG (Milan Breast Cancer Study Group): Bernard Peissel, Jacopo Azzollini, Dario Zimbalatti, Daniela Zaffaroni, Bernardo Bonanni, Mariarosaria Calvello, Davide Bondavalli, Aliana Guerrieri Gonzaga, Monica Marabelli, Irene Feroce, and the personnel of the Cogentech Cancer Genetic Test Laboratory. We thank the coordinators, the research staff and especially the MMHS participants for their continued collaboration on research studies in breast cancer. MSKCC thanks Marina Corines, Lauren Jacobs. MTLGEBCS would like to thank Martine Tranchant (CHU de Québec–Université Laval Research Center), Marie-France Valois, Annie Turgeon and Lea Heguy (McGill University Health Center, Royal Victoria Hospital; McGill University) for DNA extraction, sample management and skillful technical assistance. J.S. is Chair holder of the Canada Research Chair in Oncogenetics. MYBRCA thanks study participants and research staff (particularly Patsy Ng, Nurhidayu Hassan, Yoon Sook-Yee, Daphne Lee, Lee Sheau Yee, Phuah Sze Yee and Norhashimah Hassan) for their contributions and commitment to this study. The NBCS Collaborators would like to thank the Oslo Breast Cancer Research Consortium, OSBREAC (breastcancerresearch.no/osbreac/), for providing samples and phenotype data. NBHS and SBCGS thank study participants and research staff for their contributions and commitment to the studies. We would like to thank the participants and staff of the Nurses’ Health Study and Nurses’ Health Study II for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data. OFBCR thanks Teresa Selander, Nayana Weerasooriya. ORIGO thanks E. Krol-Warmerdam, and J. Blom for patient accrual, administering questionnaires, and managing clinical information. The ORIGO survival data were retrieved from the Leiden hospital-based cancer registry system (ONCDOC) with the help of Dr. J. Molenaar. PBCS thanks Louise Brinton, Mark Sherman, Neonila Szeszenia-Dabrowska, Beata Peplonska, Witold Zatonski, Pei Chao, Michael Stagner. The ethical approval for the POSH study is MREC /00/6/69, UKCRN ID: 1137. We thank staff in the Experimental Cancer Medicine Centre (ECMC) supported Faculty of Medicine Tissue Bank and the Faculty of Medicine DNA Banking resource. PREFACE thanks Sonja Oeser and Silke Landrith. PROCAS thanks NIHR for funding. RBCS thanks Petra Bos, Jannet Blom, Ellen Crepin, Elisabeth Huijskens, Anja Kromwijk-Nieuwlaat, Annette Heemskerk, the Erasmus MC Family Cancer Clinic. We thank the SEARCH and EPIC teams. SGBCC thanks the participants and research coordinator Ms Tan Siew Li. SKKDKFZS thanks all study participants, clinicians, family doctors, researchers and technicians for their contributions and commitment to this study. We thank the SUCCESS Study teams in Munich, Duesseldorf, Erlangen and Ulm. SZBCS thanks Ewa Putresza. UCIBCS thanks Irene Masunaka. UKBGS thanks Breast Cancer Now and the Institute of Cancer Research for support and funding of the Breakthrough Generations Study, and the study participants, study staff, and the doctors, nurses and other health care providers and health information sources who have contributed to the study. We acknowledge NHS funding to the Royal Marsden/ICR NIHR Biomedical Research Centre. BCAC is funded by Cancer Research UK [C1287/A16563, C1287/A10118], the European Union’s Horizon 2020 Research and Innovation Programme (grant numbers 634935 and 633784 for BRIDGES and B-CAST respectively), and by the European Community’s Seventh Framework Programme under grant agreement number 223175 (Grant Number HEALTH-F2-2009-223175) (COGS). The EU Horizon 2020 Research and Innovation Programme funding source had no role in study design, data collection, data analysis, data interpretation or writing of the report. Genotyping of the OncoArray was funded by the NIH Grant U19 CA148065, and Cancer UK Grant C1287/A16563 and the PERSPECTIVE project supported by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research (grant GPH-129344) and, the Ministère de l’Économie, Science et Innovation du Québec through Genome Québec and the PSR-SIIRI-701 grant, and the Quebec Breast Cancer Foundation. Funding for the iCOGS infrastructure came from: the European Community’s Seventh Framework Programme under grant agreement No. 223175 (HEALTH-F2-2009-223175) (COGS), Cancer Research UK (C1287/A10118, C1287/A10710, 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, and Komen Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research Fund. The DRIVE Consortium was funded by U19 CA148065. The Australian Breast Cancer Family Study (ABCFS), BCFR-NY, BCFR-PA, BCFR-UTAH, the Northern California Breast Cancer Family Registry (NC-BCFR) and Ontario Familial Breast Cancer Registry (OFBCR) were supported by grant UM1 CA164920 from the

National Cancer Institute (USA). 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 USA Government or the BCFR. The ABCFS was also supported by the National Health and Medical Research Council of Australia, the New South Wales Cancer Council, the Victorian Health Promotion Foundation (Australia) and the Victorian Breast Cancer Research Consortium. J.L.H. is a National Health and Medical Research Council (NHMRC) Senior Principal Research Fellow. M.C.S. is a NHMRC Senior Research Fellow. The ABCS study was supported by the Dutch Cancer Society [grants NKI 2007-3839; 2009 4363]. The Australian Breast Cancer Tissue Bank (ABCTB) was supported by the National Health and Medical Research Council of Australia, The Cancer Institute NSW and the National Breast Cancer Foundation. C.L.C is a NHMRC Principal Research Fellow. The ACP study is funded by the Breast Cancer Research Trust, UK and KM and AL are supported by the NIHR Manchester Biomedical Research Centre and by the ICEP (“This work was also supported by CRUK [grant number C18281/A19169]”). The AHS study is supported by the intramural research program of the National Institutes of Health, the National Cancer Institute (grant number Z01-CP010119), and the National Institute of Environmental Health Sciences (grant number Z01-ES049030). The work of the BBCC was partly funded by ELAN-Fond of the University Hospital of Erlangen. The BBCC is funded by Cancer Research UK and Breast Cancer Now and acknowledges NHS funding to the NIHR Biomedical Research Centre, and the National Cancer Research Network (NCRN). The BCEES was funded by the National Health and Medical Research Council, Australia and the Cancer Council Western Australia and acknowledges funding from the National Breast Cancer Foundation (J.S.). The BREast Oncology GALician Network (BREGAN) is funded by Acción Estratégica de Salud del Instituto de Salud Carlos III FIS PI12/02125/Cofinanciado FEDER; Acción Estratégica de Salud del Instituto de Salud Carlos III FIS Intrasalud (PI13/01136); Programa Grupos Emergentes, Cancer Genetics Unit, Instituto de Investigación Biomedica Galicia Sur. Xerencia de Xestión Integrada de Vigo-SERGAS, Instituto de Salud Carlos III, Spain; Grant 10CSA012E, Consellería de Industria Programa Sectorial de Investigación Aplicada, PEME I + D e I + D Suma del Plan Gallego de Investigación, Desarrollo e Innovación Tecnológica de la Consellería de Industria de la Xunta de Galicia, Spain; Grant EC11-192. Fomento de la Investigación Clínica Independiente, Ministerio de Sanidad, Servicios Sociales e Igualdad, Spain; and Grant FEDER-Innterconecta. Ministerio de Economía y Competitividad, Xunta de Galicia, Spain. The BSUCH study was supported by the Dietmar-Hopp Foundation, the Helmholtz Society and the German Cancer Research Center (DKFZ). The CAMA study was funded by Consejo Nacional de Ciencia y Tecnología (CONACyT) (SALUD-2002-C01-7462). Sample collection and processing was funded in part by grants from the National Cancer Institute (NCI R01CA120120 and K24CA169004). CBCS is funded by the Canadian Cancer Society (grant #313404) and the Canadian Institutes of Health Research. CCGP is supported by funding from the University of Crete. The CECILE study was supported by Fondation de France, Institut National du Cancer (INCa), Ligue Nationale contre le Cancer, Agence Nationale de Sécurité Sanitaire, de l’Alimentation, de l’Environnement et du Travail (ANSES), Agence Nationale de la Recherche (ANR). The CGPS was supported by the Chief Physician Johan Boserup and Lise Boserup Fund, the Danish Medical Research Council, and Herlev and Gentofte Hospital. COLBCCC is supported by the German Cancer Research Center (DKFZ), Heidelberg, Germany. Diana Torres was in part supported by a postdoctoral fellowship from the Alexander von Humboldt Foundation. The American Cancer Society funds the creation, maintenance, and updating of the CPSII cohort. The CTS was supported by the California Breast Cancer Act of 1993, the California Breast Cancer Research Fund (contract 97-10500) and the National Institutes of Health (R01 CA77398, K05 CA136967, UM1 CA164917, and U01 CA199277). Collection of cancer incidence data was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885. HAC receives support from the Lon V Smith Foundation (LVS39420). The University of Westminster curates the DietCompLyf database funded by the charity Against Breast Cancer (Registered Charity No. 1121258) and the NCRN. The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by: Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l’Éducation Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center (DKFZ), Federal Ministry of Education and Research (BMBF) (Germany); the Hellenic Health Foundation, the Stavros Niarchos Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); Health Research Fund (FIS), PI13/00061 to Granada, PI13/01162 to EPIC-Murcia, Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, ISCIII RETIC (RD06/0020) (Spain); Cancer Research UK (14136 to EPIC-Norfolk; C570/A16491 and C8221/A19170 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-Norfolk, MR/M012190/1 to EPIC-Oxford) (United Kingdom). The ESTHER study was supported by a grant from the Baden Württemberg Ministry of Science, Research and Arts. Additional cases were recruited in the context of the VERDI study, which was supported by a grant from the German Cancer Aid (Deutsche Krebshilfe). FHRISK is funded from NIHR grant PGfAR 0707-10031. DGE is supported by the all Manchester NIHR Biomedical Research Centre (IS-BRC-1215-20007). The GC-HBOC (German Consortium of Hereditary Breast and Ovarian Cancer) is supported by the German Cancer Aid (grant no 110837, coordinator: R.K.S., Cologne). This work was also funded by 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). The GENICA was funded by the Federal Ministry of Education and Research (BMBF) Germany grants 01KW9975/5, 01KW9976/8, 01KW9977/0 and 01KW0114, the Robert Bosch Foundation, Stuttgart, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the

Ruhr University Bochum (IPA), Bochum, as well as the Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany. The GEPARSIXTO study was conducted by the German Breast Group GmbH. The GESBC was supported by the Deutsche Krebshilfe e. V. [70492] and the German Cancer Research Center (DKFZ). The HABCS study was supported by the Claudia von Schilling Foundation for Breast Cancer Research, by the Lower Saxonian Cancer Society, by the Friends of Hannover Medical School and by the Rudolf Bartling Foundation. The HEBCS was financially supported by the Helsinki University Central Hospital Research Fund, Academy of Finland (266528), the Finnish Cancer Society, and the Sigrid Juselius Foundation. The HERPACC was supported by MEXT Kakenhi (No. 170150181 and 26253041) from the Ministry of Education, Science, Sports, Culture and Technology of Japan, by a Grant-in-Aid for the Third Term Comprehensive 10-Year Strategy for Cancer Control from Ministry Health, Labour and Welfare of Japan, by Health and Labour Sciences Research Grants for Research on Applying Health Technology from Ministry Health, Labour and Welfare of Japan, by National Cancer Center Research and Development Fund, and “Practical Research for Innovative Cancer Control (15ck0106177h0001)” from Japan Agency for Medical Research and development, AMED, and Cancer Bio Bank Aichi. The HMBCS and HUBCS were funded by the German Research Foundation (Do761/10-1) and by the Rudolf Bartling Foundation. The HUBCS was further supported by a grant from the German Federal Ministry of Research and Education (RUS08/017), and by the Russian Foundation for Basic Research and the Federal Agency for Scientific Organizations for support the Bioresource collections and RFBR grants 14-04-97088, 17-29-06014 and 17-44-020498. Financial support for KARBAC was provided through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet, the Swedish Cancer Society, The Gustav V Jubilee foundation and Bert von Kantzows foundation. The KARMA study was supported by Märít and Hans Rausings Initiative Against Breast Cancer. The KBCP was financially supported by the special Government Funding (EVO) of Kuopio University Hospital grants, Cancer Fund of North Savo, the Finnish Cancer Organizations, and by the strategic funding of the University of Eastern Finland. The KOHBRA study was partially supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), and the National R&D Program for Cancer Control, Ministry of Health & Welfare, Republic of Korea (HI16C1127; 1020350; 1420190). LMBC is supported by the ‘Stichting tegen Kanker’. DL is supported by the FWO. The MABCS study is funded by the Research Centre for Genetic Engineering and Biotechnology “Georgi D. Efremov” and supported by the German Academic Exchange Program, DAAD. The MARIE study was supported by the Deutsche Krebshilfe e. V. [70-2892-BRI, 106332, 108253, 108419, 110826, 110828], the Hamburg Cancer Society, the German Cancer Research Center (DKFZ) and the Federal Ministry of Education and Research (BMBF) Germany [01KH0402]. MBCSG is supported by grants from the Italian Association for Cancer Research (AIRC) and by funds from the Italian citizens who allocated the 5/1000 share of their tax payment in support of the Fondazione IRCCS Istituto Nazionale Tumori, according to Italian laws (INT-Institutional strategic projects “5 × 1000”). The MCBCS was supported by the NIH grants CA192393, CA116167, CA176785 an NIH Specialized Program of Research Excellence (SPORE) in Breast Cancer [CA116201], and the Breast Cancer Research Foundation and a generous gift from the David F. and Margaret T. Grohne Family Foundation. MCCC cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further supported by Australian NHMRC grants 209057 and 396414, and by infrastructure provided by Cancer Council Victoria. Cases and their vital status were ascertained through the Victorian Cancer Registry (VCR) and the Australian Institute of Health and Welfare (AIHW), including the National Death Index and the Australian Cancer Database. The MEC was supported by NIH grants CA63464, CA54281, CA098758, CA132839 and CA164973. The MISS study is supported by funding from ERC-2011-294576 Advanced grant, Swedish Cancer Society, Swedish Research Council, Local hospital funds, Berta Kamprad Foundation, Gunnar Nilsson. The MMHS study was supported by NIH grants CA97396, CA128931, CA116201, CA140286 and CA177150. MSKCC is supported by grants from the Breast Cancer Research Foundation and Robert and Kate Niehaus Clinical Cancer Genetics Initiative. The work of MTLGEBCS was supported by the Quebec Breast Cancer Foundation, the 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. MYBRCA is funded by research grants from the Malaysian Ministry of Higher Education (UM.C/HIR/MOHE/06) and Cancer Research Malaysia. MYMAMMO is supported by research grants from Yayasan Sime Darby LPGA Tournament and Malaysian Ministry of Higher Education (RP046B-15HTM). The NBCS has received funding from the K.G. Jebsen Centre for Breast Cancer Research; the Research Council of Norway grant 193387/V50 (to A-L Børresen-Dale and V.N.K.) and grant 193387/H10 (to A-L Børresen-Dale and V.N.K.), South Eastern Norway Health Authority (grant 39346 to A-L Børresen-Dale) and the Norwegian Cancer Society (to A-L Børresen-Dale and V.N.K.). The NBHS was supported by NIH grant R01CA100374. Biological sample preparation was conducted the Survey and Biospecimen Shared Resource, which is supported by P30 CA68485. The Carolina Breast Cancer Study (NCBCS) was funded by Komen Foundation, the National Cancer Institute (P50 CA058223, U54 CA156733, U01 CA179715), and the North Carolina University Cancer Research Fund. The NGOBCS was supported by the National Cancer Center Research and Development Fund. The NHS was supported by NIH grants P01 CA87969, UM1 CA186107, and U19 CA148065. The NHS2 was supported by NIH grants UM1 CA176726 and U19 CA148065. The ORIGO study was supported by the Dutch Cancer Society (RUL 1997-1505) and the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL CP16). The PBCS was funded by Intramural Research Funds of the National Cancer Institute, Department of Health and Human Services, USA. Genotyping for PLCO was supported by the Intramural Research Program of the National Institutes of Health, NCI, Division of Cancer Epidemiology and Genetics. The PLCO is supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics and supported by contracts from the Division of Cancer Prevention, National Cancer Institute, National Institutes of Health. The POSH study is funded by Cancer Research UK (grants C1275/A11699, C1275/C22524, C1275/A19187, C1275/A15956 and



Breast Cancer Campaign 2010PR62, 2013PR044. PROCAS is funded from NIHR grant PGfAR 0707-10031. The RBCS was funded by the Dutch Cancer Society (DDHK 2004-3124, DDHK 2009-4318). The SASBAC study was supported by funding from the Agency for Science, Technology and Research of Singapore (A\*STAR), the US National Institute of Health (NIH) and the Susan G. Komen Breast Cancer Foundation. The SBCGS was supported primarily by NIH grants R01CA64277, R01CA148667, UMCA182910, and R37CA70867. Biological sample preparation was conducted the Survey and Biospecimen Shared Resource, which is supported by P30 CA68485. The scientific development and funding of this project were, in part, supported by the Genetic Associations and Mechanisms in Oncology (GAME-ON) Network U19 CA148065. SEARCH is funded by Cancer Research UK [C490/A10124, C490/A16561] and supported by the UK National Institute for Health Research Biomedical Research Centre at the University of Cambridge. The University of Cambridge has received salary support for PDPP from the NHS in the East of England through the Clinical Academic Reserve. SEBCS was supported by the BRL (Basic Research Laboratory) program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (2012-0000347). SGBCC is funded by the NUS start-up Grant, National University Cancer Institute Singapore (NCIS) Centre Grant and the NMRC Clinician Scientist Award. Additional controls were recruited by the Singapore Consortium of Cohort Studies-Multi-ethnic cohort (SCCS-MEC), which was funded by the Biomedical Research Council, grant number: 05/1/21/19/425. The Sister Study (SISTER) is supported by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences (Z01-ES044005 and Z01-ES049033). The Two Sister Study (2SISTER) was supported by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences (Z01-ES044005 and Z01-ES102245), and, also by a grant from Susan G. Komen for the Cure, grant FAS0703856. SKKDKFZS is supported by the DKFZ. The SMC is funded by the Swedish Cancer Foundation. The SZBCS was supported by Grant PBZ\_KBN\_122/P05/2004. The TNBCC was supported by: a Specialized Program of Research Excellence (SPORE) in Breast Cancer (CA116201), a grant from the Breast Cancer Research Foundation, a generous gift from the David F. and Margaret T. Grohne Family Foundation and the Ohio State University Comprehensive Cancer Center. The TWBCS is supported by the Taiwan Biobank project of the Institute of Biomedical Sciences, Academia Sinica, Taiwan. The UCIBCS component of this research was supported by the NIH [CA58860, CA92044] and the Lon V Smith Foundation [LVS39420]. The UKBGS is funded by Breast Cancer Now and the Institute of Cancer Research (ICR), London. ICR acknowledges NHS funding to the NIHR Biomedical Research Centre. The UKOPS study was funded by The Eve Appeal (The Oak Foundation) and supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. The USRT Study was funded by Intramural Research Funds of the National Cancer Institute, Department of Health and Human Services, USA. The WAABCS study was supported by grants from the National Cancer Institute of the National Institutes of Health (R01 CA89085 and P50 CA125183 and the D43 TW009112 grant), Susan G. Komen (SAC110026), the Dr. Ralph and Marian Falk Medical Research Trust, and the Avon Foundation for Women.

### Author Contributions

Study design: Thilo Dörk, Alison M. Dunning, Paul D.P. Pharoah, Detlev Schindler, and Douglas F. Easton. Data management: Manjeet K. Bolla, Qin Wang, Joe Dennis. Data and material contributions: Thilo Dörk, Paolo Peterlongo, Arto Mannermaa, Manjeet K. Bolla, Qin Wang, Joe Dennis, Thomas Ahearn, Irene L. Andrulis, Hoda Anton-Culver, Volker Arndt, Kristan J. Aronson, Annelie Augustinsson, Laura E. Beane Freeman, Matthias W. Beckmann, Alicia Beeghly, Sabine Behrens, Marina Bermisheva, Carl Blomqvist, Natalia V. Bogdanova, Stig E. Bojesen, Hiltrud Brauch, Hermann Brenner, Barbara Burwinkel, Federico Canzian, Tsun L. Chan, Jenny Chang-Claude, Stephen J. Chanock, Ji-Yeob Choi, Hans Christiansen, Christine L. Clarke, Fergus J. Couch, Kamila Czene, Mary B. Daly, Isabel dos-Santos-Silva, Miriam Dwek, Diana M. Eccles, Arif B. Ekici, Mikael Eriksson, D. Gareth Evans, Peter A. Fasching, Jonine Figueroa, Henrik Flyger, Lin Fritschi, Marika Gabrielson, Manuela Gago-Dominguez, Chi Gao, Susan M. Gapstur, Montserrat Garcia-Closas, José A. García-Sáenz, Mia M. Gaudet, Graham G. Giles, Mark S. Goldberg, David E. Goldgar, Pascal Guénel, Lothar Haeblerle, Christopher A. Haiman, Niclas Häkansson, Per Hall, Ute Hamann, Mikael Hartman, Jan Hauke, Alexander Hein, Peter Hillemann, Frans B.L. Hogervorst Maartje J. Hooning, John L. Hopper, Tony Howell, Dezheng Huo, Hidemi Ito, Motoki Iwasaki, Anna Jakubowska, Wolfgang Janni, Esther M. John, Audrey Jung, Rudolf Kaaks, Daehee Kang, Pooja Middha Kapoor, Elza Khusnutdinova, Sung-Won Kim, Cari M. Kitahara, Stella Koutros, Peter Kraft, Vessela N. Kristensen, Ava Kwong, Diether Lambrechts, Loïc Le Marchand, Jingmei Li, Sara Lindström, Martha Linet, Wing-Yee Lo, Jirong Long, Artitaya Lophatananon, Jan Lubiński, Mehdi Manoochehri, Siranoush Manoukian, Sara Margolin, Elena Martinez, Keitaro Matsuo, Dimitris Mavroudis, Alfons Menon, Usha Menon, Roger L. Milne, Nur Aishah Mohd Taib, Kenneth Muir, Anna Marie Mulligan, Susan L. Neuhausen, Heli Nevanlinna, Patrick Neven, William G. Newman, Kenneth Offit, Olufunmilayo I. Olopade, Andrew F. Olshan, Janet E. Olson, Håkan Olsson, Sue K. Park, Tjoung-Won Park-Simon, Julian Peto, Dijana Plaseska-Karanfilska, Esther Pohl-Rescigno, Nadege Presneau, Brigitte Rack, Paolo Radice, Muhammad U. Rashid, Gad Rennert, Hedy S. Rennert, Atocha Romero, Matthias Ruebner, Emmanouil Saloustros, Marjanka K. Schmidt, Rita K. Schmutzler, Michael O. Schneider, Minouk J. Schoemaker, Christopher Scott, Chen-Yang Shen, Xiao-Ou Shu, Jacques Simard, Susan Slager, Snezhana Smichkoska, Melissa C. Southey, John J. Spinelli, Jennifer Stone, Harald Surowy, Anthony J. Swerdlow, Rulla M. Tamimi, William J. Tapper, Soo H. Teo, Mary Beth Terry, Amanda E. Toland, Rob A.E.M. Tollenaar, Diana Torres, Gabriela Torres-Mejía, Melissa A. Troester, Thérèse Truong, Shoichiro Tsugane, Michael Untch, Celine M. Vachon, Ans M.W. van den Ouweland, Elke M. van Veen, Joseph Vijai, Camilla Wendt, Alicja Wolk, Jyh-Cherng Yu, Wei Zheng, Argyrios Ziogas, Elad Ziv, ABCCTB Investigators, NBCS Collaborators, Alison M. Dunning, Paul D.P. Pharoah, Peter Devilee, Douglas F. Easton. Data analyses: Thilo Dörk, Joe Dennis; Manuscript writing: Thilo Dörk, Paolo Peterlongo, Arto Mannermaa, M.K.B., Detlev Schindler, Peter Devilee and Douglas F. Easton; Manuscript correction and approval: all authors.



## Additional Information

**Supplementary information** accompanies this paper at <https://doi.org/10.1038/s41598-019-48804-y>.

**Competing Interests:** The authors declare no competing interests.

**Publisher's note:** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2019

## Consortia ABCTB Investigators

Rosemary Balleine<sup>169</sup>, Robert Baxter<sup>170</sup>, Stephen Braye<sup>171</sup>, Jane Carpenter<sup>154</sup>, Jane Dahlstrom<sup>172,173</sup>, John Forbes<sup>174</sup>, C. Soon Lee<sup>175</sup>, Deborah Marsh<sup>176</sup>, Adrienne Morey<sup>177</sup>, Nirmala Pathmanathan<sup>178</sup>, Rodney Scott<sup>179,180</sup>, Peter Simpson<sup>181</sup>, Allan Spigelman<sup>182</sup>, Nicholas Wilcken<sup>183,184</sup>, Desmond Yip<sup>173,185</sup> & Nikolajs Zeps<sup>186</sup>

## NBCS Collaborators

Anne-Lise Børresen-Dale<sup>92,93</sup>, Grethe I. Grenaker Alnæs<sup>92</sup>, Kristine K. Sahlberg<sup>92,155,164</sup>, Lars Ottestad<sup>92</sup>, Rolf Kåresen<sup>93,157</sup>, Ellen Schlichting<sup>157</sup>, Marit Muri Holmen<sup>158</sup>, Toril Sauer<sup>93,159</sup>, Vilde Haakensen<sup>92</sup>, Olav Engebråten<sup>93,160,161</sup>, Bjørn Naume<sup>93,161</sup>, Alexander Fosså<sup>161,162</sup>, Cecile E. Kiserud<sup>161,162</sup>, Kristin V. Reinertsen<sup>161,162</sup>, Åslaug Helland<sup>92,161</sup>, Margit Riis<sup>157</sup> & Jürgen Geisler<sup>93,163</sup>

<sup>169</sup>Pathology West ICPMR, Westmead, Sydney, NSW, Australia. <sup>170</sup>Kolling Institute of Medical Research, University of Sydney, Royal North Shore Hospital, Sydney, NSW, Australia. <sup>171</sup>Pathology North, John Hunter Hospital, Newcastle, NSW, Australia. <sup>172</sup>Department of Anatomical Pathology, ACT Pathology, Canberra Hospital, Canberra, ACT, Australia. <sup>173</sup>ANU Medical School, Australian National University, Canberra, ACT, Australia. <sup>174</sup>Department of Surgical Oncology, Calvary Mater Newcastle Hospital, Australian New Zealand Breast Cancer Trials Group, and School of Medicine and Public Health, University of Newcastle, Newcastle, NSW, Australia. <sup>175</sup>School of Science and Health, The University of Western Sydney, Sydney, NSW, Australia. <sup>176</sup>Hormones and Cancer Group, Kolling Institute of Medical Research, Royal North Shore Hospital, University of Sydney, Sydney, NSW, Australia. <sup>177</sup>SydPath St Vincent's Hospital, Sydney, NSW, Australia. <sup>178</sup>Department of Tissue Pathology and Diagnostic Oncology, Pathology West, Westmead Breast Cancer Institute, Westmead Hospital, Sydney, NSW, Australia. <sup>179</sup>Centre for Information Based Medicine, Hunter Medical Research Institute, Newcastle, NSW, Australia. <sup>180</sup>Priority Research Centre for Cancer, School of Biomedical Sciences and Pharmacy, Faculty of Health, University of Newcastle, Newcastle, NSW, Australia. <sup>181</sup>The University of Queensland: UQ Centre for Clinical Research and School of Medicine, Brisbane, QLD, Australia. <sup>182</sup>Hereditary Cancer Clinic, St Vincent's Hospital, The Kinghorn Cancer Centre, Sydney, NSW, Australia. <sup>183</sup>Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, NSW, Australia. <sup>184</sup>Sydney Medical School - Westmead, University of Sydney, Sydney, NSW, Australia. <sup>185</sup>Department of Medical Oncology, The Canberra Hospital, Canberra, ACT, Australia. <sup>186</sup>St John of God Perth Northern Hospitals, Perth, WA, Australia.