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## Candidate genetic modifiers for breast and ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers

A full list of authors and affiliations appears at the end of the article.

### Abstract

**Background**—*BRCA1* and *BRCA2* mutation carriers are at substantially increased risk for developing breast and ovarian cancer. The incomplete penetrance coupled with the variable age at diagnosis in carriers of the same mutation suggests the existence of genetic and non-genetic modifying factors. In this study we evaluated the putative role of variants in many candidate modifier genes.

**Methods**—Genotyping data from 15,252 *BRCA1* and 8,211 *BRCA2* mutation carriers, for known variants (n=3,248) located within or around 445 candidate genes, were available through the iCOGS custom-designed array. Breast and ovarian cancer association analysis was performed within a retrospective cohort approach.

**Results**—The observed p-values of association ranged between 0.005–1.000. None of the variants was significantly associated with breast or ovarian cancer risk in either *BRCA1* or *BRCA2* mutation carriers, after multiple testing adjustments.

**Conclusion**—There is little evidence that any of the evaluated candidate variants act as modifiers of breast and/or ovarian cancer risk in *BRCA1* or *BRCA2* mutation carriers.

**Impact**—Genome-wide association studies have been more successful at identifying genetic modifiers of *BRCA1/2* penetrance than candidate gene studies.

### Keywords

*BRCA1 BRCA2* mutations; *BRCA*-mutation carriers; Breast cancer risk; Ovarian cancer risk; Candidate genetic risk modifiers

### Introduction

Germline *BRCA1* or *BRCA2* mutations substantially increase the risk of developing breast and ovarian cancer over those of the general population (1). The penetrance is incomplete and combined with the observed variability in age at cancer diagnosis in carriers of identical mutations, suggests the existence of genetic and/or environmental modifying factors. Direct evidence for genetic modifiers of breast and ovarian cancer risk for *BRCA1* and *BRCA2*

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Corresponding authors: Paolo Peterlongo, PhD, IFOM, Fondazione Istituto FIRC di Oncologia Molecolare, Via Adamello 16, 20139, Milan, Italy, Tel +39.02.57430.3812; fax: +39.02.57430.3231; paolo.peterlongo@ifom.eu. Eitan Friedman, MD, PhD, The Susanne-Levy Gertner Oncogenetics Unit, The Danek Gertner Institute of Genetics, Chaim Sheba Medical Center, Tel-Hashomer, 52621, Israel, Tel: 972-3-530-3173; fax: 972-3-535-7308; eitan.friedman@sheba.health.gov.il or feitan@post.tau.ac.il.

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mutation carriers has been provided through genome-wide association studies (GWAS) (2). In parallel, multiple variants in candidate genes that affect BRCA1 or BRCA2 protein expression, act along the same biological pathways, or physically interact with BRCA1 or BRCA2 proteins have been evaluated as putative modifiers of *BRCA1/2* mutations (reviewed in 3). However, only a handful of these factors were confirmed and independently validated as “true modifiers” (4). The aim of the present study was to assess the putative modifier effect of 3,248 sequence alterations in 445 candidate genes on breast/ovarian cancer risk in 23,463 *BRCA1* and *BRCA2* mutation carriers.

## Materials and methods

### Recruitment and data collection

All study participants were women, >18 years old, carrying a deleterious germline mutation in either *BRCA1* or *BRCA2*. DNA samples and phenotypic data were submitted by 54 study centers participating in the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) (5). Recruitment strategies, clinical, demographic, and phenotypic data collected from each participant, and quality control procedures, have previously been reported (4,5). All study participants took part in research studies at the parent institutions under ethically-approved protocols as detailed (4,5).

### Sequence variants genotyped

DNA samples were genotyped using the custom Illumina iCOGS array which included 211,155 single nucleotide polymorphisms (SNPs) as previously described (<http://www.nature.com/icogs/primer/cogs-project-and-design-of-the-icogs-array/>; 6). We report results from 3,248 SNPs from 445 candidate genes proposed by 17 PIs (=projects). The rationale for selecting the SNPs or genes as candidate cancer risk modifiers in *BRCA1* and *BRCA2* mutation carriers is shown in Table 1. The list of SNPs included in the study and their gene location (if any) is provided in Supplementary Table 1. Genotyping quality control procedures were carried out as reported elsewhere (6).

### Statistical analysis

Associations were evaluated within a retrospective cohort framework, by modeling the retrospective likelihood of the observed genotypes conditional on the disease phenotypes (4,7). The associations between genotype and breast or ovarian cancer risk were assessed using the 1 d.f. score test statistic based on this retrospective likelihood while accounting for the non-independence among related individuals (8). All analyses were stratified by country of residence and used calendar-year and cohort-specific breast and ovarian cancer incidence rates for *BRCA1* and *BRCA2* mutation carriers. Details are provided elsewhere (2).

## Results

A total of 23,463 mutation carriers were included (15,252 *BRCA1*, 8,211 *BRCA2* carriers), 12,127 with breast cancer (7,797 *BRCA1*, 4,330 *BRCA2* carriers), 3,093 with ovarian cancer (2,462 *BRCA1*, 631 *BRCA2* carriers), and 9,220 cancer-free carriers (5,788 *BRCA1*, 3,432 *BRCA2* carriers). All 3,248 SNPs were tested as genetic risk modifiers for both breast

and ovarian cancer in BRCA1 and BRCA2 mutation carriers depending on the selection rationale (Table 1). For each SNP, the number of individuals with genotype data, minor allele frequencies (MAF), values of the  $X^2$  score test statistic, approximate hazard ratio (HR) estimates based on the score test statistic (7), overall P values and retrospective likelihood HR are shown in Supplementary Table 2. Since project 12 was based on the hypothesis that estrogens contribute to breast cancer pathogenesis, these 139 SNPs were stratified by somatic estrogen receptor status (Supplementary Table 3). None of the SNPs tested showed significant evidence of association with breast and/or ovarian cancer risk, as a single tested variant or after adjusting for multiple testing. Indeed, there were fewer associations at a nominal  $P < 0.05$  or  $P < 0.01$  than would be expected by chance (Table 2).

## Discussion

In this study, there were no discernible effects for the genotyped SNPs on either breast or ovarian cancer risk in *BRCA1* or *BRCA2* mutation carriers. Despite the lack of evidence of association between these specific variants and breast/ovarian cancer risk for *BRCA1/BRCA2* mutation carriers, these genes may still modify cancer risk by other sequence alterations that are not represented on the iCOGS platform, by epigenetic alterations in gene expression, or in combination and interaction with other polymorphisms, that in concert have an overall effect on cancer risk.

In conclusion, the genotyped SNPs in the candidate modifier genes evaluated here have no major role in breast or ovarian cancer risk modification in either *BRCA1* or *BRCA2* mutation carriers. Our results suggest that a candidate gene approach where the selected SNPs have little a priori biological plausibility is of limited value in identifying modifier genes, unlike agnostic genome-wide associations which have been more successful (8). Applying more advanced technologies, (whole exome/genome sequencing) and targeting phenotypically distinct mutation carriers may also offer further insights into modifier genes' identity.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Authors

Paolo Peterlongo<sup>1,2</sup>, Jenny Chang-Claude<sup>3</sup>, Kirsten B. Moysich<sup>4</sup>, Anja Rudolph<sup>3</sup>, Rita K. Schmutzler<sup>5,6,7</sup>, Jacques Simard<sup>8</sup>, Penny Soucy<sup>8</sup>, Rosalind A. Eeles<sup>9</sup>, Douglas F. Easton<sup>10</sup>, Ute Hamann<sup>11</sup>, Stefan Wilkening<sup>12</sup>, Bowang Chen<sup>13</sup>, Matti A. Rookus<sup>14</sup>, Marjanka K Schmidt<sup>15</sup>, Frederieke H. van der Baan<sup>14</sup>, Amanda B. Spurdle<sup>16</sup>, Logan C. Walker<sup>17</sup>, Felicity Lose<sup>16</sup>, Ana-Teresa Maia<sup>18</sup>, Marco Montagna<sup>19</sup>, Laura Matricardi<sup>19</sup>, Jan Lubinski<sup>20</sup>, Anna Jakubowska<sup>20</sup>, Encarna B. Gómez Garcia<sup>21</sup>, Olufunmilayo I. Olopade<sup>22</sup>, Robert L. Nussbaum<sup>23</sup>, Katherine L. Nathanson<sup>24</sup>, Susan M. Domchek<sup>24</sup>, Timothy R. Rebbeck<sup>25</sup>, Banu K. Arun<sup>26</sup>, Beth Y. Karlan<sup>27</sup>, Sandra Orsulic<sup>27</sup>, Jenny Lester<sup>27</sup>, Wendy K. Chung<sup>28</sup>, Alex Miron<sup>29</sup>, Melissa C. Southey<sup>30</sup>, David E. Goldgar<sup>31</sup>, Sandra S. Buys<sup>32</sup>, Ramunas Janavicius<sup>33</sup>, Cecilia M. Dorfling<sup>34</sup>, Elizabeth J. van Rensburg<sup>34</sup>, Yuan Chun

Ding<sup>35</sup>, Susan L. Neuhausen<sup>35</sup>, Thomas V. O. Hansen<sup>36</sup>, Anne-Marie Gerdes<sup>37</sup>, Bent Ejlersten<sup>38</sup>, Lars Jønson<sup>36</sup>, Ana Osorio<sup>39,40</sup>, Cristina Martínez-Bouzas<sup>41</sup>, Javier Benitez<sup>39,42</sup>, Edye E. Conway<sup>43</sup>, Kathleen R. Blazer<sup>44</sup>, Jeffrey N. Weitzel<sup>45</sup>, Siranoush Manoukian<sup>46</sup>, Bernard Peissel<sup>46</sup>, Daniela Zaffaroni<sup>46</sup>, Giulietta Scuvera<sup>46</sup>, Monica Barile<sup>47</sup>, Filomena Ficarazzi<sup>1,48</sup>, Frederique Mariette<sup>1,48</sup>, Stefano Fortuzzi<sup>1,48</sup>, Alessandra Viel<sup>49</sup>, Giuseppe Giannini<sup>50</sup>, Laura Papi<sup>51</sup>, Aline Martayan<sup>52</sup>, Maria Grazia Tibiletti<sup>53</sup>, Paolo Radice<sup>46</sup>, Athanassios Vratimos<sup>54</sup>, Florentia Fostira<sup>54</sup>, Judy E. Garber<sup>55</sup>, Alan Donaldson<sup>56</sup>, Carole Brewer<sup>57</sup>, Claire Foo<sup>58</sup>, D. Gareth R. Evans<sup>59</sup>, Debra Frost<sup>10</sup>, Diana Eccles<sup>60</sup>, Angela Brady<sup>61</sup>, Jackie Cook<sup>62</sup>, Marc Tischkowitz<sup>63</sup>, Julian Adlard<sup>64</sup>, Julian Barwell<sup>65</sup>, Lisa Walker<sup>66</sup>, Louise Izatt<sup>67</sup>, Lucy E. Side<sup>68</sup>, M. John Kennedy<sup>69,70</sup>, Mark T. Rogers<sup>71</sup>, Mary E. Porteous<sup>72</sup>, Patrick J. Morrison<sup>73</sup>, Radka Platte<sup>10</sup>, Rosemarie Davidson<sup>74</sup>, Shirley V. Hodgson<sup>75</sup>, Steve Ellis<sup>10</sup>, Trevor Cole<sup>76</sup>, Andrew K. Godwin<sup>77</sup>, Kathleen Claes<sup>78</sup>, Tom Van Maerken<sup>78</sup>, Alfons Meindl<sup>79</sup>, Andrea Gehrig<sup>80</sup>, Christian Sutter<sup>81</sup>, Christoph Engel<sup>82</sup>, Dieter Niederacher<sup>83</sup>, Doris Steinemann<sup>84</sup>, Hansjoerg Plendl<sup>85</sup>, Karin Kast<sup>86</sup>, Kerstin Rhiem<sup>5,6,87</sup>, Nina Ditsch<sup>88</sup>, Norbert Arnold<sup>89</sup>, Raymonda Varon-Mateeva<sup>90</sup>, Barbara Wappenschmidt<sup>5,6,87</sup>, Shan Wang-Gohrke<sup>91</sup>, Brigitte Bressac-de Paillerets<sup>92,93</sup>, Bruno Buecher<sup>94</sup>, Capucine Delnatte<sup>95</sup>, Claude Houdayer<sup>94,96</sup>, Dominique Stoppa-Lyonnet<sup>94,96,97</sup>, Francesca Damiola<sup>98</sup>, Isabelle Coupier<sup>99,100</sup>, Laure Barjhoux<sup>100</sup>, Laurence Venat-Bouvet<sup>101</sup>, Lisa Golmard<sup>94</sup>, Nadia Boutry-Kryza<sup>102</sup>, Olga M. Sinilnikova<sup>98,102</sup>, Olivier Caron<sup>103</sup>, Pascal Pujol<sup>99,104</sup>, Sylvie Mazoyer<sup>98</sup>, Muriel Belotti<sup>94</sup>, Marion Piedmonte<sup>106</sup>, Michael L. Friedlander<sup>107</sup>, Gustavo C. Rodriguez<sup>108</sup>, Larry J Copeland<sup>109</sup>, Miguel de la Hoya<sup>110</sup>, Pedro Perez Segura<sup>111</sup>, Heli Nevanlinna<sup>112,113</sup>, Kristiina Aittomäki<sup>114</sup>, Theo A.M. van Os<sup>115</sup>, Hanne E.J. Meijers-Heijboer<sup>116</sup>, Annemarie H. van der Hout<sup>117</sup>, Maaikje P.G. Vreeswijk<sup>118</sup>, Nicoline Hoogerbrugge<sup>119</sup>, Margreet G.E.M. Ausems<sup>120</sup>, Helena C. van Doorn<sup>121</sup>, J. Margriet Collée<sup>122</sup>, Edith Olah<sup>123</sup>, Orland Diez<sup>124,125,126,127</sup>, Ignacio Blanco<sup>128</sup>, Conxi Lazaro<sup>129</sup>, Joan Brunet<sup>130</sup>, Lidia Feliubadalo<sup>131</sup>, Cezary Cybulski<sup>20</sup>, Jacek Gronwald<sup>20</sup>, Katarzyna Durda<sup>20</sup>, Katarzyna Jaworska-Bieniek<sup>20</sup>, Grzegorz Sukiennicki<sup>20</sup>, Adalgeir Arason<sup>131,132</sup>, Jocelyne Chiquette<sup>133</sup>, Manuel R. Teixeira<sup>134,135</sup>, Curtis Olswold<sup>136</sup>, Fergus J. Couch<sup>137</sup>, Noralane M. Lindor<sup>138</sup>, Xianshu Wang<sup>139</sup>, Csilla I. Szabo<sup>140</sup>, Kenneth Offit<sup>141</sup>, Marina Corines<sup>142</sup>, Lauren Jacobs<sup>142</sup>, Mark E. Robson<sup>141</sup>, Liyang Zhang<sup>143</sup>, Vijai Joseph<sup>141</sup>, Andreas Berger<sup>144</sup>, Christian F. Singer<sup>144</sup>, Christine Rappaport<sup>144</sup>, Daphne Geschwantler Kaulich<sup>144</sup>, Georg Pfeiler<sup>144</sup>, Muy-Kheng M. Tea<sup>144</sup>, Catherine M. Phelan<sup>145</sup>, Mark H. Greene<sup>146</sup>, Phuong L. Mai<sup>146</sup>, Gad Rennert<sup>147</sup>, Anna Marie Mulligan<sup>148,149</sup>, Gord Glendon<sup>150</sup>, Sandrine Tchatchou<sup>151</sup>, Irene L. Andrulis<sup>151,152</sup>, Amanda Ewart Toland<sup>153</sup>, Anders Bojesen<sup>154</sup>, Inge Sokilde Pedersen<sup>155</sup>, Mads Thomassen<sup>156</sup>, Uffe Birk Jensen<sup>157</sup>, Yael Laitman<sup>158</sup>, Johanna Rantala<sup>159</sup>, Anna von Wachenfeldt<sup>160</sup>, Hans Ehrencrona<sup>161,162</sup>, Marie Stenmark Askmalm<sup>163</sup>, Åke Borg<sup>164</sup>, Karoline B. Kuchenbaecker<sup>10</sup>, Lesley McGuffog<sup>10</sup>, Daniel Barrowdale<sup>10</sup>, Sue Healey<sup>16</sup>, Andrew Lee<sup>10</sup>, Paul D.P. Pharoah<sup>165</sup>, Georgia Chenevix-Trench<sup>16</sup>, Antonis C. Antoniou<sup>10</sup>, and Eitan Friedman<sup>158</sup> **on behalf of EMBRACE<sup>10,105,14,166</sup> on behalf of GEMO Study Collaborators<sup>105,14,166</sup> on behalf of HEBON<sup>14,166</sup> on behalf of KConFab Investigators<sup>166</sup>**

## Affiliations

<sup>1</sup>IFOM, Fondazione Istituto FIRC di Oncologia Molecolare, Milan, Italy <sup>2</sup>Unit of Molecular Bases of Genetic Risk and Genetic Testing, Department of Preventive and Predictive Medicine, Fondazione IRCCS Istituto Nazionale Tumori (INT), Milan, Italy <sup>3</sup>Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany <sup>4</sup>Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY, USA <sup>5</sup>Center for Hereditary Breast and Ovarian Cancer, Medical Faculty, University Hospital Cologne, Germany <sup>6</sup>Center for Integrated Oncology (CIO), Medical Faculty, University Hospital Cologne, Germany <sup>7</sup>Center for Molecular Medicine Cologne (CMMC), University of Cologne, Germany, on behalf of the German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC) <sup>8</sup>Centre Hospitalier Universitaire de Québec Research Center and Laval University, Quebec City, Canada <sup>9</sup>Oncogenetics Team, The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, UK <sup>10</sup>Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, UK <sup>11</sup>Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany <sup>12</sup>Genomic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany <sup>13</sup>Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany <sup>14</sup>Department of Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands <sup>15</sup>Division of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands <sup>16</sup>Department of Genetics and Computational Biology, QIMR Berghofer, Brisbane, Australia <sup>17</sup>Department of Pathology, University of Otago, Christchurch, New Zealand <sup>18</sup>Department of Biomedical Sciences and Medicine, Gambelas Campus, University of Algarve, Portugal <sup>19</sup>Immunology and Molecular Oncology Unit, Istituto Oncologico Veneto IOV - IRCCS, Padua, Italy <sup>20</sup>Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland <sup>21</sup>Department of Clinical Genetics, MUMC, Maastricht, The Netherlands <sup>22</sup>Center for Clinical Cancer Genetic, Department of Medicine and Human Genetics, University of Chicago Medical Center, Chicago, USA <sup>23</sup>Department of Medicine and Institute for Human Genetics, University of California, San Francisco, USA <sup>24</sup>Department of Medicine, Abramson Cancer Center, Perelman School of Medicine at the University of Pennsylvania, USA <sup>25</sup>Department of Epidemiology and Biostatistics, Abramson Cancer Center, Perelman School of Medicine at the University of Pennsylvania, USA <sup>26</sup>University of Texas MD Anderson Cancer Center, Houston, TX, USA <sup>27</sup>Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, USA <sup>28</sup>Departments of Pediatrics and Medicine, Columbia University, New York, NY, USA <sup>29</sup>Department of Genetics and Genomics at Case Western Reserve Medical School, Cleveland, Ohio, USA <sup>30</sup>Genetic Epidemiology Laboratory, Department of Pathology, University of Melbourne, Parkville, Australia <sup>31</sup>Department of Dermatology, University of Utah School of Medicine, Salt Lake City, Utah, USA <sup>32</sup>Department of Oncological Sciences, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City,



USA <sup>33</sup>Vilnius University Hospital Santariskiu Clinics, Hematology, Oncology and Transfusion Medicine Center, Dept. of Molecular and Regenerative Medicine; State Research Institute Centre for Innovative medicine, Vilnius, Lithuania <sup>34</sup>Department of Genetics, University of Pretoria, Pretoria, South Africa <sup>35</sup>Department of Population Sciences, Beckman Research Institute of City of Hope, Duarte, CA, USA <sup>36</sup>Center for Genomic Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark <sup>37</sup>Department of Clinical Genetics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark <sup>38</sup>Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark <sup>39</sup>Biomedical Network on Rare Diseases (CIBERER), Madrid, Spain <sup>40</sup>Human Genetics Group, Spanish National Cancer Centre (CNIO), Madrid, Spain <sup>41</sup>Molecular Genetics Laboratory, Department of Biochemistry, Cruces Hospital Barakaldo, 48903-Barakaldo-Bizkaia, Spain <sup>42</sup>Human Genetics Group and Genotyping Unit, Spanish National Cancer Centre (CNIO), Madrid, Spain <sup>43</sup>Saint Alphonsus Regional Medical Center, care of City of Hope Clinical Cancer Genetics Community Research Network, Duarte, California 91010, USA <sup>44</sup>Clinical Cancer Genetics, City of Hope, 1500 East Duarte Road, Duarte, California 91010 USA <sup>45</sup>Clinical Cancer Genetics, City of Hope, 1500 East Duarte Road, Duarte, California 91010 USA (for the City of Hope Clinical Cancer Genetics Community Research Network) <sup>46</sup>Unit of Medical Genetics, Department of Preventive and Predictive Medicine, Fondazione IRCCS Istituto Nazionale Tumori (INT), Milan, Italy <sup>47</sup>Division of Cancer Prevention and Genetics, Istituto Europeo di Oncologia, Milan, Italy <sup>48</sup>Cogentech Cancer Genetic Test Laboratory, Milan, Italy <sup>49</sup>Division of Experimental Oncology 1, CRO Aviano National Cancer Institute, Aviano (PN), Italy <sup>50</sup>Department of Molecular Medicine, Sapienza University, Rome, Italy <sup>51</sup>Unit of Medical Genetics, Department of Biomedical, Experimental and Clinical Sciences, University of Florence, Florence, Italy <sup>52</sup>Unit of Genetic Counseling, Medical Oncology Department, Istituto Nazionale Tumori Regina Elena, Rome, Italy <sup>53</sup>UO Anatomia Patologica, Ospedale di Circolo-Università dell'Insubria, Varese, Italy <sup>54</sup>Molecular Diagnostics Laboratory, INRASTES, National Centre for Scientific Research "Demokritos", Aghia Paraskevi Attikis, Athens, Greece <sup>55</sup>Dana-Farber Cancer Institute, Boston, MA, USA <sup>56</sup>Clinical Genetics Department, St Michael's Hospital, Bristol, UK <sup>57</sup>Department of Clinical Genetics, Royal Devon & Exeter Hospital, Exeter, UK <sup>58</sup>Cheshire & Merseyside Clinical Genetics Service, Liverpool Women's NHS Foundation Trust, Liverpool, UK <sup>59</sup>Genetic Medicine, Manchester Academic Health Sciences Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK <sup>60</sup>University of Southampton, Faculty of Medicine, Southampton University Hospitals NHS Trust, Southampton, UK <sup>61</sup>North West Thames Regional Genetics Service, Kennedy-Galton Centre, Harrow, UK <sup>62</sup>Sheffield Clinical Genetics Service, Sheffield Children's Hospital, Sheffield, UK <sup>63</sup>Department of Clinical Genetics, East Anglian Regional Genetics Service, Addenbrookes Hospital, Cambridge, UK <sup>64</sup>Yorkshire Regional Genetics Service, Leeds, UK <sup>65</sup>Leicestershire Clinical Genetics Service, University Hospitals of Leicester NHS Trust, UK <sup>66</sup>Oxford Regional Genetics Service, Churchill Hospital,

Oxford, UK <sup>67</sup>Clinical Genetics, Guy's and St. Thomas' NHS Foundation Trust, London, UK <sup>68</sup>North East Thames Regional Genetics Service, Great Ormond Street Hospital for Children NHS Trust, London, UK <sup>69</sup>Academic Unit of Clinical and Molecular Oncology, Trinity College Dublin, Eire <sup>70</sup>St James's Hospital, Dublin, Eire <sup>71</sup>All Wales Medical Genetics Services, University Hospital of Wales, Cardiff, UK <sup>72</sup>South East of Scotland Regional Genetics Service, Western General Hospital, Edinburgh, UK <sup>73</sup>Centre for Cancer Research and Cell Biology, Queens University of Belfast, Department of Medical Genetics, Belfast HSC Trust, Belfast, UK <sup>74</sup>Ferguson-Smith Centre for Clinical Genetics, Yorkhill Hospitals, Glasgow, UK <sup>75</sup>Medical Genetics Unit, St George's, University of London, UK <sup>76</sup>West Midlands Regional Genetics Service, Birmingham Women's Hospital Healthcare NHS Trust, Edgbaston, Birmingham, UK <sup>77</sup>Department of Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City, KS, USA <sup>78</sup>Center for Medical Genetics, Ghent University, Ghent, Belgium <sup>79</sup>Department of Gynaecology and Obstetrics, Division of Tumor Genetics, Klinikum rechts der Isar, Technical University Munich, Germany <sup>80</sup>Institute of Human Genetics, University Würzburg, Würzburg, Germany <sup>81</sup>University Heidelberg, Heidelberg, Germany <sup>82</sup>Institute for Medical Informatics, Statistics and Epidemiology University of Leipzig, Leipzig, Germany <sup>83</sup>University Düsseldorf, Dusseldorf, Germany <sup>84</sup>Hannover Medical School, Hanover, Germany <sup>85</sup>Institute of Human Genetics, University Hospital of Schleswig-Holstein/University Kiel, Kiel, Germany <sup>86</sup>University Dresden, Dresden, Germany <sup>87</sup>Center for Molecular Medicine Cologne (CMMC), University of Cologne, Germany <sup>88</sup>Department of Gynaecology and Obstetrics, University Munich, Munich, Germany <sup>89</sup>University Hospital of Schleswig-Holstein/University Kiel, Kiel, Germany <sup>90</sup>Institute of Human Genetics, Charite Berlin, Germany <sup>91</sup>Department of Gynaecology and Obstetrics, University Hospital Ulm, Germany <sup>92</sup>INSERM U946, Fondation Jean Dausset, Paris, France <sup>93</sup>Service de Génétique, Institut de Cancérologie Gustave Roussy, Villejuif, France <sup>94</sup>Institut Curie, Department of Tumour Biology, Paris, France <sup>95</sup>Centre René Gauducheau, Nantes, France <sup>96</sup>Université Paris Descartes, Sorbonne Paris Cité, France <sup>97</sup>Institut Curie, INSERM U830, Paris, France <sup>98</sup>INSERM U1052, CNRS UMR5286, Université Lyon 1, Centre de Recherche en Cancérologie de Lyon, Lyon, France <sup>99</sup>Unité d'Oncogénétique, CHU Arnaud de Villeneuve, Montpellier, France <sup>100</sup>Unité d'Oncogénétique, CRLCC Val d'Aurelle, Montpellier, France <sup>101</sup>Department of Medical Oncology, Centre Hospitalier Universitaire Dupuytren, Limoges, France <sup>102</sup>Unité Mixte de Génétique Constitutionnelle des Cancers Fréquents, Hospices Civils de Lyon – Centre Léon Bérard, Lyon, France <sup>103</sup>Consultation de Génétique, Département de Médecine, Institut de Cancérologie Gustave Roussy, Villejuif, France <sup>104</sup>INSERM 896, CRCM Val d'Aurelle, Montpellier, France <sup>105</sup>GEMO study: National Cancer Genetics Network «UNICANCER Genetic Group», France <sup>106</sup>Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY, USA <sup>107</sup>Australia New Zealand Gynaecological Oncology Group (ANZGOG), Coordinating Centre, Camperdown, Australia <sup>108</sup>Division of Gynecologic Oncology, NorthShore University HealthSystem, Evanston, IL, USA <sup>109</sup>Ohio State University,

Department of Obstetrics and Gynecology, Hilliard, OH, USA <sup>110</sup>Molecular Oncology Laboratory, Hospital Clinico San Carlos, IdISSC, Madrid, Spain <sup>111</sup>Department of Oncology, Hospital Clinico San Carlos, IdISSC, Madrid, Spain <sup>112</sup>Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Helsinki, Finland <sup>113</sup>University of Helsinki, Helsinki, Finland <sup>114</sup>Department of Clinical Genetics, Helsinki University Central Hospital, Helsinki, Finland <sup>115</sup>Department of Clinical Genetics, Academic Medical Center, Amsterdam, The Netherlands <sup>116</sup>Department of Clinical Genetics, VU University Medical Centre, Amsterdam, The Netherlands <sup>117</sup>Department of Genetics, University Medical Center, Groningen University, Groningen, The Netherlands <sup>118</sup>Department of Human Genetics, Leiden University Medical Center (LUMC), Leiden, The Netherlands <sup>119</sup>Department of Human Genetics, Radboud University Medical Centre, Nijmegen, The Netherlands <sup>120</sup>Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands <sup>121</sup>Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Erasmus University MC Cancer Institute, Rotterdam, The Netherlands <sup>122</sup>Department of Clinical Genetics, Family Cancer Clinic, Erasmus University Medical Center, Rotterdam, The Netherlands <sup>123</sup>Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary <sup>124</sup>Oncogenetics Group, University Hospital Vall d'Hebron, Barcelona, Spain <sup>125</sup>Universitat Autònoma de Barcelona, Barcelona, Spain <sup>126</sup>Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain <sup>127</sup>Vall d'Hebron Research Institute (VHIR), Barcelona, Spain <sup>128</sup>Genetic Counseling Unit, Hereditary Cancer Program, IDIBELL-Catalan Institute of Oncology, Barcelona, Spain <sup>129</sup>Molecular Diagnostic Unit, Hereditary Cancer Program, IDIBELL-Catalan Institute of Oncology, Barcelona, Spain <sup>130</sup>Genetic Counseling Unit, Hereditary Cancer Program, IDIBGI-Catalan Institute of Oncology, Girona, Spain <sup>131</sup>BMC, Faculty of Medicine, University of Iceland, Reykjavik, Iceland <sup>132</sup>Department of Pathology, Landspítali University Hospital, Reykjavik, Iceland <sup>133</sup>Unité de Recherche en Santé des Populations, Centre des Maladies du Sein Deschênes-Fabia, Centre de Recherche FRSQ du Centre Hospitalier Affilié Universitaire de Québec, Québec, QC, Canada <sup>134</sup>Biomedical Sciences Institute (ICBAS), Porto University, Porto, Portugal <sup>135</sup>Department of Genetics, Portuguese Oncology Institute, Porto, Portugal <sup>136</sup>Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA <sup>137</sup>Department of Laboratory Medicine and Pathology, and Health Sciences Research, Mayo Clinic, Rochester, MN, USA <sup>138</sup>Health Sciences Research, Mayo Clinic, Scottsdale, AZ, USA <sup>139</sup>Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA <sup>140</sup>National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA <sup>141</sup>Clinical Genetics Research Laboratory, Memorial Sloan-Kettering Cancer Center, New York, NY, USA <sup>142</sup>Clinical Genetics Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA <sup>143</sup>Diagnostic Molecular Genetics Laboratory, Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA <sup>144</sup>Department of OB/GYN and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria <sup>145</sup>Department of Cancer Epidemiology, Moffitt Cancer Center, Tampa, Florida, USA <sup>146</sup>Clinical



Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD, USA <sup>147</sup>Clalit National Cancer Control Center, Haifa, Israel <sup>148</sup>Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada <sup>149</sup>Laboratory Medicine Program, University Health Network, Toronto, Ontario, Canada <sup>150</sup>Ontario Cancer Genetics Network: Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada <sup>151</sup>Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada <sup>152</sup>Departments of Molecular Genetics and Laboratory Medicine and Pathobiology, University of Toronto, Ontario, Canada <sup>153</sup>Division of Human Cancer Genetics, Departments of Internal Medicine and Molecular Virology, Immunology and Medical Genetics, Comprehensive Cancer Center, The Ohio State University, Columbus, OH, USA <sup>154</sup>Department of Clinical Genetics, Vejle Hospital, Vejle, Denmark <sup>155</sup>Section of Molecular Diagnostics, Department of Biochemistry, Aalborg University Hospital, Aalborg, Denmark <sup>156</sup>Department of Clinical Genetics, Odense University Hospital, Odense C, Denmark <sup>157</sup>Department of Clinical Genetics, Aarhus University Hospital, Aarhus, Denmark <sup>158</sup>Sheba Medical Center, Tel Aviv, Israel <sup>159</sup>Department of Clinical Genetics, Karolinska University Hospital, Stockholm, Sweden <sup>160</sup>Department of Oncology, Karolinska University Hospital, Stockholm, Sweden <sup>161</sup>Department of Clinical Genetics, Lund University Hospital, Lund, Sweden <sup>162</sup>Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden <sup>163</sup>Division of Clinical Genetics, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden <sup>164</sup>Department of Oncology, Lund University, Lund, Sweden <sup>165</sup>Department of Oncology, University of Cambridge, Cambridge, UK <sup>166</sup>kConFab: Kathleen Cuninghams Consortium for Research into Familial Breast Cancer – Peter MacCallum Cancer Center, Melbourne, Australia

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Table 1

Description of the 17 projects included in the study.

Project	Rationale for testing SNPs as risk modifiers for breast cancer and ovarian cancer in BRCA1-mutation carriers	Number of SNPs included	Reference
1	Previous data suggested that irradiation response genes whose expression is associated with BRCA1 and BRCA2 mutation status are enriched for the presence of common genetic modifiers of breast cancer risk.	18	<b>Walker LC et al.</b> Evidence for SMAD3 as a modifier of breast cancer risk in BRCA2 mutation carriers. <i>Breast Cancer Res.</i> 2010;12(6):R102.
2	X chromosome SNPs shown to be associated with risk of breast cancer in the CGEMS breast cancer study were considered.	11	<b>Hunter DJ et al.</b> A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. <i>Nat Genet.</i> 2007 Jul;39(7):870-4.
3	Previous data suggested that the "del" allele of rs3834129 was associated with increased breast cancer risk in BRCA1-mutation carriers.	1	<b>Catucci I et al.</b> The CASP8 rs3834129 polymorphism and breast cancer risk in BRCA1 mutation carriers. <i>Breast Cancer Res Treat.</i> 2011 Feb;125(3):855-60.
4	Search for risk modifiers of BRCA1 5382insC-mutation carriers was performed by a pooled GWAS in 124 women diagnosed with breast cancer (< 45 years) and 119 unaffected controls (> 50 years at last follow up) from Poland. The highest-ranked SNPs from the pooled GWAS were selected.	137	None
5	The proposed SNPs are related to genes in regulatory T-cell (Treg) cell and myeloid derived suppressor cell (MDSC) pathways. Both pathways play a role in cancer immunosuppression.	2637	<b>Schreiber RD et al.</b> Cancer immunoeediting: integrating immunity's roles in cancer suppression and promotion. <i>Science.</i> 2011;331(6024):1565-1570
6	The proposed SNPs were associated with breast density. <b>These SNPs were tested only as modifier of breast cancer risk.</b>	72	<b>Storde JS et al.</b> Mammographic density and matrix metalloproteinases in breast tissue. <i>Cancer Microenviron.</i> 2010;3(1):57-65. <b>Guo YP et al.</b> Growth factors and stromal matrix proteins associated with mammographic densities. <i>Cancer Epidemiol Biomarkers Prev.</i> 2001;10(3):243-8. <b>Verheus M et al.</b> Common genetic variation in the IGF-1 gene, serum IGF-1 levels and breast density. <i>Breast Cancer Res Treat.</i> 2008;112(1):109-22. <b>Diorio C et al.</b> Genetic polymorphisms involved in insulin-like growth factor (IGF) pathway in relation to mammographic breast density and IGF levels. <i>Cancer Epidemiol Biomarkers Prev.</i> 2008;17(4):880-8. <b>Diorio C et al.</b> Vitamin D pathway polymorphisms in relation to mammographic breast density. <i>Cancer Epidemiol Biomarkers Prev.</i> 2008;17(9):2505-8.
7	SNPs or (SNPs in) genes, were considered according to following criteria. <b>a)</b> affecting circadian rhythms; <b>b)</b> interacting with CLOCK; <b>c)</b> involved in binding IGF-1 to binding proteins; <b>d)</b> in progesterone receptor gene and previously found associated with BC and OVC risk; <b>e)</b> related to disease treatment.	20	<b>Hoffman AE et al.</b> CLOCK in breast tumorigenesis: genetic, epigenetic, and transcriptional profiling analyses. <i>Cancer Res.</i> 2010;70(4):1459-68. <b>Kelemen LE et al.</b> Genetic variation in stromal proteins decorin and lumican with breast cancer: investigations in two case-control studies. <i>Breast Cancer Res.</i> 2008;10(6):R98. <b>Patel AV et al.</b> IGF-1, IGFBP-1, and IGFBP-3 polymorphisms predict circulating IGF levels but not breast cancer risk: findings from the Breast and Prostate Cancer Cohort Consortium (BPC3). <i>PLoS One.</i> 2008;3(7):e2578.
8	All these SNPs are located in selenoprotein genes and are involved in selenium metabolism; selenium is known to be associated with cancer risk.	11	<b>Oestergaard MZ et al.</b> Interactions between genes involved in the antioxidant defence system and breast cancer risk. <i>Br J Cancer.</i> 2006;95(4):525-31. <b>Méplan C et al.</b> Association between Polymorphisms in Glutathione Peroxidase and Selenoprotein P Genes, Glutathione Peroxidase Activity, HRT Use and Breast Cancer Risk. <i>PLoS One.</i> 2013;8(9):e73316. <b>Udler M et al.</b> Common germline genetic variation in antioxidant defense genes and survival after diagnosis of breast cancer. <i>J Clin Oncol.</i> 2007;25(21):3015-23. <b>Sutherland A et al.</b> Polymorphisms in the selenoprotein S and 15-kDa selenoprotein genes are associated with altered susceptibility to colorectal cancer. <i>Genes Nutr.</i> 2010;5(3):215-23.
9	Previous data suggested that the rs1045485 SNP modified disease penetrance of breast and ovarian cancer in BRCA1 and BRCA2 mutation carriers.	1	<b>Engel C et al.</b> Association of the variants CASP8 D302H and CASP10 V410I with breast and ovarian cancer risk in BRCA1 and BRCA2 mutation carriers. <i>Cancer Epidemiol Biomarkers Prev.</i> 2010;19(11):2859-68.

Project	Rationale for testing SNPs as risk modifiers for breast cancer and ovarian cancer in BRCA-mutation carriers	Number of SNPs included	Reference
10	The proposed SNPs are located within the <i>PARP1</i> gene that plays a key role in the repair of DNA single-strand breaks.	3	<b>Gonçalves A et al.</b> Poly(ADP-ribose) polymerase-1 mRNA expression in human breast cancer: a meta-analysis. <i>Breast Cancer Res Treat.</i> 2011;127(1):273–81.
11	SNPs were considered because of observations based on evidences of recent positive selection and presence in the same genomic region of genes, a) coding for BRCA1 interacting proteins; b) involved in cancer or breast cancer; c) involved in DNA damage response and interacting with TP53.	13	<b>Voight BF et al.</b> A map of recent positive selection in the human genome. <i>PLoS Biol.</i> 2006; 4:e72. <b>Lappalainen T et al.</b> Genomic landscape of positive natural selection in Northern European populations. <i>Eur J Hum Genet.</i> 2010;18(4):471–8.
12	Steroid hormones such as estrogens play an important role in the etiology of breast cancer contributing to tumor growth by promoting cell proliferation. SNPs in candidate genes involved in sex steroid metabolism were considered. <b>The SNPs were tested also as breast cancer risk modifiers considering estrogen receptor status of BRCA-mutation carriers (see Supplementary Table 3)</b>	139	<b>Labrie F et al.</b> Endocrine and intracrine sources of androgens in women: inhibition of breast cancer and other roles of androgens and their precursor dehydroepiandrosterone. <i>Endocr Rev.</i> 2003;24(2):152–82.
13	<i>RAD51C</i> is a breast cancer gene. SNPs located within, or in close proximity to <i>RAD51C</i> were selected.	17	<b>Meindl A et al.</b> Germline mutations in breast and ovarian cancer pedigrees establish <i>RAD51C</i> as a human cancer susceptibility gene. <i>Nat Genet.</i> 2010;42(5):410–4.
14	The highest-ranked SNPs from a GWAS based on 700 hereditary breast cancer cases and 1,200 controls were selected.	142	None
15	SNP rs2981582 in <i>FGFR2</i> is strongly associated with risk of breast cancer and acting as a risk modifier in <i>BRCA2</i> mutation carriers. Rs2981582 may also influence the risk of ovarian cancer among <i>BRCA1/2</i> -mutation carriers. <b>This SNP was tested only as modifier of ovarian cancer risk.</b>	1	<b>Easton DF et al.</b> Genome-wide association study identifies novel breast cancer susceptibility loci. <i>Nature.</i> 2007;447(7148):1087–1093. <b>Hunter DJ et al.</b> A genome-wide association study identifies alleles in <i>FGFR2</i> associated with risk of sporadic postmenopausal breast cancer. <i>Nat Genet.</i> 2007;39(7): 870–874. <b>Antoniou AC et al.</b> Common breast cancer predisposition alleles are associated with breast cancer risk in <i>BRCA1</i> and <i>BRCA2</i> mutation carriers. <i>Am J Hum Genet.</i> 2008;82(4):937–948.
16	The rs10895068 SNP in the promoter of the progesterone receptor ( <i>PR</i> ) gene (+331G/A) has been reported to be associated with endometrial cancer risk. Our previous study in 220 patients from BC and OC families showed a marginal association of the +331A allele with OC risk. <b>This SNP was tested only as modifier of ovarian cancer risk.</b>	1	<b>Vivo ID et al.</b> A functional polymorphism in the promoter of the progesterone receptor gene associated with endometrial cancer risk. <i>Proc Natl Acad Sci U S A.</i> 2002;99(19):12263–12268. <b>Romano A et al.</b> Impact of two functional progesterone receptor polymorphisms (PRP): +331G/A and PROGINS on the cancer risks in familial breast/ovarian cancer. <i>Open Cancer J.</i> 2007;1:1–8.
17	The proposed SNPs were selected according to the hypothesis that different levels of expression of the remaining normal allele in <i>BRCA2</i> mutation carriers may be associated with variable penetrance of <i>BRCA2</i> mutations.	24	<b>Maia AT et al.</b> Effects of <i>BRCA2</i> cis-regulation in normal breast and cancer risk amongst <i>BRCA2</i> mutation carriers. <i>Breast Cancer Res.</i> 2012;14(2):R63

**Table 2**

Observed and expected number of SNPs with p-values &lt;0.05 and &lt;0.01

Category	Tumor	Number of SNPs tested*	Number of SNPs with p-value<0.01 (expected)	Number of SNPs with p-value<0.05 (expected)
BRCA1	BrCa	3232	25 (32)	202 (162)
BRCA1	OvCa	3160	13 (32)	146 (158)
BRCA2	BrCa	3230	5 (32)	96 (161)
BRCA2	OvCa	3157	6 (32)	131 (159)

\* Not all the 3,248 SNPs were tested in each category/tumor group