Prostate cancer risks for male *BRCA1* and *BRCA2* mutation carriers: a prospective cohort study

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Abstract

Background

BRCA1 and *BRCA2* mutations have been associated with prostate cancer (PCa) risk but a wide range of risk estimates has been reported, based on retrospective studies.

Objective

To estimate relative and absolute PCa risks associated with *BRCA1/2* mutations, and to assess risk-modification by age, family history and mutation location.

Design, Setting, and Participants

Prospective cohort study of male *BRCA1* (*n*=376) and *BRCA2* carriers (*n*=447) identified through clinical genetics centres in the UK and Republic of Ireland (median follow-up: 5.9 and 5.3 yr, respectively).

Outcome Measurements and Statistical Analysis

Standardised incidence/mortality ratios (SIRs/SMRs) relative to population incidences or mortality rates, absolute risks and hazard ratios (HRs), estimated using cohort and survival analysis methods.

Results and Limitations

Sixteen *BRCA1* and 26 *BRCA2* carriers were diagnosed with PCa during follow-up. *BRCA2* carriers had a SIR of 4.45 (95% confidence interval [CI] 2.99-6.61), and absolute PCa risk of 27% (95% CI 17%-41%) and 60% (95% CI 43%-78%) by ages 75 and 85, respectively. For *BRCA1* carriers, the overall SIR was 2.35 (95% CI 1.43-3.88); the corresponding SIR at ages<65 was 3.57 (95% CI 1.68-7.58). However, the *BRCA1* SIR varied between 0.74 and 2.83 in sensitivity analyses to assess potential screening effects. PCa risks for *BRCA2* carriers increased with family history (HR per affected relative=1.68, 95% CI 0.99-2.85). *BRCA2* mutations in the region bounded by positions c.2831–c.6401 were associated with an SIR of 2.46 (95% CI 1.07-5.64) compared to population incidences, corresponding to a lower PCa risk (HR=0.37, 95% CI 0.14-0.96) than for mutations outside the region. *BRCA2* carriers had a stronger association with Gleason score≥7 (SIR=5.07, 95% CI 3.20-8.02) than Gleason score≤6 PCa (SIR=3.03, 95% CI 1.24-7.44), and increased risk of death from PCa (SMR=3.85, 95% CI 1.44-10.3). Limitations include potential screening effects for these known mutation carriers; however, the *BRCA2* results were robust to multiple sensitivity analyses.

Conclusions

The results substantiate PCa risk patterns indicated by retrospective analyses for *BRCA2* carriers, including further evidence of association with aggressive PCa, and give some support for a weaker association in *BRCA1* carriers.

Patient Summary

In this study we followed unaffected men who were known to carry mutations in the *BRCA1* and *BRCA2* genes, to investigate whether they are at higher risk of developing prostate cancer compared to the general population. We found that carriers of *BRCA2* mutations have a high risk of developing

prostate cancer, particularly more aggressive prostate cancer, and that this risk varied by family history of prostate cancer and the location of the mutation within the gene.

Introduction

Deleterious mutations in the tumour suppressor genes *BRCA1* and *BRCA2* are associated with high risks of breast and ovarian cancer [1,2], and have been implicated in the genetic susceptibility to prostate cancer (PCa). Retrospective studies have reported that *BRCA2* mutations are associated with relative risks (RRs) of PCa in the range 2—6 [3–12]. RR estimates were reported to be higher at younger ages, in the range 6—9 below age 65 [3,5,12–14], and *BRCA2* carriers present more often with aggressive PCa [7,8]. The evidence of association between *BRCA1* mutations and PCa risk is inconsistent, with reported RRs in the range 0.4—4 [4,6–9,11,12,15–18]. A meta-analysis in 2011 concluded that there is insufficient evidence for an association between *BRCA1* mutations and PCa risk [19], but two studies have reported statistically significant RRs of 2—4 for *BRCA1* carriers below age 65 [16,20]. Studies have also reported variation in PCa risks by mutation location or type [5,7,9,12,21,22].

There are only a few estimates of absolute risks of PCa for *BRCA1/2* mutation carriers and those are based on retrospective studies [3,5,6,12,14,16,20,21]. Given the rapidly rising population PCa incidences in the PSA testing era, retrospective absolute risk estimates may not be representative of the risks for mutation carriers currently seen in genetics clinics. Only two small prospective cohort studies of male *BRCA1/2* carriers have been reported [11,23], the largest of which followed 137 *BRCA1* and 71 *BRCA2* carriers for an average of 5.1 yr, and did not show an association with PCa [23].

In the present study, we report age-specific PCa risk estimates based on a large prospective cohort of male *BRCA1* and *BRCA2* carriers. We present relative and absolute risks, investigate variability in these risks by family history and mutation location, and consider the risk of developing high-grade PCa.

Materials and Methods

EMBRACE study participants

The Epidemiological Study of Familial Breast Cancer (EMBRACE; http://ccge.medschl.cam.ac.uk/embrace/) is a cohort study of *BRCA1* and *BRCA2* mutation carriers initiated in 1998. Participants were recruited through clinical genetics centres across the UK and Republic of Ireland, and were counselled with regards to their mutation status. This analysis included all male participants without PCa diagnosis at recruitment who carried mutations considered to be pathogenic based on widely accepted criteria (ENIGMA consortium; https://enigmaconsortium.org/). All participants completed a baseline questionnaire which included information on known and suspected cancer risk factors, medical history and personal and family cancer history. Follow-up data were collected through linkage with national registers covering England, Wales and Scotland, and questionnaires collected two, five and ten yr post-baseline. For self-reported cancers, confirmation was sought from the participating clinics. For the present study, the end of follow-up was set as 30th June 2016 to ensure that cancer diagnoses were likely to have

been reported at the time of the last record linkage (performed on 4th October 2016), or as the date of the last returned questionnaire if one was available after 30th June 2016.

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

Statistical analysis

We prospectively followed the participants from the completion of their baseline questionnaire until their age at diagnosis of PCa, age of death, age at the end-of-follow-up, or age 85, whichever occurred first. A diagnosis of another cancer or of prostatic intraepithelial neoplasia were not considered as censoring events. Analogously, we followed the participants for deaths due to PCa.

We compared the observed PCa incidence and PCa mortality to that expected from population incidences and PCa-specific mortality rates (Office for National Statistics, https://www.ons.gov.uk/), using standardised incidence ratios (SIRs) or standardised mortality ratios (SMRs) computed with Poisson regression. We used the Kaplan—Meier estimator to estimate absolute risks, and Cox regression to test for differences in risk between subgroups.

We classified men who had at least one first- or second-degree relative diagnosed with PCa as having positive PCa family history, and assessed trends in risks with the number of affected relatives. We investigated differences in risk by mutation position using pre-specified definitions of regions that have demonstrated different associations with PCa risk in published studies [5,9,12,21,22]. To assess the association of *BRCA1/2* mutations with clinical PCa subtypes based on biopsy Gleason score (GS), we compared the observed number of PCa diagnoses by GS subtypes to those expected given population GS-specific incidences. We used competing risk estimators to estimate absolute risks of these clinical subtypes. Because data on GSs were not available for all PCas, we used multiple imputation to avoid omission of PCa events.

For the main analysis, we included men with previous non-prostate cancers, did not censor for non-prostate cancers during follow-up, and considered follow-up up to the last questionnaire if available after the last record linkage. We assessed the impact of these assumptions in sensitivity analyses. We also repeated the analysis after omitting pathogenic missense mutations to assess the impact of such less clearly deleterious mutations.

Mutation carriers may be offered a different screening and diagnosis regimen than men in the general population [24]. We performed further analyses to assess the potential impact of such differential screening. First, we performed landmark analyses where follow-up was initiated six or twelve mo after baseline. Second, based on previous findings that observed PCa incidences are 1.4-1.9 times higher for men undergoing PSA screening at regular intervals as compared to unscreened

men [25], we estimated SIRs relative to population incidences multiplied by adjustment factors of 1.6 and 1.9. To obtain absolute risk estimates, we used weighted Kaplan—Meier estimators. Furthermore, in October 2005 the UK-based IMPACT screening trial started recruiting *BRCA1/2* carriers [26]. Although the exact overlap between the studies is unclear, to investigate the impact on risk estimates we assessed PCa risks separately for participants from IMPACT-recruiting centres and their person-time from October 2005 and after; and, the person-time of participants from these centres before October 2005 in addition to the entire person-time of participants from non-IMPACT-recruiting centres.

Statistical analysis was performed using R (version 3.4.4) [27]. Full details of all methods are given in Supplementary appendix 1.

Results

Prostate cancer

In total, 16 out of 376 *BRCA1* and 26 out of 447 *BRCA2* mutation carriers were diagnosed with PCa during a median follow-up of 5.9 and 5.3 yr, respectively (Table 1). All PCa diagnoses were either confirmed through registry linkage or through the participating clinics.

Carrying a *BRCA1* mutation was associated with a SIR of 2.35 (95% confidence interval [CI], 1.43-3.88) of PCa relative to population incidences, whereas the SIR for *BRCA2* carriers was 4.45 (95% CI 2.99-6.61). For *BRCA1* carriers, the SIR for ages<65 was 3.57 (95% CI 1.68-7.58) and the SIR for ages≥65 was 1.86 (95% CI 0.96-3.59). The SIR estimates by age were similar for *BRCA2* carriers (ages<65: SIR=3.99, 95% CI 1.88-8.49; ages≥65: SIR=4.64, 95% CI 2.91-7.41). The estimated absolute risk of PCa was 21% (95% CI 13%-34%) by age 75 and 29% (95% CI 17%-45%) by age 85 for *BRCA1* carriers. The corresponding PCa risks for *BRCA2* carriers were 27% (95% CI 17%-41%) and 60% (95% CI 43%-78%), respectively (Table 2; Figure 1A-B).

For men with a positive family history, the SIRs were 3.17 (95% CI 0.97-10.37) for *BRCA1* and 7.31 (95% CI 3.40-15.72) for *BRCA2* carriers. The corresponding SIRs for carriers without family history were 2.34 (95% CI 1.35-4.07) and 3.87 (95% CI 2.40-6.23), respectively. For *BRCA2* carriers, the hazard ratio (HR) per affected relative was 1.68 (95% CI 0.99-2.85; Table 2; Figure 1C-D).

Men with *BRCA2* mutations located in the central region of the gene (c.2831–c.6401; ovarian cancer cluster region [OCCR], wide definition [2,21]; Supplementary appendix 1) were at significantly lower risk of PCa than men with mutations outside this region (HR=0.37, 95% CI 0.14-0.96). However, mutations both within (SIR=2.46, 95% CI 1.07-5.64) and outside (SIR=5.88, 95% CI 3.75-9.22) the OCCR were associated with elevated PCa risks. When *BRCA2* mutations were grouped according to the narrow definition of the OCCR (c.3847–c.6275) [2,21] the difference in PCa risk for mutations within and outside the OCCR was attenuated (HR=0.42, 95% CI 0.16-1.09; Table 3). The proportional

hazards assumption was violated for this model (Schoenfeld residuals test, p=0.005); the corresponding Kaplan—Meier curves revealed that the risks were similar between the OCCR and non-OCCR mutation carriers at younger ages but deviated at older ages (Figure 1E-F). The difference in risk between OCCR and non-OCCR mutation carriers (wide definition) was not statistically significant but of similar magnitude after adjusting for family history (adjusted HR=0.40, 95% CI 0.15-1.07) and after omitting Ashkenazi mutation carriers (HR=0.43, 95% CI 0.15-1.24; Table 3).

Gleason-score-specific prostate cancer

For *BRCA1* carriers, the SIR was higher for GS≤6 (SIR=3.50, 95% CI 1.67-7.35) than GS≥7 PCa (SIR=1.80, 95% CI 0.89-3.65). In contrast, for *BRCA2* carriers the SIR was higher for GS≥7 (SIR=5.07, 95% CI 3.20-8.02) than GS≤6 PCa (SIR=3.03, 95% CI 1.24-7.44; Table 4). By age 85, the absolute risks for GS≤6 and GS≥7 PCa were 12% (95% CI 5.0%-23%) and 16% (95% CI 6.4%-30%) for *BRCA1*, and 9.3% (95% CI 2.9%-20%) and 51% (95% CI 30%-69%) for *BRCA2* carriers, respectively.

Prostate cancer mortality

Two *BRCA1* and four *BRCA2* carriers died from their incident PCa during the follow-up. Compared to population PCa-specific mortality rates, the SMR was 1.75 (95% CI 0.44-6.90) for *BRCA1* and 3.85 (95% CI 1.44-10.3) for *BRCA2* carriers.

Sensitivity analyses

The estimated SIRs remained similar under alternative inclusion or censoring assumptions (Table 5). Of the 42 diagnoses of PCa, nine occurred within the first six mo after study entry (Supplementary table 1). In the landmark analyses, where follow-up was initiated six or twelve mo after study entry, SIRs were lower for both *BRCA1* (six-month landmark: SIR=2.02, 95% CI 1.17-3.50; twelve-month landmark: SIR=2.15, 95% CI 1.24-3.73) and *BRCA2* carriers (six-month landmark: SIR=3.68, 95% CI 2.35-5.75; twelve-month landmark: SIR=3.37, 95% CI 2.08-5.47) but remained statistically significant. In the six-month landmark analysis, the estimated absolute PCa risk by age 85 was 26% (95% CI 15%-43%) for *BRCA1* and 55% (95% CI 36%-75%) for *BRCA2* carriers. When compared to a hypothetical population with higher PCa incidence, the association remained significant for *BRCA2* carriers (adjustment factor 1.9: SIR=2.34, 95% CI 1.57-3.48). The overall association was not significant for *BRCA1* carriers (adjustment factor 1.9: SIR=1.24, 95% CI 0.75-2.04), but the association for ages<65 remained significant with the lower, 1.6 adjustment factor (SIR=2.23, 95% CI 1.05-4.73). The corresponding absolute risk by age 85 when adjusted by a factor of 1.9, was 17% (95% CI 8%-26%) for *BRCA1* and 41% (95% CI 22%-59%) for *BRCA2* mutation carriers. When the landmark analysis was applied assuming higher population incidences, only the overall association between *BRCA2* mutations and PCa risk remained significant (SIR=2.30, 95% CI 1.47-3.60; Table 5).

When follow-up was restricted to the period prior to the initiation of the IMPACT screening trial [26], in addition to the entire follow-up of participants from non-IMPACT-recruiting centres, there was no association with PCa risk for *BRCA1* carriers (SIR=0.74, 95% CI 0.18-3.04). This was however based on a small sample size and the 95% CI overlapped with that of the estimate for *BRCA1* carriers from IMPACT-recruiting centres with follow-up after October 2005 (SIR=2.83, 95% CI 1.67-4.81). The point estimates were similar for *BRCA2* carriers followed without potential overlap with the IMPACT trial period and recruiting centres (SIR=3.57, 95% CI 1.29-9.85) and those whose follow-up potentially overlapped with IMPACT (SIR=4.54, 95% CI 2.96-6.99). The SIR for ages<65 for *BRCA2* carriers with no potential overlap with IMPACT was 6.75 (95% CI 1.98-23.0; Table 5).

When follow-up was initiated six mo after baseline, the SIRs for *BRCA1* carriers were similar for GS≤6 (SIR=2.26, 95% CI 0.86-5.91) and GS≥7 PCa (SIR=1.90, 95% CI 0.93-3.85), in contrast to the main results. However, the difference in the GS-specific SIR estimates remained for *BRCA2* carriers (GS≤6: SIR=2.01, 95% CI 0.60-6.80; GS≥7: SIR=4.39, 95% CI 2.63-7.31; Table 4). Based on this analysis, the absolute risks by age 85 for *BRCA1* carriers were 7.8% (95% CI 2.2%-18%) for GS≤6 and 18% (95% CI 7.1%-33%) for GS≥7 PCa. For *BRCA2* carriers the corresponding risks were 7.1% (95% CI 1.4%-19%) and 47% (95% CI 25%-66%), respectively.

Discussion

We have estimated the risks of PCa for male *BRCA1* and *BRCA2* mutation carriers using data from a large prospective cohort. The results substantiate previous reports from retrospective studies of a strong association between *BRCA2* mutations and PCa risk, and give some support for a similar but weaker association for mutations in the *BRCA1* gene, particularly at younger ages.

Depending on assumptions, we found that *BRCA2* carriers are at 2—5 times higher risk of PCa compared to men in the general population, which is consistent with previous RR estimates in the range 2—6 [3–12]. Our *BRCA2* RR estimates did not vary substantially with age, in contrast with previous studies which suggest higher RRs at younger ages [3,5,12–14]. However, the higher RR estimate at ages<65 for the subset of *BRCA2* carriers with no potential overlap with the IMPACT screening trial suggests that the similarities in the associations by age might be due to potential screening effects. Due to the small number of events at younger ages the precision of the estimates was however low. In line with previous studies [4,6–9,11,12,15–18,20], our findings indicate that *BRCA1* mutations are at most associated with a moderate PCa risk at younger ages, with RR estimates in the range 2—4 for ages below 65 yr. The evidence of association is weak at older ages, with our RR estimates varying between 1—2. Much larger studies are required to clarify the association between *BRCA1* mutations and PCa risk.

The estimated cumulative risk of developing PCa by age 85 was 29% (95% CI 17%-45%) for *BRCA1* and 60% (95% CI 43%-78%) for *BRCA2* carriers. However, absolute PCa risks depend on the employed screening regimen, and the PCa risks were lower in analyses that assessed the impact of potentially prevalent cancers and the excess PCa risk in PSA-screened individuals. Although our RR estimates are similar to previous estimates, the absolute risk estimates from the present study are

higher compared to estimates from retrospective studies. Previous absolute PCa risk estimates by ages 65 to 80 range from 3%—9% for *BRCA1* carriers [6,16,20] and 15%—34% for *BRCA2* carriers (Supplementary table 2) [3,5,6,12,14,21]. It is plausible that absolute risk estimates based on historical data are not representative of the absolute PCa risks for *BRCA1/2* carriers in the PSA testing era. Prospective risk estimates may be more informative for counselling current mutation carriers. Only two previous prospective studies on PCa risk for male *BRCA1/2* carriers have been reported but were limited by small sample sizes and wide CIs for their RR estimates, and neither presented absolute risk estimates. In a prospective cohort of 62 carriers from the US, *BRCA2* mutations were associated with increased PCa risk (SIR=4.89, 95% CI 1.96-10.08) but there was no significant association for *BRCA1* carriers (SIR=3.81, 95% CI 0.77-11.13) [11]. An Israeli study observed only three prospective PCas in 210 unaffected *BRCA1/2* carriers (median follow-up: 5.1 yr) and chose not to report a prospective RR estimate [23].

The results indicate that PCa risks for mutation carriers increase with the number of affected relatives, consistent with findings in the general population [28]. This is also consistent with the hypothesis that other familial factors modify PCa risks for mutation carriers, and with recent observations that common PCa susceptibility genetic variants [29] modify PCa risks for *BRCA1/2* carriers [30]. This emphasises the importance of considering family history and other risk-modifying genetic factors when counselling male *BRCA1/2* carriers. However, it is possible that mutation carriers with family history of PCa are more likely to be screened or biopsied than mutation carriers without a PCa family history; this may also partly explain the higher observed risk.

We found *BRCA1* carriers to be at higher risk of GS≤6 disease, but after omitting diagnoses in the initial six mo after study recruitment, the associations with high- and low-grade disease were similar. *BRCA1* carriers were not at significantly increased risk of PCa mortality, though the CI of the SMR estimate was wide. A lack of association between *BRCA1* mutations and PCa grade is in line with published data [7,8], and the higher SIR for GS≤6 disease might reflect a higher propensity for diagnosing indolent low-grade tumours that would not have been detected in the absence of the discovery of a deleterious mutation. Conversely, our results suggest that *BRCA2* mutations are associated with a more aggressive PCa phenotype: the association was stronger with GS≥7 than GS≤6 tumours. Furthermore, we observed a significant association between *BRCA2* mutations and PCa mortality. Associations with high-grade disease and PCa mortality is consistent with previous reports for *BRCA2* carriers [7,8], and suggests that the *BRCA2* findings are less affected by screening effects.

BRCA2 mutations both within and outside the OCCR were associated with elevated PCa risks. However, our results suggest that carriers of mutations within the OCCR are at comparatively lower risk than carriers of mutations outside the OCCR, consistent with previous findings [5,21]. It is also consistent with reports of lower PCa risks for carriers of the *BRCA2* c.5946delT Ashkenazi Jewish founder mutation, which is located in the OCCR [22]. The results however contrast with a UK study which reported an HR of 2.92 (95% CI 1.54-5.54) for OCCR compared to non-OCCR mutations [9]. However, this study was based on a retrospective cohort of *BRCA2* carriers and their relatives and analyses were not adjusted for the ascertainment process.

Strengths of the study include the nationwide recruitment of mutation carriers, which supports the generalisability of our findings. Furthermore, this is the largest prospective cohort of men with deleterious *BRCA1/*2 mutations to date, and the prospective study-design allows for direct estimation of both relative and absolute risks. We have provided risk estimates by family history and mutation location.

Despite our study being the largest prospective study to report to date, the precision of our estimates is still limited by a moderate sample size and number of incident PCas and PCa deaths. The results by GS are limited by potential inaccuracies in tumour grading based on biopsies; however, since mutation carriers were recruited through a UK-wide study and SIRs were computed relative to national GS-specific incidences (which will have similar inaccuracies), variability in pathological grading is unlikely to have resulted in a systematic bias. Other limitations include a possible oversampling of men with a family history of PCa, as a result of the recruitment through clinical genetics centres. While this allowed us to obtain estimates applicable to mutation carriers both with and without family history, the overall risk might be somewhat overestimated compared to the average *BRCA1/2* carrier in the population. In addition, known mutation carriers who undergo genetic counselling may receive enhanced screening compared to men from the general population. More specifically, during the study period, the IMPACT screening trial [26] also recruited male *BRCA1/2* carriers, and therefore some overlap between IMPACT and EMBRACE is likely. Given the background prevalence of indolent PCas that are undetectable in the absence of screening [31] and our observed clustering of PCa diagnoses shortly after study entry, it is plausible that some of these PCas would not have been discovered in the absence of diagnostic measures taken as a result of the discovery of a mutation. When we initiated follow-up six or twelve mo after study entry the estimated RRs were attenuated for both *BRCA1* and *BRCA2* carriers, but remained statistically significant. Furthermore, known mutation carriers may be subjected to a different screening regimen over an extended period of time as compared to men in the general population [24]. To assess this we compared the observed PCa incidence to that expected from population incidences adjusted by screening effect sizes estimated in the ERSPC trial [25]. The SIRs for *BRCA2* carriers remained significant, but the excess risk for *BRCA1* carriers was not consistently significant, and was significant only for ages below 65. This adjustment is limited by the assumption of a constant average screening effect on the population PCa incidences, based on the published estimates by ERSPC [25]. The ERSPC data also suggest that the effect of screening may be time-dependent with a probable decrease in screening effect sizes with time since initiation of screening [25]. This time-dependency was not considered in this analysis and can result in a potential overestimation of SIRs, if the true effect of screening on population incidences is higher than the assumed average during the follow-up period. However, our adjustment used the highest published average PSA screening effect size from ERSPC, and assumes that no screening occurs in the general population, which is unlikely given the rates of opportunistic screening [32] and may result in an attenuation of the SIR estimates. After using both a six-month landmark to control for the detection of prevalent PCas, and higher population incidences, the SIRs remained significant only for *BRCA2* carriers. These may however represent extreme over-adjustments. Finally, when we restricted the follow-up to recruiting centres and/or time-periods not overlapping with the recruitment to the IMPACT trial, we found no association between *BRCA1* mutations and PCa risk. This might suggest that the observed association for *BRCA1* carriers is driven by screening-induced diagnoses of indolent tumours, but caution is needed in the interpretation as the sample size used for this subgroup analysis was small. In contrast, the strength of association was similar for *BRCA2* carriers regardless of the potential overlap with IMPACT. Assuming that clinically significant tumours are likely to be diagnosed

regardless of screening regimen, this observation is consistent with the hypothesis that *BRCA2* mutations are associated with risk of more aggressive disease. It provides further evidence that the association between *BRCA2* mutations and PCa risk is unlikely to be explained by screening effects.

Conclusion

This prospective analysis has substantiated previous reports on the RRs of PCa for *BRCA1* and *BRCA2* mutation carriers from retrospective studies, and has provided direct estimates of absolute PCa risks by family history and mutation characteristics. The results will be informative in the counselling of men who carry *BRCA1* or *BRCA2* mutations.

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Figure and Table legends

Figure 1: Absolute prostate cancer risks for *BRCA1* and *BRCA2* mutation carriers, with the number at risk at each age on the x-axis.
A: Overall.
B: Overall, with follow-up initiated six mo after study entry.
C: By family history.
D: By family history, with follow-up initiated six mo after study entry.
E: By the *BRCA2* ovarian cancer cluster region (OCCR, wide definition) [2,21].
F: By the *BRCA2* ovarian cancer cluster region (OCCR, wide definition) [2,21], with follow-up initiated six mo after study entry.
Family history was defined as having at least one first- or second-degree relative with a prostate cancer diagnosis at the time of study entry.

Table 1: Participant characteristics.

Table 2: Standardised incidence ratios and absolute risks of prostate cancer for *BRCA1* and *BRCA2* mutation carriers, overall and by age and family history.

Table 3: Standardised incidence ratios and absolute risks of prostate cancer for *BRCA2* mutation carriers, by location of the mutation within the *BRCA2* gene.

Table 4: Gleason-score specific standardised incidence ratios of prostate cancer for *BRCA1* and *BRCA2* mutation carriers.

Table 5: Sensitivity analyses.

Supplementary appendix 1: Full details on the statistical analysis.

Supplementary table 1: Incidence rate by time since baseline.

Supplementary table 2: Published age-specific absolute prostate cancer risk estimates and 95% confidence intervals.

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Conflict of interest statement

All authors declare that they have no conflict of interest.

Table 1: Participant characteristics.

Initially recruited	**998**			
Excluded: mutation in both *BRCA1* and *BRCA2*	4			
	***BRCA1* carriers**		***BRCA2* carriers**	
Initially recruited	**451**		**543**	
Excluded: variant of unknown significance	3		3	
Excluded: previous prostate cancer diagnosis	14		37	
Excluded: age≥85 at baseline	1		0	
Excluded: no follow-up beyond baseline	57		56	
Included	**N=376[a]**		**N=447[a]**	
Characteristics	**n**	**(%)**	**n**	**(%)**
Year of study entry				
1999[b]-2004	69	(18%)	48	(11%)
2005-2010	144	(38%)	172	(38%)
2011-2016	163	(43%)	227	(51%)
Age at study entry, years				
Median [inter-quartile range]	54.0 [43.2-64.1]		51.4 [41.5-63.6]	
19-44	103	(27%)	155	(35%)
45-54	97	(26%)	105	(23%)
55-64	96	(26%)	102	(23%)
65-74	65	(17%)	66	(15%)
75-83	15	(4.0%)	19	(4.3%)
Follow-up time[c], years				
Median [inter-quartile range]	5.9 [3.0-10.1]		5.3 [2.6-8.9]	
Family history of prostate cancer[d]				
No	297	(79%)	328	(73%)
Yes	48	(13%)	87	(19%)
Unknown: At least one male relative with unknown cancer site	14	(3.7%)	16	(3.6%)
Missing data	17	(4.5%)	16	(3.6%)
Previous non-prostate cancer diagnosis				
No	355	(94%)	390	(87%)
Yes	21[e]	(5.6%)	57[e]	(13%)
Non-prostate cancer diagnosis during follow-up				
No	349	(93%)	429[f]	(96%)
Yes	27[g]	(7.2%)	18[g]	(4.0%)
Prostate cancer diagnosis				
	n=16		n=26	
Age at prostate cancer diagnosis, years				
Median [inter-quartile range]	66.0 [61.9-71.7]		71.4 [62.8-77.5]	
Diagnostic modality				
Screening	11	(69%)	14	(54%)
Clinical symptoms	3	(19%)	7	(27%)
Missing data	2	(13%)	5	(19%)

PSA at diagnosis, ng/mL				
Median [inter-quartile range]	5.0 [3.6-5.9]		6.2 [4.3-21.6]	
Clinical stage				
T1	1	(6.3%)	4	(15%)
T2	7	(44%)	12	(46%)
T3	4	(25%)	2	(7.7%)
T4	0	(0%)	1	(3.8%)
TX	1	(6.3%)	1	(3.8%)
Missing data	3	(19%)	6	(23%)
Gleason score				
≤6	7	(44%)	4	(15%)
3+4	4	(25%)	7	(27%)
4+3	0	(0%)	3	(12%)
≥8	2	(13%)	5	(19%)
Missing data	3	(19%)	7	(27%)

[a] *BRCA1*: 309 singletons, 23 families with two relatives, 4 families with three relatives, 1 family with four relatives, 1 family with five relatives.
BRCA2: 353 singletons, 36 families with two relatives, 6 families with three relatives, 1 family with four relatives.
[b] Study recruitment was initiated in August 1998 but the first male participant was recruited in February 1999.
[c] Calculated using the reverse Kaplan-Meier method.
[d] At least one first- or second-degree relative diagnosed with prostate cancer.
[e] Includes 4 *BRCA1* and 35 *BRCA2* carriers with male breast cancer.
[f] Includes 3 *BRCA2* carriers who were diagnosed with high-grade prostatic intraepithelial neoplasia and who did not develop any malignant tumours.
[g] Includes 1 *BRCA1* and 2 *BRCA2* carriers with male breast cancer, and 2 *BRCA1* and 3 *BRCA2* carriers with pancreatic cancer.

Table 2: Standardised incidence ratios and absolute risks of prostate cancer for *BRCA1* and *BRCA2* mutation carriers, overall and by age and family history.

Gene	Group	n	Person-years	Observed events	Incidence rate per 1000 person-years (95% CI)		Expected events	SIR (95% CI)		Kaplan-Meier cumulative prostate cancer risk[a] (95% CI)	
Overall											
BRCA1	Age 19-44	103	510.0	0	0.00		0.00	0.00		0%	
	Age 45-54	134	556.0	2	3.60	(0.90-14.4)	0.21	9.56	(2.39-38.2)	3.5%	(0.87%-13%)
	Age 55-64	162	707.3	5	7.07	(2.92-17.1)	1.75	2.86	(1.18-6.94)	9.9%	(4.8%-20%)
	Age 65-74	138	539.1	7	13.0	(6.15-27.4)	3.32	2.11	(1.00-4.46)	21%	(13%-34%)
	Age 75-84	53	192.9	2	10.4	(2.57-41.9)	1.51	1.32	(0.33-5.33)	29%	(17%-45%)
	Age 19-64	296	1773.3	7	3.95	(1.88-8.31)	1.96	3.57	(1.68-7.58)	10%	(4.8%-20%)
	Age 65-84	153	731.9	9	12.3	(6.39-23.7)	4.84	1.86	(0.96-3.59)	29%	(17%-45%)
	Overall	376	2505.3	16	6.39	(3.91-10.4)	6.80	2.35	(1.43-3.88)	29%	(17%-45%)
BRCA2	Age 19-44	155	622.9	0	0.00		0.01	0.00		0%	
	Age 45-54	173	720.1	4	5.56	(2.05-15.0)	0.27	14.7	(5.43-39.8)	5.4%	(2.1%-14%)
	Age 55-64	171	593.2	3	5.06	(1.63-15.7)	1.47	2.04	(0.65-6.36)	10%	(5.0%-21%)
	Age 65-74	134	463.3	9	19.4	(9.93-38.0)	2.88	3.13	(1.60-6.12)	27%	(17%-41%)
	Age 75-84	51	155.0	10	64.5	(33.2-125.4)	1.21	8.25	(4.25-16.0)	60%	(43%-78%)
	Age 19-64	362	1936.2	7	3.62	(1.71-7.65)	1.75	3.99	(1.88-8.49)	10%	(5.0%-21%)
	Age 65-84	153	618.2	19	30.7	(19.3-49.0)	4.09	4.64	(2.91-7.41)	60%	(43%-78%)
	Overall	447	2554.4	26	10.2	(6.92-15.0)	5.85	4.45	(2.99-6.61)	60%	(43%-78%)
By family history of prostate cancer[b]											
BRCA1	No family history	311	2110.0	13	6.16	(3.58-10.6)	5.55	2.34	(1.35-4.07)	31%	(17%-50%)
	Family history	48	264.8	3	11.3	(3.54-36.3)	0.95	3.17	(0.97-10.4)[c]	28%	(9.8%-64%)
BRCA2	No family history	344	1969.9	18	9.14	(5.75-14.5)	4.65	3.87	(2.40-6.23)	47%	(31%-65%)
	Family history	87	481.4	7	14.5	(6.78-31.2)	0.96	7.31	(3.40-15.7)[d]	—[e]	

Abbreviations

CI: confidence interval. SIR: standardised incidence ratio. HR: hazard ratio.

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[a] Estimated cumulative prostate cancer risk by the end of each age interval, or age 85.

[b] At least one first- or second-degree relative diagnosed with prostate cancer.

[c] *BRCA1* carriers: HR per affected first- or second-degree relative = 1.33 (95% CI 0.42-4.20).

[d] *BRCA2* carriers: HR per affected first- or second-degree relative = 1.68 (95% CI 0.99-2.85).

[e] Age 85 prostate cancer risk estimate not available due to a low number of individuals left in the follow-up. At age 75, the cumulative PCa risk estimate was 43% (18%-80%) for *BRCA2* carriers with family history and 22% (12%-36%) for *BRCA2* carriers without family history.

Table 3: Standardised incidence ratios and absolute risks of prostate cancer for *BRCA2* mutation carriers, by location of the mutation within the *BRCA2* gene.

Mutation location	n	Person-years	Observed events	Incidence rate per 1000 person-years (95% CI)		Expected events	SIR (95% CI)		Kaplan-Meier cumulative PCa risk[a] (95% CI)		HR (95% CI)		HR adjusted for family history (95% CI)		HR excluding Ashkenazi founder mutation carriers[b] (95% CI)	
***BRCA2* Ovarian cancer cluster region (OCCR), wide definition** [2,21]																
5' to c.2830 or c.6402 to 3' (Non-OCCR)	267	1489.2	20	13.4	(8.64-20.9)	3.40	5.88	(3.75-9.22)	11% 30% 83% 10% 22%	(4.3%-28%) (17%-49%) (61%-96%) (3.4%-29%) (11%-43%)	Reference		Reference		Reference	
c.2831 to c.6401 (OCCR)	178	1054.4	6	5.69	(2.54-12.8)	2.44	2.46	(1.07-5.64)	22%	(11%-43%)	0.37	(0.14-0.96)	0.40	(0.15-1.07)	0.43	(0.15-1.24)
Indeterminable	2															
***BRCA2* Ovarian cancer cluster region (OCCR), narrow definition** [2,21]																
5' to c.3846 or c.6276 to 3' (Non-OCCR)	284	1581.8	20	12.6	(8.14-19.7)	3.56	5.62	(3.59-8.81)	10% 29% 80% 11% 23%	(4.0%-26%) (16%-48%) (59%-94%) (3.7%-31%) (11%-45%)	Reference		Reference		Reference	
c.3847 to c.6275 (OCCR)	161	961.8	6	6.24	(2.78-14.0)	2.28	2.63	(1.14-6.04)	23%	(11%-45%)	0.42	(0.16-1.09)	0.46	(0.17-1.22)	0.50	(0.17-1.45)
Indeterminable	2															
***BRCA2* Prostate cancer cluster region (PCCR)** [12]																
5' to c.6372 or c.6493 to 3' (Non-PCCR)	444	2540.0	26	10.2	(6.95-15.1)	5.83	4.46	(3.00-6.64)	10% 27% 61% 0%	(5.0%-21%) (17%-41%) (43%-79%)	Reference					
c.6373 to c.6492 (PCCR)	3	14.4	0	0.00		0.02	0.00		0% 0%		Not done					

Abbreviations

CI: confidence interval. SIR: standardised incidence ratio. HR: hazard ratio.

[a] Estimated cumulative prostate cancer risk by ages 65, 75 and 85, respectively.

[b] Carriers of c.5946delT.

Table 4: Gleason-score specific standardised incidence ratios of prostate cancer for *BRCA1* and *BRCA2* mutation carriers.

Gene	n	Person-years	Events with unknown Gleason score	Gleason score	Observed events	Expected events	Without imputations		Multiple imputations[a]		Multiple imputations and six-month landmark	
							SIR	(95% CI)	SIR	(95% CI)	SIR	(95% CI)
BRCA1	373	2488.9	3									
				≤6	7	2.19	3.25	(1.54-6.88)	3.50	(1.67-7.35)	2.26	(0.86-5.91)
				≥7	6	4.61	1.32	(0.59-2.98)	1.80	(0.89-3.65)	1.90	(0.93-3.85)
BRCA2	440	2537.4	7									
				≤6	4	1.83	2.23	(0.83-5.97)	3.03	(1.24-7.44)	2.01	(0.60-6.80)
				≥7	15	4.02	3.80	(2.27-6.38)	5.07	(3.20-8.02)	4.39	(2.63-7.31)

Abbreviations

CI: confidence interval. SIR: standardised incidence ratio.

[a] Pooled estimates from 100 imputations using Multivariate Imputation by Chained Equations. The following covariates were used for the imputation: Prostate cancer status, Gleason score, PSA at diagnosis, Clinical stage, Diagnostic modality (screening/clinical), Mutation gene (*BRCA1/2*), Year of birth, Age at study entry, Age at follow-up, Family history (number of affected first- and second-degree relatives).

Table 5: Sensitivity analyses.

Sensitivity analysis	Gene	Group	n	Person-years	Observed events	Events per 1000 person-years (95% CI)		Expected events	SIR (95% CI)		Kaplan-Meier cumulative PCa risk[a] (95% CI)	
Excluding men with previous non-prostate cancers	*BRCA1*	Age 19-64	286	1724.5	7	4.06	(1.91-8.61)	1.90	3.68	(1.73-7.81)	10%	(5.0%-20%)
		Age 65-84	141	659.6	9	13.6	(7.09-26.2)	4.32	2.08	(1.08-4.01)	32%	(19%-50%)
		Overall	355	2384.1	16	6.71	(4.09-11.0)	6.23	2.57	(1.56-4.23)	32%	(19%-50%)
	BRCA2	Age 19-64	342	1859.8	7	3.76	(1.78-7.96)	1.62	4.32	(2.03-9.21)	11%	(5.3%-22%)
		Age 65-84	110	454.0	11	24.2	(13.3-44.3)	2.95	3.72	(2.03-6.82)	60%	(34%-87%)
		Overall	390	2313.8	18	7.78	(4.90-12.4)	4.57	3.94	(2.45-6.32)	60%	(34%-87%)
Censoring for non-prostate cancers in the follow-up	*BRCA1*	Age 19-64	296	1740.9	7	4.02	(1.91-8.46)	1.90	3.68	(1.74-7.81)	10%	(5.0%-20%)
		Age 65-84	151	684.5	9	13.1	(6.84-25.3)	4.51	2.00	(1.04-3.85)	30%	(18%-48%)
		Overall	376	2425.4	16	6.60	(4.04-10.8)	6.41	2.50	(1.52-4.11)	30%	(18%-48%)
	BRCA2	Age 19-64	362	1919.4	7	3.65	(1.72-7.71)	1.73	4.06	(1.91-8.63)	10%	(5.1%-21%)
		Age 65-84	150	599.8	18	30.0	(18.6-48.5)	3.97	4.53	(2.80-7.32)	59%	(42%-78%)
		Overall	447	2519.2	25	9.92	(6.69-14.7)	5.70	4.39	(2.93-6.57)	59%	(42%-78%)
Censoring all on 30th June 2016	*BRCA1*	Age 19-64	296	1751.7	7	4.00	(1.90-8.41)	1.92	3.64	(1.72-7.72)	10%	(4.9%-20%)
		Age 65-84	148	713.0	8	11.2	(5.62-22.4)	4.71	1.70	(0.85-3.40)	28%	(17%-44%)
		Overall	376	2464.7	15	6.09	(3.67-10.1)	6.64	2.26	(1.35-3.78)	28%	(17%-44%)
	BRCA2	Age 19-64	362	1895.7	7	3.69	(1.75-7.81)	1.71	4.10	(1.93-8.74)	10%	(5.1%-21%)
		Age 65-84	153	599.7	19	31.7	(19.9-50.6)	3.97	4.79	(3.00-7.65)	61%	(43%-79%)
		Overall	447	2495.4	26	10.4	(7.08-15.3)	5.67	4.58	(3.08-6.82)	61%	(43%-79%)
Excluding missense mutation carriers	*BRCA1*	Age 19-64	288	1741.0	7	4.02	(1.91-8.46)	1.94	3.61	(1.70-7.65)	10%	(4.9%-20%)
		Age 65-84	152	721.5	9	12.5	(6.48-24.0)	4.77	1.89	(0.98-3.64)	29%	(18%-45%)
		Overall	368	2462.5	16	6.50	(3.97-10.6)	6.71	2.38	(1.45-3.93)	29%	(18%-45%)
	BRCA2	Age 19-64	358	1924.2	7	3.64	(1.72-7.69)	1.75	4.00	(1.88-8.50)	10%	(5.0%-21%)
		Age 65-84	148	593.8	18	30.3	(18.8-48.9)	3.91	4.60	(2.85-7.43)	61%	(43%-79%)
		Overall	438	2517.9	25	9.93	(6.69-14.7)	5.67	4.41	(2.94-6.61)	61%	(43%-79%)
	BRCA1	Age 19-64	262	1535.8	5	3.26	(1.34-7.89)	1.64	3.05	(1.26-7.40)	8.2%	(3.5%-19%)

		Age 65-84	134	623.6	7	11.2	(5.34-23.6)	4.14	1.69	(0.80-3.56)	27%	(15%-47%)
		Overall	332	2159.3	12	5.56	(3.15-9.81)	5.78	2.08	(1.17-3.68)	27%	(15%-47%)
Excluding Ashkenazi founder mutation carriers[b]	*BRCA2*	Age 19-64	330	1769.3	6	3.39	(1.51-7.62)	1.55	3.86	(1.71-8.72)	9.8%	(4.5%-21%)
		Age 65-84	136	533.0	19	35.6	(22.3-57.0)	3.53	5.38	(3.36-8.60)	65%	(46%-83%)
		Overall	405	2302.4	25	10.9	(7.32-16.1)	5.09	4.91	(3.28-7.36)	65%	(46%-83%)
Follow-up initiated 6 months after baseline	*BRCA1*	Age 19-64	268	1631.6	5	3.06	(1.27-7.42)	1.84	2.72	(1.12-6.58)	7.3%	(3.1%-17%)
		Age 65-84	149	691.7	8	11.6	(5.79-23.1)	4.59	1.74	(0.87-3.49)	26%	(15%-43%)
		Overall	352	2323.3	13	5.60	(3.24-9.68)	6.43	2.02	(1.17-3.50)	26%	(15%-43%)
	BRCA2	Age 19-64	335	1761.7	5	2.84	(1.17-6.87)	1.61	3.10	(1.28-7.54)	8.5%	(3.6%-19%)
		Age 65-84	141	577.2	15	26.0	(15.5-43.7)	3.83	3.92	(2.33-6.60)	55%	(36%-75%)
		Overall	414	2338.8	20	8.55	(5.51-13.3)	5.44	3.68	(2.35-5.75)	55%	(36%-75%)
Follow-up initiated 12 months after baseline	*BRCA1*	Age 19-64	256	1500.4	5	3.33	(1.37-8.09)	1.73	2.89	(1.19-7.02)	7.8%	(3.3%-18%)
		Age 65-84	144	650.3	8	12.3	(6.14-24.6)	4.33	1.85	(0.92-3.71)	27%	(15%-45%)
		Overall	341	2150.7	13	6.04	(3.49-10.5)	6.06	2.15	(1.24-3.73)	27%	(15%-45%)
	BRCA2	Age 19-64	313	1600.4	5	3.12	(1.29-7.57)	1.49	3.37	(1.38-8.21)	8.9%	(3.8%-20%)
		Age 65-84	136	535.7	12	22.4	(12.6-39.8)	3.56	3.37	(1.89-6.00)	51%	(31%-74%)
		Overall	400	2136.1	17	7.96	(4.95-12.8)	5.05	3.37	(2.08-5.47)	51%	(31%-74%)
Comparison to population incidences increased by a factor of ×1.6 [25][c]	*BRCA1*	Age 19-64	296	1773.3	7	3.95	(1.88-8.31)	3.14	2.23	(1.05-4.73)	6.3%	(1.6%-11%)
		Age 65-84	153	731.9	9	12.3	(6.39-23.7)	7.74	1.16	(0.60-2.24)	19%	(8.8%-30%)
		Overall	376	2505.3	16	6.39	(3.91-10.4)	10.9	1.47	(0.89-2.42)	19%	(8.8%-30%)
	BRCA2	Age 19-64	362	1936.2	7	3.62	(1.71-7.65)	2.81	2.49	(1.17-5.31)	6.6%	(1.7%-11%)
		Age 65-84	153	618.2	19	30.7	(19.3-49.0)	6.55	2.90	(1.82-4.63)	46%	(27%-65%)
		Overall	447	2554.4	26	10.2	(6.92-15.0)	9.35	2.78	(1.87-4.13)	46%	(27%-65%)
Comparison to population incidences increased by a factor of ×1.9 [25][c]	*BRCA1*	Age 19-64	296	1773.3	7	3.95	(1.88-8.31)	3.72	1.88	(0.89-3.99)	5.4%	(1.6%-9.3%)
		Age 65-84	153	731.9	9	12.3	(6.39-23.7)	9.19	0.98	(0.51-1.89)	17%	(8.0%-26%)
		Overall	376	2505.3	16	6.39	(3.91-10.4)	12.9	1.24	(0.75-2.04)	17%	(8.0%-26%)
	BRCA2	Age 19-64	362	1936.2	7	3.62	(1.71-7.65)	3.33	2.10	(0.99-4.47)	5.6%	(1.5%-9.8%)
		Age 65-84	153	618.2	19	30.7	(19.3-49.0)	7.77	2.44	(1.53-3.90)	41%	(22%-59%)
		Overall	447	2554.4	26	10.2	(6.92-15.0)	11.1	2.34	(1.57-3.48)	41%	(22%-59%)
	BRCA1	Age 19-64	268	1631.6	5	3.06	(1.27-7.42)	2.94	1.70	(0.70-4.11)	4.8%	(0.87%-8.7%)

Follow-up initiated 6 months after baseline, and comparison to population incidences increased by a factor of ×1.6 [25][c]		Age 65-84	149	691.7	8	11.6	(5.79-23.1)	7.34	1.09	(0.54-2.18)	18%	(7.1%-28%)
		Overall	352	2323.3	13	5.60	(3.24-9.68)	10.3	1.26	(0.73-2.19)	18%	(7.1%-28%)
	BRCA2	Age 19-64	335	1761.7	5	2.84	(1.17-6.87)	2.58	1.94	(0.80-4.72)	5.5%	(0.67%-10%)
		Age 65-84	141	577.2	15	26.0	(15.5-43.7)	6.12	2.45	(1.46-4.12)	40%	(19%-61%)
		Overall	414	2338.8	20	8.55	(5.51-13.3)	8.70	2.30	(1.47-3.60)	40%	(19%-61%)
All participants until 1st October 2005, and participants from centres not recruiting to the IMPACT screening trial [26] after 1st October 2005	*BRCA1*	Age 19-64	115	497.5	0	0.00		1.38	0.00		0%	
		Age 65-84	54	208.3	2	9.60	(2.31-39.9)	3.07	1.05	(0.24-4.55)	11%	(2.9%-39%)
		Overall	147	705.8	2	2.83	(0.69-11.6)	2.72	0.74	(0.18-3.04)	11%	(2.9%-39%)
	BRCA2	Age 19-64	113	439.7	3	6.82	(2.11-22.0)	0.67	6.75	(1.98-23.0)	20%	(6.6%-50%)
		Age 65-84	34	108.7	1	9.20	(1.27-66.7)	0.68	1.48	(0.20-10.7)	36%	(13%-75%)
		Overall	134	548.4	4	7.29	(2.69-19.8)	1.12	3.57	(1.29-9.85)	36%	(13%-75%)
Participants from centres recruiting to the IMPACT screening trial [26] after 1st October 2005	*BRCA1*	Age 19-64	241	1275.8	7	5.49	(2.61-11.5)	1.42	4.93	(2.33-10.4)	14%	(6.7%-26%)
		Age 65-84	120	523.7	7	13.4	(6.43-27.8)	3.52	1.99	(0.95-4.15)	34%	(20%-53%)
		Overall	310	1799.5	14	7.78	(4.63-13.1)	4.94	2.83	(1.67-4.81)	34%	(20%-53%)
	BRCA2	Age 19-64	298	1496.4	4	2.67	(1.00-7.17)	1.42	2.81	(1.04-7.60)	7.7%	(2.9%-19%)
		Age 65-84	129	509.5	18	35.3	(21.8-57.2)	3.42	5.27	(3.25-8.54)	62%	(44%-80%)
		Overall	372	2006.0	22	11.0	(7.16-16.8)	4.84	4.54	(2.96-6.99)	62%	(44%-80%)

Abbreviations

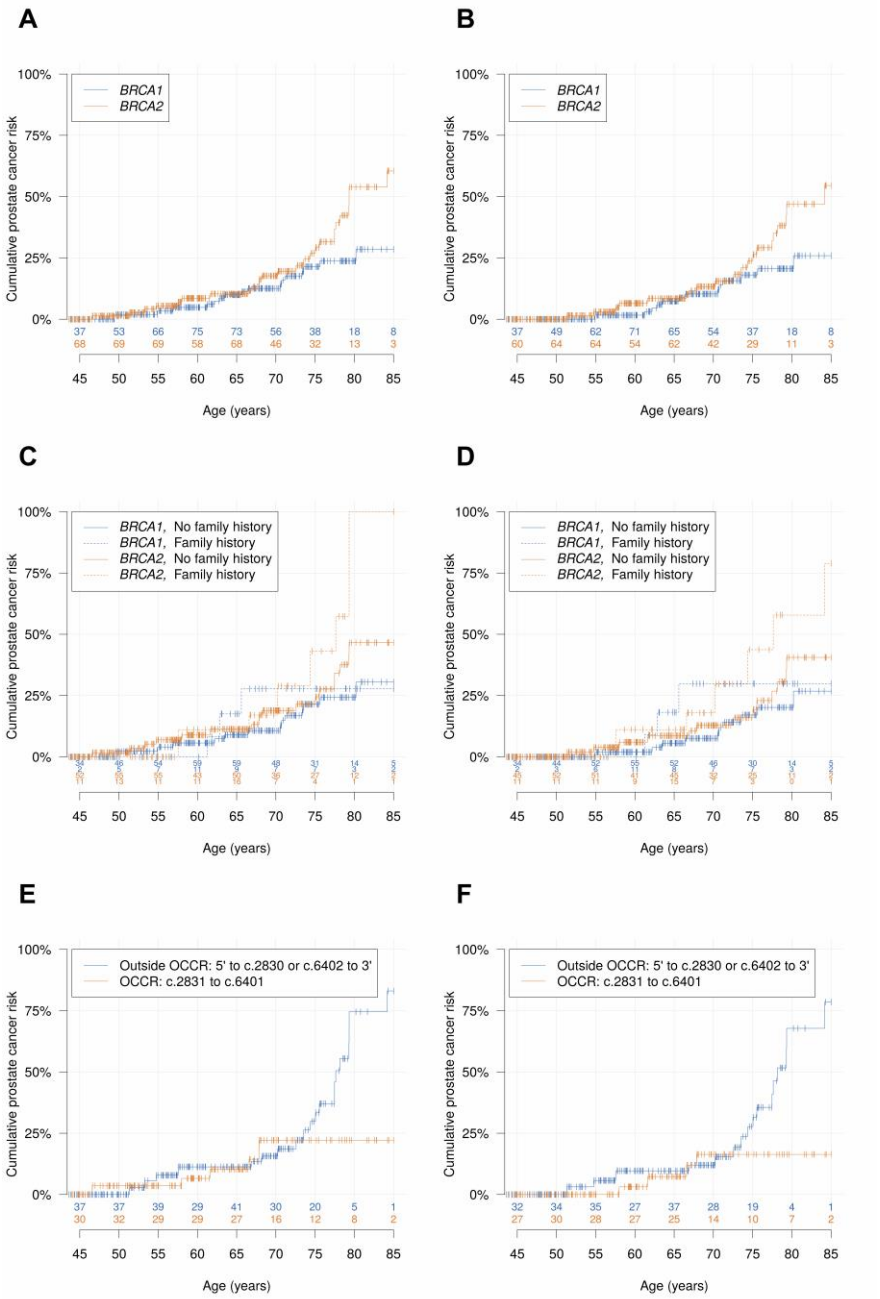
CI: confidence interval. SIR: standardised incidence ratio.

[a] Estimated cumulative prostate cancer risk by the end of each age interval, or age 85.

[b] *BRCA1*: c.68_69delAG and c.5266dupC; *BRCA2*: c.5946delT.

[c] The absolute risks were estimated using a Kaplan-Meier estimator weighted by the inverse of the adjustment factor for men with events.

Figure 1: Absolute prostate cancer risks for *BRCA1* and *BRCA2* mutation carriers, with the number at risk at each age on the x-axis.
A: Overall.
B: Overall, with follow-up initiated six mo after study entry.
C: By family history.
D: By family history, with follow-up initiated six mo after study entry.
E: By the *BRCA2* ovarian cancer cluster region (OCCR, wide definition) [2,21].
F: By the *BRCA2* ovarian cancer cluster region (OCCR, wide definition) [2,21], with follow-up initiated six mo after study entry.
Family history was defined as having at least one first- or second-degree relative with a prostate cancer diagnosis at the time of study entry.



Supplementary appendix 1: Full details on the statistical analysis

We prospectively followed the participants from the completion of their baseline questionnaire until their age at diagnosis of prostate cancer, age of death, age at the end of follow-up, or age 85, whichever occurred first. A diagnosis of another cancer or of prostatic intraepithelial neoplasia were not considered as censoring events. In all analyses the event of interest was a prostate cancer diagnosis. We calculated the total follow-up time using the reverse Kaplan—Meier method [1].

We compared the observed prostate cancer incidences in study participants to those expected from population incidences (Cancer registration statistics, England, Office for National Statistics, https://www.ons.gov.uk/), using standardised incidence ratios (SIR) computed with Poisson regression. For this purpose we used age-and-calendar-period specific incidences (available in five-year age bands for individual years 1998 to 2016). Analyses were carried out separately for *BRCA1* and *BRCA2* mutation carriers. To estimate the absolute risks for mutation carriers, we used the counting process formulation of the Kaplan—Meier estimator to account for varying ages at study entry. Cox regression was used to test for differences in risk between subgroups of mutation carriers (e.g. by family history or mutation characteristics). We classified men who had at least one first- or second-degree family member diagnosed with PCa as having positive PCa family history, and assessed trends in risks with the number of affected first- and second-degree relatives.

Analogously, we followed the participants for prostate-cancer-specific mortality from the completion of their baseline questionnaire until their age at death due to prostate cancer, or age at death due to other causes, age at the end of follow-up, or age 85. We computed prostate-cancer-specific standardised mortality ratios (SMR) compared to age-and-calendar-period-specific population prostate cancer mortality rates (available in five-year age bands for individual years 1998 to 2016; Deaths registered in England and Wales, England and Wales, Office for National Statistics, https://www.ons.gov.uk/).

To investigate differences in risk by mutation characteristics, we grouped mutations on the basis of mutation position within the genes. The grouping was pre-specified, using previously published definitions of regions that have demonstrated different associations with PCa risk [2–7]. The mutation locations were specified using HGVS nomenclature (http://varnomen.hgvs.org/), using cDNA reference sequences NM_007294.3 (*BRCA1*) and NM_000059.3 (*BRCA2*) and reference genome hg18. In HGVS nomenclature, the nucleotide numbering is from the A of the ATG translation initiator codon. For deletions or insertions where the position was uncertain the change was assumed to have occurred at the most 3' position. Specifically for *BRCA2*, we assessed differences between mutations in the central region of the gene, known as the ovarian cancer cluster region (OCCR) [2], and mutations outside this region. For this purpose we used both the wide definition (c.2831 to c.6401) [2,3,8] and the narrow definition (c.3847 to c.6275) of the OCCR [2,3,8]. Similarly, we compared risks for mutations within a recently proposed prostate cancer cluster region (PCCR): c.6373 to c.6492 [7], to mutations located outside this region. However, only three men had a mutation in this PCCR, and hence we could not assess the differences in risk on the basis of this definition. The analyses by mutation position were adjusted for family history of prostate cancer,

and we assessed the impact of carriers of Ashkenazi founder mutations on the mutation location results by excluding this subgroup.

To account for the correlation between male relatives we used sandwich estimators based on family-specific clusters for the standard errors in all Poisson and Cox regression models [9]. We used the Schoenfeld residuals test to assess the Cox regression proportional hazards assumption.

We assessed the association of *BRCA1/2* mutations with clinical subtypes of PCa based on biopsy Gleason score (GS), by comparing the observed number of PCa diagnoses by GS subtypes to those expected given population GS-specific incidences. The GS-specific incidences were calculated using the age-and-calendar-period-specific population distribution of GSs (GS≤6 or ≥7; England, Public Health England, available in five-year age bands in three-calendar-year bands for 1995-2016). For the SIR calculations, diagnosis of a competing PCa subtype ended the follow-up without an event. To estimate absolute risks of these clinical subtypes, we used competing risk estimators [10]. Because data on GSs were not available in the EMBRACE study for all PCas, we used multiple imputation to avoid omission of PCa events.

Missing values were imputed using Multivariate Imputation by Chained Equations [11], based on the following variables: Prostate cancer status, Gleason score, PSA at diagnosis, Clinical stage, Diagnostic modality (screening/clinical), Mutation gene (*BRCA1/2*), Year of birth, Age at study entry, Age at follow-up, and Family history (number of affected first- and second-degree relatives). All variables were complete for all participants except for Family history, and tumour characteristics for 10 of the men with a known PCa. We used polytomous logistic regression to impute categorical variables and predictive mean matching for continuous variables. The imputation was repeated 100 times, and for the results by GS we present the resulting estimates after pooling the separate estimates calculated from each of the 100 repetitions.

For the main analysis, we allowed men with previous non-prostate cancers to be included, did not censor for non-prostate cancers during follow-up, and considered follow-up up to the last questionnaire if available after the last record linkage. We assessed the impact of these inclusion and censoring criteria by excluding men with previous non-prostate cancers, and in separate analyses by censoring men at the age of any non-prostate cancers (excluding non-melanoma skin cancers), or on 30th June 2016.

The analysis included carriers of missense mutations that have been classified as pathogenic based on the ENIGMA criteria (https://enigmaconsortium.org/); since such mutations may be associated with different risks than protein truncating mutations, we carried out a sensitivity analysis in which we omitted these missense mutations (eight *BRCA1* and nine *BRCA2* carriers).

Mutation carriers may be offered a different screening and diagnosis regimen than men in the general population [12]. Hypothetically, this might manifest in two ways: (1) early screening and

detection of indolent PCas shortly after the detection of a mutation, and (2) enhanced screening for PCa over an extended period of time. To address this we performed a number of sensitivity analyses to assess the potential impact of such differential screening. Firstly, we performed landmark analyses where follow-up was initiated six or twelve months after baseline. Second, based on previous findings that observed PCa incidences are 1.4-1.9 times higher for men undergoing PSA screening at regular intervals as compared to unscreened men [13], we compared the observed PCa rates in our sample to population incidences multiplied by adjustment factors of 1.6 and 1.9. To obtain corresponding absolute risk estimates, we used weighted Kaplan—Meier estimators with bootstrap estimates for the standard errors (1000 repetitions). In this analysis, participants with incident PCa where assigned weights proportional to the inverse of the screening adjustment factor. Furthermore, in October 2005 the UK-based IMPACT screening trial started recruiting *BRCA1/2* participants [14]. Although the exact overlap between IMPACT and EMBRACE is unclear, we assessed PCa risks separately for the follow-up that was potentially overlapping with the IMPACT trial and the non-overlapping follow-up. For this, we separately considered the person-time from October 2005 of participants from centres that recruited to IMPACT, and the person-time of participants from IMPACT-recruiting centres before the initiation of IMPACT in addition to the entire person-time of participants from non-IMPACT-recruiting centres.

We used R software (version 3.4.4) [15] for the statistical analysis.

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Supplementary table 1: Incidence rate by time since baseline.

Gene	Time since baseline	n	Person-years	Observed events	Incidence rate per 1000 person-years
BRCA1					
	0–6 mo	376	181.97	3	16.49
	6 mo–1 yr	352	172.61	0	0.00
	1–2 yr	341	337.00	2	5.93
	2–3 yr	334	302.46	1	3.31
	3–4 yr	279	262.75	5	19.03
	4–5 yr	251	240.08	1	4.17
	5–10 yr	231	725.81	4	5.51
	10–15 yr	94	247.95	0	0.00
BRCA2					
	0–6 mo	447	215.59	6	27.83
	6 mo–1 yr	414	202.69	3	14.80
	1–2 yr	400	389.08	4	10.28
	2–3 yr	381	332.76	4	12.02
	3–4 yr	303	278.21	5	17.97
	4–5 yr	257	249.17	0	0.00
	5–10 yr	241	710.77	3	4.22
	10–15 yr	87	163.59	1	6.11

Supplementary table 2: Published age-specific absolute prostate cancer risk estimates and 95% confidence intervals.

Gene	Publication	Study design	Setting	Age								
				45	50	55	60	65	70	75	80	85
BRCA1												
	Thompson, Easton and Breast Cancer Linkage Consortium, 2002 [1]	Retrospective, Case-family cohort	Europe		0.04% (0.03-0.06%)				2.64% (1.95-3.57%)			
			North America		0.12% (0.07-0.21%)				7.67% (4.77-12.20%)			
	Risch et al, 2006 [2]	Retrospective, Case-family cohort	Canada								7.4% (0.59-63%)	
	Leongamorn-lert et al, 2012 [3]	Retrospective, Descriptive case series compared to historical population estimates	UK					8.60%				
	Present analysis	Prospective, Cohort	UK and Republic of Ireland	0%	2.0% (0.28-13%)	3.5% (0.87-13%)	4.8% (1.6-14%)	9.9% (4.8-20%)	13% (6.7-23%)	21% (13-34%)	24% (15-37%)	29% (17-45%)
BRCA2												
	The Breast Cancer Linkage Consortium, 1999 [4]	Retrospective, Case-family cohort	Europe and North America		0.1% (0.1-0.2%)		1.6% (0.9-2.3%)		7.5% (5.7-9.3%)		19.8% (15.2-24.2%)	
	Thompson and Easton, 2001 [5]	Retrospective, Case-family cohort	Europe and North America								Non-OCCR mutations: 33.6% (25.1-44.1%) OCCR mutations: 19.2% (10.7-33.1%)	
	van Asperen et al, 2005 [6]	Retrospective, Cohort	The Netherlands		0.1% (0.0-0.5%)		0.8% (0.0-2.3%)		5.2% (1.7-8.7%)		17.3% (12.5-22.0%)	

Risch et al, 2006 [2]	Retrospective, Case-family cohort	Canada								31% (13-62%)	
Kote-Jarai et al, 2011 [7]	Retrospective, Descriptive case series compared to historical population estimates	UK					15%				
Roed Nielsen et al, 2016 [8]	Retrospective, Cohort	Denmark								18.8% (16.6-21.9%)	
Present analysis	Prospective, Cohort	UK and Republic of Ireland	0%	1.4% (0.19-9.2%)	5.4% (2.1-14%)	8.5% (3.9-18%)	10% (5.0-21%)	18% (10-29%)	27% (17-41%)	54% (39-71%)	60% (43-78%)

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