Brief Correspondence

Prostate Cancer Risk by BRCA2 Genomic Regions

Tommy Nyberg a,b,*, Debra Frost a, Daniel Barrowdale a, D. Gareth Evans b, Elizabeth Bancroft c,d, Julian Adlard e, Munaza Ahmed f, Julian Barwell g, Angela F. Brady h, Carole Brewer i, Jackie Cook l, Rosemarie Davidson k, Alan Donaldson l, Jacqueline Eason m, Helen Gregory n, Alex Henderson o, Louise Izatt p, M. John Kennedy q, Claire Miller r, Patrick J. Morrison s, Alex Murray u, Kai-Ren Ong v, Mary Porteous w, Caroline Pottinger x, Mark T. Rogers y, Lucy Side z, Katie Snape aa, Vishakha Tripathi p, Lisa Walker bb, Marc Tischkowitz cc, Rosalind Eelles cd, Douglas F. Easton a,b, Antonis C. Antoniou a,b

a Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; b Manchester Regional Genetics Service, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK; c Oncogenetics Team, Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK; d Cancer Genetics Unit, Royal Marsden NHS Foundation Trust, London, UK; e Yorkshire Regional Genetics Service, Leeds Teaching Hospitals NHS Trust, Leeds, UK; f North East Thames Regional Genetics Service, Great Ormond Street Hospital for Children NHS Trust, London, UK; g Leicester Clinical Genetics Service, University Hospitals of Leicester NHS Trust, Leicester, UK; h North West Thames Regional Genetics Service, London North West Healthcare NHS Trust, London, UK; i Peninsula Clinical Genetics Service, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK; j North Trent Clinical Genetics Service, Sheffield Children’s NHS Foundation Trust, Sheffield, UK; k West of Scotland Regional Genetics Service, NHS Greater Glasgow and Clyde, Glasgow, UK; l South Western Regional Genetics Service, University Hospitals Bristol NHS Foundation Trust, Bristol, UK; m Nottingham Centre for Medical Genetics, Nottingham University Hospitals NHS Trust, Nottingham, UK; n North of Scotland Regional Genetics Service, NHS Grampian, Aberdeen, UK; o Northern Genetics Service, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK; p South East Thames Regional Genetics Service, Guy’s and St Thomas’ NHS Foundation Trust, London, UK; q St James’s Hospital, Dublin, Republic of Ireland; r National Centre for Medical Genetics, Dublin, Republic of Ireland; s Merseyside and Cheshire Clinical Genetics Service, Liverpool Women’s NHS Foundation Trust, Liverpool, UK; t Northern Ireland Regional Genetics Service, Belfast Health and Social Care Trust, Belfast, UK; u Medical Genetics Services for Wales, Abertawe Bro Morgannwg University Health Board, Swansea, UK; v West Midlands Regional Genetics Service, Birmingham Women’s and Children’s NHS Foundation Trust, Birmingham, UK; w South East of Scotland Regional Genetics Service, NHS Lothian, Edinburgh, UK; x Medical Genetics Services for Wales, Betsi Cadwaladr University Health Board, Bodelwyddan, UK; y All Wales Medical Genetics Service, NHS Wales, Cardiff, UK; z Wessex Clinical Genetics Service, University Hospital Southampton NHS Foundation Trust, Southampton, UK; a South West Thames Regional Genetics Service, St George’s University Hospitals NHS Foundation Trust, London, UK; b Oxford Regional Genetics Service, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; c Department of Medical Genetics, National Institute for Health Research Cambridge Biomedical Research Centre, University of Cambridge, Cambridge, UK

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Abstract

A BRCA2 prostate cancer cluster region (PCCR) was recently proposed (c.7914 to 3′) wherein pathogenic variants (PVs) are associated with higher prostate cancer (PCa) risk than PVs elsewhere in the BRCA2 gene. Using a prospective cohort study of 447 male BRCA2 PV carriers recruited in the UK and Ireland from 1998 to 2016, we estimated standardised incidence ratios (SIRs) compared with population incidences and assessed variation in risk by PV location. Carriers of PVs in the PCCR had a PCa SIR of 8.33 (95% confidence interval [CI] 4.46–15.6) and were at a higher risk of PCa than carriers of other BRCA2 PVs (SIR = 3.31, 95% CI 1.97–5.57; hazard ratio = 2.34, 95% CI 1.09–5.03). PCCR PVs

* These authors contributed equally.

† Corresponding author. Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Cambridge CB1 8RN, UK. Tel.: +44 (0)1223 748646; Fax: +44 (0)1223 748628. E-mail address: ten25@medschl.cam.ac.uk (T. Nyberg).
We recently reported prostate cancer (CaP) risk estimates for pathogenic variants (PVs) in *BRCA2*, based on a prospective cohort of male carriers [1]. Variability in cancer risks due to genotype-phenotype correlations may allow for more individualised counselling and screening. We noted that PVs within the so-called ovarian cancer cluster region (OCCR) in exon 11 of the gene [2–4] were associated with a lower CaP risk than other *BRCA2* PVs [1,3,4]. PVs in the OCCR have consistently been shown to be associated with an increased ovarian cancer risk but a decreased breast cancer risk [2,3,5,6], although the precise boundaries of the OCCR [5,3] and the mechanisms behind this risk variation remain uncertain. It has been proposed that the likelihood that a PV triggers nonsense-mediated mRNA decay varies by genomic region [7,8] so that OCCR PVs might produce a truncated or alternatively spliced protein the capability of which to suppress tumours varies by cancer type [2,3,5,7,8], but there is currently no experimental support for this hypothesis [7]. Shortly after the publication of our manuscript, Patel and coworkers [8] proposed the existence of a prostate cancer cluster region (PCCR) at the 3′ end of *BRCA2*, based on retrospective cohort data. This retrospective study reported that men with *BRCA2* PVs in the proposed PCCR have a higher risk of CaP (hazard ratio [HR] = 1.78, 95% confidence interval [CI] 1.25–2.52), particularly Gleason score ≥8 CaPs (HR = 3.11, 95% CI 1.63–5.95), than men with PVs in the reference region c.1001 to c.7913, but did not present estimates of the absolute CaP risk for PCCR PV carriers [8]. In order to substantiate or refute this association, and to provide direct estimates of the absolute risk of CaP for carriers of *BRCA2* PCCR PVs, we have reanalysed our prospective data.

The prospective cohort comprised 447 male *BRCA2* CaP carriers who were recruited to the EMBRACE study (http://ccge.medschl.cam.ac.uk/embrace/) through clinical genetics centres in the UK and Ireland between 1998 and 2016 at a median age of 51.4 yr (interquartile range 41.5–63.6 yr). The participants were counselled with regard to their PV. Detailed information on the cohort and on inclusion criteria, data collection, follow-up, and statistical analysis approach is available in our recent publication [1]. The participants’ PVs (listed in Supplementary Table S1) were grouped on the basis of position within the *BRCA2* gene, based on the proposed PCCR (c.7914 to 3′ [8]; HGVS nomenclature [http://varnames.hgvs.org/]; using cDNA reference sequence NM_000059.3 and reference genome hg18) and the wide definition of the OCCR (c.2831 to c.6401) [1–4]. We additionally considered the region bounded by c.756 and c.1000 in which Patel and coworkers [8] found evidence of an increased CaP risk, but due to a small sample size (n = 1) we could not estimate the CaP risk associated with this region. Here, we also present floating absolute risks (FARs) [9] to enable risk comparisons between any of the considered genomic regions.

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

Twenty-six participants developed CaP during a median follow-up of 5.3 yr (interquartile range 2.6–8.9 yr) [1]. Carriers of PVs in the PCCR (n = 93) had a CaP standardised incidence ratio (SIR) of 8.33 (95% CI 4.46–15.6), whereas carriers of PVs elsewhere in *BRCA2* (n = 354) had an SIR of 3.31 (95% CI 1.97–5.57) compared with population incidences. This corresponds to a significantly higher CaP risk associated with PVs in the PCCR than PVs not in the PCCR (HR = 2.34, 95% CI 1.09–5.03; Table). Compared with PVs in the region c.1001 to c.7913 [8], PCCR PVs were associated with an HR of 2.09 (95% CI 0.98–4.45). As previously reported, the SIR for carriers of PVs in the wide definition of the OCCR (n = 178) was 2.46 (95% CI 1.07–5.64) [1], and the risk for carriers of PCCR PVs was also significantly higher than that for OCCR PV carriers (HR = 3.41, 95% CI 1.27–9.16). The SIR for PVs located in the region bounded by the OCCR and the PCCR (c.6402 to c.7913; n = 66) was estimated to be 6.14 (95% 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% CI 1.48–8.26). The FARs for the comparison of risks across the four regions suggested that the observed increased risk associated with PVs in the PCCR may partly be driven by the lower risk associated with PVs in the OCCR (Table). The proportional hazard assumption was violated for the model with all genomic regions fitted (Schoenfeld residual test, p = 0.003); in line with this the corresponding Kaplan-Meier plot indicated that the risks might be similar between OCCR and PCCR PV carriers at younger ages but deviate at older ages. PCCR PV carriers had an estimated cumulative CaP risk of 44% (95% CI 23–72%) by the age of 75 yr and 78% (95% CI 54–94%) by age 85 yr. After omitting the first 6 mo of follow-up to assess the possible effect of screening-associated diagnoses of indolent CaPs, the corresponding estimates were 41% (95% CI 20–73%) and 69% (95% CI 42–91%), respectively (Fig. 1).

The difference in CaP risk for PVs in the PCCR versus that in the OCCR remained statistically significant after adjusting...
Table 1 – Prostate cancer risk by location of BRCA2 pathogenic variant.

| 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 with 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 with 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) | 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 (2.18–17.13) | 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      |               |                 |                                               |                 |             |             |             |

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

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

for family history of PCa (number of first- and second-degree relatives diagnosed with PCa; adjusted HR = 3.00, 95% CI 1.06–8.54) or geographical location (adjusted HR = 3.79, 95% CI 1.41–10.2). This difference remained similar after omitting the first 6 mo of follow-up (HR = 3.96, 95% CI 1.18–13.3), related individuals (HR = 4.29, 95% CI 1.30–14.2), and carriers of PVs 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 1.36–10.4). When carriers of the Ashkenazi founder PV c.5946delT (n = 42), which is located in the OCCR, was omitted, the difference in PCa risk between PCCR and OCCR PV carriers was not statistically significant, but the HR estimate was of similar magnitude (HR = 2.89, 95% CI 0.98–8.53; Supplementary Table S2).

We did not observe a higher risk of Gleason score ≥8 PCa for PVs in the PCCR than for PVs not in the PCCR (HR = 0.87, 95% CI 0.12–6.34) or in the region c.1001 to c.7913 (HR = 0.79, 95% CI 0.11–5.69). However, the HRs did not differ significantly from those for Gleason score ≤7 PCa (PCCR 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: HR = 2.94, 95% CI 1.11–7.80; test for heterogeneity, p = 0.088).

Our results corroborate the observation that carriers of PVs in the PCCR of the BRCA2 gene [8] are at a higher risk of PCa than other BRCA2 PV carriers. Patel and coworkers [8] reported an HR of 1.78 (95% CI 1.25–2.52) compared with PVs in the region c.1001 to c.7913, consistent with our HR estimate of 2.09 (95% CI 0.98–4.45). Our findings do not support a stronger association with a more aggressive phenotype, but these estimates were based on a small number of cases and the associated CIs are wide. PV carriers may receive enhanced screening, which may lead to biases in comparisons against the population incidence [1]. However, current screening practices do not differ by BRCA2 PV

Fig. 1 – Absolute prostate cancer risk (A) by location of BRCA2 pathogenic variant and (B) by location of BRCA2 pathogenic variant and with follow-up initiated 6 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. OCCR = ovarian cancer cluster region; PCCR = prostate cancer cluster region.
location, and so this is unlikely to have confounded the comparisons between the BRCA2 genomic regions. A much larger cohort of unaffected carriers with longer follow-up is required to provide more precise PV-specific risk estimates and to further clarify whether the observed variation in risk reflects lower risks associated with PVs outside the OCR and PCCR than the risk associated with PCCR PVs, or solely a lower risk associated with PVs in the OCR.

**Author contributions:** Tommy Nyberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Antoniou, Nyberg, Easton.

**Acquisition of data:** Frost, Barrowdale, Bancroft, Easton, Eeles, Evans, Tischkowitz, Adlard, Ahmed, Barwell, Brady, Brewer, Cook, Davidson, Donaldson, Eason, Gregory, Izatt, Kennedy, Miller, Morrison, Murray, Ong, Porteous, Pottinger, Rogers, Side, Snape, Tripathi, Walker.

**Analysis and interpretation of data:** Nyberg, Antoniou, Easton.

**Drafting of the manuscript:** Nyberg, Antoniou, Easton.

**Critical revision of the manuscript for important intellectual content:** Evans, Frost, Barrowdale, Bancroft, Eeles, Tischkowitz, Adlard, Ahmed, Barwell, Brady, Brewer, Cook, Davidson, Donaldson, Eason, Gregory, Izatt, Kennedy, Miller, Morrison, Murray, Ong, Porteous, Pottinger, Rogers, Side, Snape, Tripathi, Walker.

**Statistical analysis:** Nyberg, Antoniou, Easton.

**Obtaining funding:** Easton, Antoniou, Eeles, Evans.

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**Supervision:** Antoniou, Tischkowitz.

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**Appendix A. Supplementary data**

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.eurouro.2020.05.005.

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