

1 Prostate cancer risk by *BRCA2* genomic regions

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52 Abstract

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54 A *BRCA2* prostate cancer cluster region (PCCR) was recently proposed (c.7914 to 3') wherein
55 pathogenic variants (PVs) are associated with higher prostate cancer (PCa) risk than PVs elsewhere in
56 the *BRCA2* gene. Using a prospective cohort study of 447 male *BRCA2* PV carriers recruited in the UK
57 and Ireland from 1998 to 2016, we estimated standardised incidence ratios (SIRs) compared to
58 population incidences and assessed variation in risk by PV location. Carriers of PVs in the PCCR had a
59 PCa SIR of 8.33 (95% confidence interval [CI] 4.46-15.58) and were at higher risk of PCa than carriers
60 of other *BRCA2* PVs (SIR=3.31, 95% CI 1.97-5.57; hazard ratio [HR]=2.34, 95% CI 1.09-5.03). PCCR PV
61 carriers had an estimated cumulative PCa risk of 44% (95% CI 23%-72%) by age 75 and 78% (95% CI
62 54%-94%) by age 85. Our results corroborate the existence of a PCCR in *BRCA2* in a prospective
63 cohort.

64

65 Patient summary

66

67 In this report we investigated whether the risk of prostate cancer for men with a harmful mutation
68 in the *BRCA2* gene differs based on where in the gene the mutation is located. We found that men
69 with mutations in one region of *BRCA2* had a higher risk of prostate cancer than men with mutations
70 elsewhere in the gene.

71

72

73 We recently reported prostate cancer (PCa) risk estimates for pathogenic variants (PVs) in *BRCA2*,
74 based on a prospective cohort of male carriers [1]. Variability in cancer risks due to genotype-
75 phenotype correlations may allow for more individualised counselling and screening. We noted that
76 PVs within the so-called ovarian cancer cluster region (OCCR) in exon 11 of the gene [2–4] were
77 associated with lower PCa risk than other *BRCA2* PVs [1,3,4]. PVs in the OCCR have been consistently
78 shown to be associated with increased ovarian cancer risk but decreased breast cancer risk [2,3,5,6],
79 although the precise boundaries of the OCCR [3,5] and the mechanisms behind this risk variation
80 remain uncertain. It has been proposed that the likelihood that a PV triggers nonsense-mediated
81 mRNA decay varies by genomic region [7,8], so that OCCR PVs might produce a truncated or
82 alternatively spliced protein whose capability to suppress tumours varies by cancer type [2,3,5,7,8],
83 but there is currently no experimental support for this hypothesis [7]. Shortly after the publication of
84 our manuscript, Patel and co-workers proposed the existence of a prostate cancer cluster region
85 (PCCR) at the 3' end of *BRCA2*, based on retrospective cohort data [8]. This retrospective study
86 reported that men with *BRCA2* PVs in the proposed PCCR have a higher risk of PCa (hazard ratio
87 [HR]=1.78, 95% confidence interval [CI] 1.25-2.52), particularly Gleason score \geq 8 PCa (HR=3.11, 95%
88 CI 1.63-5.95), compared to men with PVs in the reference region c.1001 to c.7913, but did not
89 present estimates of the absolute PCa risk for PCCR PV carriers [8]. In order to substantiate or refute
90 this association, and to provide direct estimates of the absolute risk of PCa for carriers of *BRCA2*
91 PCCR PVs, we have reanalysed our prospective data.

92

93 The prospective cohort comprised 447 male *BRCA2* PV carriers who were recruited to the EMBRACE
94 study (<http://ccge.medschl.cam.ac.uk/embrace/>) through clinical genetics centres in the UK and
95 Ireland between 1998 and 2016 at median age of 51.4 yr (inter-quartile range 41.5-63.6 yr). The
96 participants were counselled with regard to their PV. Detailed information on the cohort and on
97 inclusion criteria, data collection, follow-up, and statistical analysis approach, is available in our
98 recent publication [1]. The participants' PVs (listed in Supplementary table 1) were grouped on the
99 basis of position within the *BRCA2* gene, based on the proposed PCCR (c.7914 to 3' [8]; HGVS
100 nomenclature [<http://varnomen.hgvs.org/>]; using cDNA reference sequence NM_000059.3 and
101 reference genome hg18) and the wide definition of the OCCR (c.2831 to c.6401) [1–4]. We
102 additionally considered the region bounded by c.756 and c.1000 in which Patel and co-workers
103 found evidence of increased PCa risk [8], but due to a small sample size (n=1) we could not estimate
104 the PCa risk associated with this region. Here, we also present floating absolute risks (FARs) [9] to
105 enable risk comparisons between any of the considered genomic regions.

106

107 The Anglia and Oxford Medical Research and Ethics Committee approved the study. All participants
108 provided written informed consent.

109

110 Twenty-six participants developed PCa during median follow-up of 5.3 yr (inter-quartile range 2.6-
111 8.9 yr) [1]. Carriers of PVs in the PCCR (n=93) had a PCa standardised incidence ratio (SIR) of 8.33
112 (95% CI 4.46-15.6), whereas carriers of PVs elsewhere in *BRCA2* (n=354) had an SIR of 3.31 (95% CI
113 1.97-5.57) compared to population incidences. This corresponds to a significantly higher PCa risk
114 associated with PVs in the PCCR compared to non-PCCR PVs (HR=2.34, 95% CI 1.09-5.03; Table 1).
115 Compared to PVs in the region c.1001 to c.7913 [8], PCCR PVs were associated with a HR of 2.09
116 (95% CI 0.98-4.45). As previously reported, the SIR for carriers of PVs in the wide definition OCCR

117 (n=178) was 2.46 (95% 1.07-5.64) [1], and the risk for carriers of PCCR PVs was also significantly
118 higher than that for OCCR PV carriers (HR=3.41, 95% CI 1.27-9.16). The SIR for PVs located in the
119 region bounded by the OCCR and the PCCR (c.6402 to c.7913; n=66) was estimated to be 6.14 (95%
120 CI 2.18-17.3), and the SIR for *BRCA2* PVs upstream of the OCCR (5' to c.2830; n=108) was 3.50 (95%
121 CI 1.48-8.26). The FARs for the comparison of risks across the four regions suggested that the
122 observed increased risk associated with PVs in the PCCR may be partly driven by the lower risk
123 associated with PVs in the OCCR (Table 1). The proportional hazards assumption was violated for the
124 model with all genomic regions fitted (Schoenfeld residuals test, p=0.003); in line with this the
125 corresponding Kaplan—Meier plot indicated that the risks might be similar between the OCCR and
126 PCCR PV carriers at younger ages but deviate at older ages. PCCR PV carriers had an estimated
127 cumulative PCa risk of 44% (95% CI 23%-72%) by age 75 and 78% (95% CI 54%-94%) by age 85. After
128 omitting the first six mo of follow-up to assess the possible effect of screening-associated diagnoses
129 of indolent PCas, the corresponding estimates were 41% (95% CI 20%-73%) and 69% (95% CI 42%-
130 91%), respectively (Figure 1).

131

132 The difference in PCa risk for PVs in PCCR vs OCCR remained statistically significant after adjusting
133 for family history of PCa (number of first- and second-degree relatives diagnosed with PCa; adjusted
134 HR=3.00, 95% CI 1.06-8.54) or geographical location (adjusted HR=3.79, 95% CI 1.41-10.2). This
135 difference remained similar after omitting related individuals (HR=4.29, 95% CI 1.30-14.2), after
136 omitting the first six mo of follow-up (HR=3.96, 95% CI 1.18-13.3), and after omitting carriers of PVs
137 in the region c.756 to c.1000 (HR=3.42, 95% CI 1.27-9.18) or missense variants (HR=3.76, 95% CI
138 1.36-10.4). When carriers of the Ashkenazi founder PV c.5946delT (n=42) which is located in the
139 OCCR was omitted, the difference in PCa risk between PCCR and OCCR PV carriers was not
140 statistically significant but the HR estimate was of similar magnitude (HR=2.89, 95% CI 0.98-8.53;
141 Supplementary table 2).

142

143 We did not observe a higher risk of Gleason score \geq 8 PCa for PVs in the PCCR compared to non-PCCR
144 PVs (HR=0.87, 95% CI 0.12-6.34), or compared to PVs in the region c.1001 to c.7913 (HR=0.79, 95%
145 CI 0.11-5.69). However, the HRs did not differ significantly from those for Gleason score \leq 7 PCa (PCCR
146 vs non-PCCR: HR=3.32, 95% CI 1.25-8.84; test for heterogeneity, p=0.052; PCCR vs c.1001 to c.7913:
147 HR=2.94, 95% CI 1.11-7.80; test for heterogeneity, p=0.088).

148

149 Our results corroborate the observation that carriers of PVs in the PCCR of the *BRCA2* gene [8] are at
150 a higher risk of PCa than other *BRCA2* PV carriers. Patel and co-workers reported a HR of 1.78 (95%
151 CI 1.25-2.52) compared to PVs in the region c.1001 to c.7913 [8], consistent with our HR estimate of
152 2.09 (95% CI 0.98-4.45). Our findings do not support a stronger association with a more aggressive
153 phenotype, but these estimates were based on a small number of cases and have wide CIs. PV
154 carriers may receive enhanced screening which may lead to biases in comparisons against the
155 population incidence [1]. However, current screening practices do not differ by *BRCA2* PV location
156 and so this is unlikely to have confounded the comparisons between the *BRCA2* genomic regions. A
157 much larger cohort of unaffected carriers with longer follow-up is required to provide more precise
158 PV-specific risk estimates, and to further clarify whether the observed variation in risk reflects lower
159 risks associated with PVs outside the OCCR and PCCR than the risk associated with PCCR PVs, or
160 solely a lower risk associated with PVs in the OCCR.

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191 Figure and Table legends

192

193 **Figure 1**

194 Absolute prostate cancer risk, (A) by location of *BRCA2* pathogenic variant, (B) by location of *BRCA2*
195 pathogenic variant and with follow-up initiated six mo after study entry.

196 The number at risk at each age is shown above the x-axis. The curves are truncated at ages when
197 fewer than five participants are at risk.

198 **Abbreviations** OCCR: ovarian cancer cluster region; PCCR: prostate cancer cluster region.

199

200 **Table 1**

201 Prostate cancer risk by location of *BRCA2* pathogenic variant.

202 **Abbreviations** SIR: standardised incidence ratio; CI: confidence interval; HR: hazard ratio; FAR:
203 floating absolute risk; PV: pathogenic variant; OCCR: ovarian cancer cluster region; PCCR: prostate
204 cancer cluster region.

205

206

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216

217 Conflict of interest statement

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219 All authors declare that they have no conflict of interest.

220

221 Data sharing statement

222

223 The data used in the analysis are available to other researchers upon request to the EMBRACE study
224 coordinators (<https://ccge.medschl.cam.ac.uk/embrace/>).

225

Figure 1 Absolute prostate cancer risk, (A) by location of *BRCA2* pathogenic variant, (B) by location of *BRCA2* pathogenic variant and with follow-up initiated six mo after study entry.

The number at risk at each age is shown above the x-axis. The curves are truncated at ages when fewer than five participants are at risk.

Abbreviations OCCR: ovarian cancer cluster region; PCCR: prostate cancer cluster region.

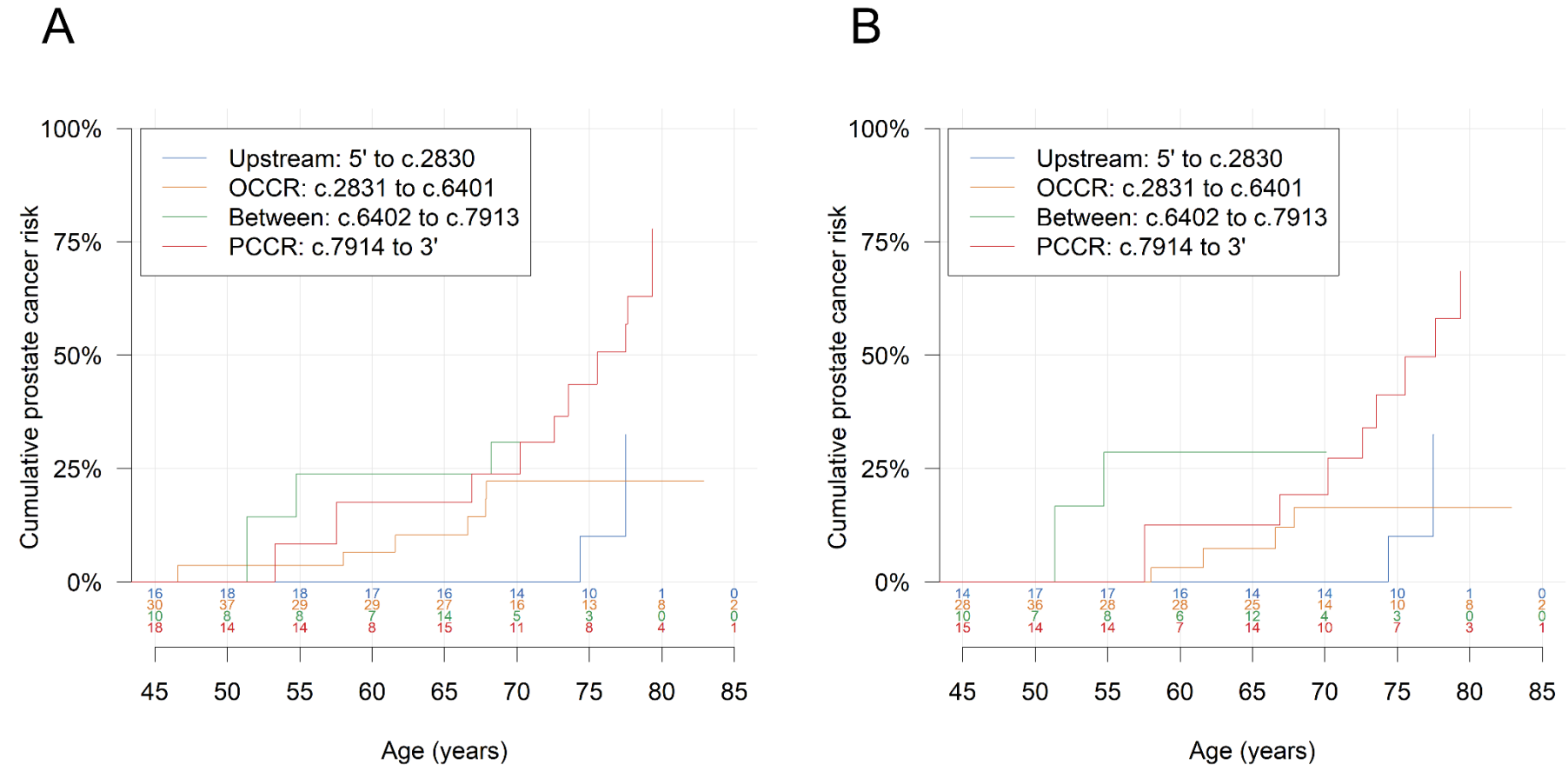


Table 1 Prostate cancer risk by location of *BRCA2* pathogenic variant.

Abbreviations SIR: standardised incidence ratio; CI: confidence interval; HR: hazard ratio; FAR: floating absolute risk; PV: pathogenic variant; PCCR: prostate cancer cluster region; OCCR: ovarian cancer cluster region.

| PV location | N | Person-years | Observed events | Incidence rate per 1000 person-years (95% CI) | Expected events | SIR (95% CI) | HR (95% CI) | FAR (95% CI) |
|--------------------------------------|-----|--------------|-----------------|---|-----------------|------------------|------------------|------------------|
| Compared to non-PCCR PVs | | | | | | | | |
| Non-PCCR (5' to c.7913) | 354 | 2029.8 | 15 | 7.39 (4.45-12.3) | 4.53 | 3.31 (1.97-5.57) | Reference | |
| PCCR (c.7914 to 3') | 93 | 524.6 | 11 | 21.0 (11.4-38.7) | 1.32 | 8.33 (4.46-15.6) | 2.34 (1.09-5.03) | |
| Compared to OCCR PVs | | | | | | | | |
| 5' to c.2830 | 108 | 625.8 | 5 | 7.99 (3.37-19.0) | 1.43 | 3.50 (1.48-8.26) | 1.72 (0.50-5.94) | 1.72 (0.70-4.24) |
| OCCR (c.2831 to c.6401) ⁱ | 178 | 1054.4 | 6 | 5.69 (2.54-12.8) | 2.44 | 2.46 (1.07-5.64) | Reference | 1.00 (0.43-2.33) |
| c.6402 to c.7913 | 66 | 338.8 | 4 | 11.8 (4.29-32.5) | 0.65 | 6.14 (2.18-17.3) | 3.23 (0.79-13.2) | 3.23 (1.15-9.11) |
| PCCR (c.7914 to 3') | 93 | 524.6 | 11 | 21.0 (11.4-38.7) | 1.32 | 8.33 (4.46-15.6) | 3.41 (1.27-9.16) | 3.41 (1.96-5.95) |
| Indeterminable | 2 | | | | | | | |

ⁱ Detailed results for carriers of PVs in the OCCR are available in a previous publication [1].

Supplementary table 1 List of *BRCA2* pathogenic variants carried by the 447 study participants.

The pathogenic variants are specified using HGVS nomenclature (<http://varnomen.hgvs.org/>), using cDNA reference sequence NM_000059.3 and reference genome hg18.

Abbreviations DL: large deletion; S: splice site.

| Genomic level | Protein level | n |
|------------------------|---------------|----------------|
| c.-227-?_67+?del | p.0 | 6 |
| c.-227-?_6841+?del | p.0 | 1 |
| c.17_18del | p.Lys6fs | 1 |
| c.22_23del | p.Arg8fs | 2 |
| c.26del | p.Pro9fs | 5 |
| c.36dup | p.Glu13* | 1 |
| c.104_110del | p.Leu35fs | 2 |
| c.314T>G | p.Leu105* | 1 |
| c.396T>A | p.Cys132* | 1 |
| c.407del | p.Asn136fs | 2 |
| c.470_474del | p.Lys157fs | 1 |
| c.516+1G>T | S | 1 |
| c.517-2A>G | S | 2 |
| c.538_539dup | p.Ser181fs | 2 |
| c.574_575del | p.Met192fs | 3 |
| c.631+1G>A | S | 1 |
| c.631+2T>G | p.Gly173fs | 5 |
| c.658_659del | p.Val220fs | 4 ⁱ |
| c.755_758del | p.Asp252fs | 19 |
| c.765_770delinsAAACAAT | p.Asn255fs | 1 |
| c.1097T>G | p.Leu366* | 1 |
| c.1189_1190insTTAG | p.Gln397fs | 7 |
| c.1231del | p.Ile411fs | 1 |
| c.1310_1313del | p.Lys437fs | 3 |
| c.1654del | p.Ser552fs | 1 |
| c.1689G>A | p.Trp563* | 3 |
| c.1787_1799del | p.Asp596fs | 2 |
| c.1813del | p.Ile605fs | 3 |
| c.1813dup | p.Ile605fs | 4 |
| c.1889del | p.Thr630fs | 1 |
| c.1929del | p.Arg645fs | 7 |
| c.2409T>G | p.Tyr803* | 3 |
| c.2606C>G | p.Ser869* | 1 |
| c.2701del | p.Ala902fs | 1 |
| c.2760del | p.Ile921fs | 1 |
| c.2808_2811del | p.Ala938fs | 10 |
| c.2870del | p.Asn957fs | 1 |
| c.3009_3010del | p.His1003fs | 1 |
| c.3158T>G | p.Leu1053* | 2 |
| c.3195_3198del | p.Asn1066fs | 2 |

| Genomic level | Protein level | n |
|----------------------|----------------------|----------|
| c.3405C>A | p.Tyr1135* | 1 |
| c.3530_3533del | p.Asp1177fs | 1 |
| c.3545_3546del | p.Phe1182* | 2 |
| c.3599_3600del | p.Cys1200* | 1 |
| c.3680_3681del | p.Leu1227fs | 1 |
| c.3785C>G | p.Ser1262* | 4 |
| c.3847_3848del | p.Val1283fs | 4 |
| c.3860del | p.Asn1287fs | 1 |
| c.4037_4038del | p.Thr1346fs | 1 |
| c.4101del | p.Lys1367fs | 1 |
| c.4137_4141del | p.Ile1380fs | 1 |
| c.4163_4164delinsA | p.Thr1388fs | 5 |
| c.4169del | p.Leu1390fs | 1 |
| c.4223del | p.Gln1408fs | 1 |
| c.4405_4409del | p.Asp1469fs | 1 |
| c.4415_4418del | p.Lys1472fs | 1 |
| c.4478_4481del | p.Glu1493fs | 10 |
| c.4525C>T | p.Gln1509* | 1 |
| c.4631dup | p.Asn1544fs | 1 |
| c.4638del | p.Phe1546fs | 1 |
| c.4648G>T | p.Glu1550* | 1 |
| c.4712_4713del | p.Glu1571fs | 2 |
| c.4828dup | p.Val1610fs | 1 |
| c.4876_4877del | p.Asn1626fs | 4 |
| c.4889C>G | p.Ser1630* | 2 |
| c.4914dup | p.Val1639fs | 1 |
| c.4936_4939del | p.Glu1646fs | 1 |
| c.4981del | p.Tyr1661fs | 1 |
| c.5073dup | p.Trp1692fs | 4 |
| c.5116_5119del | p.Asn1706fs | 3 |
| c.5141_5144del | p.Tyr1714fs | 1 |
| c.5217_5223del | p.Tyr1739* | 1 |
| c.5217T>A | p.Tyr1739* | 1 |
| c.5279C>G | p.Ser1760* | 2 |
| c.5298del | p.Asn1766fs | 1 |
| c.5303_5304del | p.Leu1768fs | 2 |
| c.5329_5334delinsG | p.Lys1777fs | 1 |
| c.5350_5351del | p.Asn1784fs | 2 |
| c.5410_5411del | p.Val1804fs | 1 |
| c.5576_5579del | p.Ile1859fs | 4 |
| c.5641_5644del | p.Lys1881fs | 1 |
| c.5655C>A | p.Cys1885* | 1 |
| c.5682C>G | p.Tyr1894* | 10 |
| c.5722_5723del | p.Leu1908fs | 2 |
| c.5835dup | p.Ser1946fs | 1 |

| Genomic level | Protein level | n |
|-----------------------|---------------|-----------------|
| c.5857G>T | p.Glu1953* | 1 |
| c.5909C>A | p.Ser1970* | 6 |
| c.5946del | p.Ser1982fs | 42 |
| c.6049A>T | p.Lys2017* | 1 |
| c.6052_6053del | p.Ser2018* | 1 |
| c.6065C>G | p.Ser2022* | 1 |
| c.6079dup | p.Arg2027fs | 1 |
| c.6081dup | p.Glu2028fs | 1 |
| c.6275_6276del | p.Leu2092fs | 27 ⁱ |
| c.6385G>T | p.Glu2129* | 1 |
| c.6405_6409del | p.Asn2135fs | 1 |
| c.6486_6489del | p.Lys2162fs | 1 |
| c.6588_6589del | p.Lys2196fs | 1 |
| c.6591_6592del | p.Glu2198fs | 5 |
| c.6602del | p.Ser2201fs | 1 |
| c.6658_6662del | p.Glu2220fs | 1 |
| c.6757_6758del | p.Leu2253fs | 2 |
| c.6829_6833del | p.Ile2278fs | 1 |
| c.6944_6947del | p.Ile2315fs | 4 |
| c.6980del | p.Leu2327* | 3 |
| c.6996_7004delins(20) | p.Cys2332fs | 3 |
| c.7008-?_7805+?del | DL | 13 |
| c.7008-?_8331+?del | DL | 1 |
| c.7069_7070del | p.Leu2357fs | 5 |
| c.7342_7343del | p.Lys2448fs | 1 |
| c.7480C>T | p.Arg2494* | 4 |
| c.7495C>T | p.Gln2499* | 1 |
| c.7543dup | p.Thr2515fs | 1 |
| c.7558C>T | p.Arg2520* | 1 |
| c.7757G>A | p.Trp2586* | 6 |
| c.7758G>A | p.Trp2586* | 2 |
| c.7762_7764delinsTT | p.Ile2588fs | 4 |
| c.7795G>T | p.Glu2599* | 1 |
| c.7884dup | p.Trp2629fs | 3 |
| c.7934del | p.Arg2645fs | 1 |
| c.7958T>C | p.Leu2653Pro | 1 |
| c.7977-1G>C | S | 4 |
| c.7977-2_-3del | S | 1 |
| c.7988A>T | p.Glu2663Val | 2 |
| c.8113dup | p.Ser2705fs | 1 |
| c.8167G>C | p.Asp2723His | 6 |
| c.8247_8248del | p.Lys2750fs | 2 |
| c.8297del | p.Thr2766fs | 9 |
| c.8395del | p.Arg2799fs | 1 |
| c.8575del | p.Gln2859fs | 9 |

| Genomic level | Protein level | n |
|--------------------|---------------|---|
| c.8633-?_8754+?del | DL | 1 |
| c.8633-?_9256+?del | DL | 2 |
| c.8756del | p.Gly2919fs | 3 |
| c.8878C>T | p.Gln2960* | 1 |
| c.8904del | p.Val2969fs | 9 |
| c.8945_8946del | p.Lys2982fs | 1 |
| c.8951C>G | p.Ser2984* | 3 |
| c.8956dup | p.Ile2986fs | 1 |
| c.9054_9055del | p.Ser3018fs | 4 |
| c.9069_9076del | p.Asn3024fs | 2 |
| c.9097dup | p.Thr3033fs | 2 |
| c.9117+1G>A | S | 1 |
| c.9117G>A | p.Val2985fs | 2 |
| c.9157del | p.Glu3053fs | 2 |
| c.9253dup | p.Thr3085fs | 2 |
| c.9257-2A>G | S | 1 |
| c.9294C>G | p.Tyr3098* | 6 |
| c.9357_9360del | p.Ile3120fs | 2 |
| c.9380G>A | p.Trp3127* | 1 |
| c.9382C>T | p.Arg3128* | 7 |
| c.9481A>T | p.Lys3161* | 1 |
| c.9490_9491del | p.Asn3164fs | 1 |
| c.9502-2A>C | S | 1 |

ⁱ One participant carried both c.658_659del and c.6275_6276del.

Supplementary table 2 Prostate cancer risk by location of *BRCA2* pathogenic variant: adjustments and sensitivity analyses.

Abbreviations HR: hazard ratio; CI: confidence interval; PV: pathogenic variant; PCCR: prostate cancer cluster region; OCCR: ovarian cancer cluster region.

| PV location | HR (95% CI) | HR adjusted for family history ⁱ (95% CI) | HR adjusted for geographical location ⁱⁱ (95% CI) | HR omitting related participants ⁱⁱⁱ (95% CI) | HR omitting the first 6 mo of follow-up (95% CI) | HR omitting carriers of PVs in c.756 to c.1000 ^{iv} (95% CI) | HR omitting missense variant carriers ^v (95% CI) | HR omitting Ashkenazi founder PV carriers ^{vi} (95% CI) |
|---------------------------------|------------------|--|--|--|--|---|---|--|
| Compared to non-PCCR PVs | | | | | | | | |
| Non-PCCR (5' to c.7913) | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference |
| PCCR (c.7914 to 3') | 2.34 (1.09-5.03) | 2.03 (0.89-4.61) | 2.50 (1.15-5.46) | 2.93 (1.23-6.97) | 2.23 (0.93-5.37) | 2.33 (1.09-5.01) | 2.56 (1.17-5.59) | 2.05 (0.94-4.48) |
| Compared to OCCR PVs | | | | | | | | |
| 5' to c.2830 | 1.72 (0.50-5.94) | 1.77 (0.53-5.98) | 1.86 (0.47-7.36) | 1.60 (0.34-7.49) | 2.55 (0.63-10.3) | 1.75 (0.51-6.03) | 1.77 (0.51-6.17) | 1.49 (0.40-5.62) |
| OCCR (c.2831 to c.6401) | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference |
| c.6402 to c.7913 | 3.23 (0.79-13.2) | 2.86 (0.65-12.7) | 4.18 (0.96-18.2) | 3.65 (0.67-19.7) | 4.03 (0.75-21.7) | 3.24 (0.80-13.2) | 3.21 (0.79-13.0) | 2.77 (0.61-12.5) |
| PCCR (c.7914 to 3') | 3.41 (1.27-9.16) | 3.00 (1.06-8.54) | 3.79 (1.41-10.2) | 4.29 (1.30-14.2) | 3.96 (1.18-13.3) | 3.42 (1.27-9.18) | 3.76 (1.36-10.4) | 2.89 (0.98-8.53) |
| Indeterminable | | | | | | | | |

ⁱ Number of first- and second-degree relatives diagnosed with prostate cancer.

ⁱⁱ Location of recruiting clinic: London; South or East England; Wales, English Midlands or North England; Scotland or Ireland.

ⁱⁱⁱ Carriers for which at least one male relative was included in the study (n=94 omitted).

^{iv} Carriers of PVs in the *BRCA2* region c.756 to c.1000 suggested to be associated with increased PCa risks by Patel et al (2020) (n=1 omitted).

^v Carriers of pathogenic missense variants (n=9 omitted).

^{vi} Carriers of c.5946delT (n=42 omitted).