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Implications of High Rates of Metastatic Prostate Cancer in *BRCA2* Mutation Carriers

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Abstract

BACKGROUND—Patients with germline *BRCA2* gene mutations (BRCA2*mut*) have more aggressive prostate cancer. Analysis of all reported germline BRCA2*mut* prostate cancer cases allows better understanding of the clinicopathologic features and survival outcomes of these men.

METHODS—A systematic review was performed with the MEDLINE database to capture articles evaluating clinicopathologic characteristics of men with BRCA2*mut* associated prostate cancer. Inclusion criteria were at least five subjects, confirmation of BRCA2*mut* status, and data for at least 2 clinical parameters of disease. Meta-analysis was performed on outcomes data. Chi-squared tests were used to compare disease features among men undergoing formal versus ad hoc screening, as well as an age of diagnosis less than versus greater than 65 years. Rates of metastatic disease among BRCA2*mut* cases were compared to rates among non-carrier control subjects and the general population using the SEER database.

RESULTS—Twelve out of 289 studies met our inclusion criteria, representing 261 BRCA2*mut* men. Among carriers, the median age at diagnosis was 62 years and median PSA was 15 ng/dl with 95% of men having a PSA>3. Over 40% of BRCA2*mut* patients had T3/T4 disease and over 25% were metastatic at presentation. Survival was worse in BRCA2*mut* men with prostate cancer when compared to non-BRCA2*mut* subjects. BRCA2*mut* carriers had significantly higher rates of metastatic disease (18%) versus non-carrier controls (8%) and the SEER population (4%).

CONCLUSIONS—BRCA2*mut* carriers are more likely to have poor risk of prostate cancer at presentation and exhibit worse oncologic outcomes relative to non-carriers, including a fourfold increase in metastatic disease. Younger men and those undergoing formal screening present with less advanced disease which supports a need for earlier identification and screening protocols. Additionally, this population may benefit from alternative therapeutic paradigms.

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Keywords

BRCA2; prostate; metastatic; aggressive; screening

INTRODUCTION

Although prostate cancer is the most common cancer diagnosed among men in the United States, overall cancer specific mortality rates remain at less than 3% [1]. Many research efforts are focused on identifying men harboring disease with high metastatic potential who may benefit from earlier screening and more focused interventions. Somatic and germline alterations in the *BRCA2* gene play an important role in human carcinogenesis by preventing homologous recombination of double stranded DNA breaks and have been associated with over 10% of metastatic prostate cancer cases [2]. Associated with hereditary breast and ovarian cancer (HBOC), approximately 1.2% of prostate cancer cases among men less than 65 years of age and 6% of metastatic castration resistant prostate cancer (mCRPC) cases carry germline BRCA2*mut* [3,4]. Men who carry germline BRCA2*mut* are up to eight times more likely to develop prostate cancer compared to non-carriers, and develop an aggressive disease variant with advanced stage and grade at presentation and poor survival outcomes [3,5-9]. These findings have been reflected in numerous studies comprised of small samples from disparate populations. While prior reports have qualitatively summarized the clinical features of germline BRCA2*mut* mutations in prostate cancer, there have been no systematic reviews of the published data [10,11]. The primary objective of this study was to formally characterize the clinicopathologic characteristics upon the diagnosis of prostate cancer in men harboring germline BRCA2*mut* via a systematic review. Secondarily, outcomes data within included studies underwent a meta-analysis.

METHODS

A systematic review was conducted with the MEDLINE database using the search phrase "*BRCA2* prostate" [12]. Inclusion criteria were at least five subjects, genetic confirmation of BRCA2*mut* mutations, data for at least two clinical parameters such as age, PSA, Gleason's score (GS), and tumor stage at diagnosis of prostate cancer. The data extracted from each study included year of publication, study type, population of interest, identified mutations, age, PSA level, GS, tumor stage, and outcomes data of overall and cause-specific survival. Tumor stage was determined by clinical [3,5-8,13-15] and surgical [3,6,9,16,17] findings. Chi-squared statistics and *P*-values were calculated to compare GS and stage among retrospective [3,5-7,9,15-19] and prospective studies [14], as well as by average age groupings (<65 [3,5,7,8,14,15] vs. >65 years [6,13,16,17]). Random effect hazard ratios were calculated for overall and cause-specific survival data with Comprehensive Meta-Analysis Software (Biostat, Inc., Englewood, NJ). A random effect model was chosen as our sample size more appropriately estimated a mean effect size rather than a true effect measure. Tests for heterogeneity included a Q score (Q) with *P*-value, an I^2 statistic, and Tau^2 [20]. To compare staging data among BRCA2*mut* carriers and the general population, both study non-carrier control subjects from included studies and the SEER 18 database were utilized. SEER database selection criteria of age at diagnosis, site, and morphology of

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prostate, year of diagnosis 2004–2012, and site and morphology of all adenocarcinoma variants (8140/2, 8140/3, 8141/2, 8141/3, 8143/2, 8143/3, 8147/3) was used. Chi-squared statistics were used to determine significant differences in categorical variables between the groups while *t*-tests were used for discrete variables. Significance was set at a *P*-value of 0.05. Weighted averages were used for continuous variables.

RESULTS

Study Selection

The MEDLINE database query resulted in 289 studies, of which 12 met inclusion criteria [3,5-9,13-17,21] (Table I). Mitra et al. consisted of preliminary findings that were later reported in the Bancroft et al. study, so it was not included in the analysis [14,18]. Similarly, the Bolton et al. study was excluded as the clinical data were previously reported in the Thorne et al. study [6,22]. Various study types were included in the analysis, including one prospective cohort, a case series, and 10 retrospective cohorts. Publication dates ranged from 1997 to 2015 with subjects from numerous countries, including Portugal, Germany, Canada, United Kingdom, Ireland, Australia, New Zealand, United States, Iceland, Spain, Denmark, Norway, India, Italy, Malaysia, Norway, Slovakia, Slovenia, Sweden, Iceland, Poland, Israel, and the Netherlands (Table I).

Clinical Characteristics

A total of 261 BRCA2*mut* men were identified among the included studies. Data regarding age at diagnosis were available in 11 studies, with a median age of 62 years (Table II). PSA levels were reported in nine studies, with a median PSA level of 15 ng/ml. PSA at diagnosis was greater than three in 95% of men, greater than 10 ng/ml in 39%, and greater than 100 ng/ml in 12% of men. Gleason score at diagnosis, provided by 11 studies, was 71% with GS ≥ 7. Staging at diagnosis, based on nine studies, revealed 40% of men with cT3/T4 disease [3,5-7,13-15] and 63% with pT3/T4 [3,8,9,14,15,17] (overall, 47% with either clinical or pathologic T3/T4). Metastatic disease was present in 26% of men at diagnosis (Table II).

Clinical features among BRCA2*mut* cases were compared to non-carrier control subjects from included study populations (Tables I and III) [3,5-9,13-17]. This analysis showed a significantly higher PSA among BRCA2*mut* men at diagnosis (median of 15.1 ng/dl, mean of 19.5 ng/dl vs. median of 11 ng/dl, mean of 11.1 ng/dl in non-carriers, $P<0.001$), a significantly higher number of GS ≥ 7 cases among BRCA2*mut* men (64% vs. 49% of non-carriers, P<0.001), significantly more overall and pathologic T3/T4 disease at presentation (41% vs. 29% of non-carriers, $P=0.006$, 63% vs. 37%, $P < 0.001$, respectively) and significantly higher rates of metastatic disease at diagnosis (26% vs. 8% of non-carriers, $P < 0.001$). No significant difference was seen for age at onset.

With the exclusion of studies with recruitment periods preceding 1995 (to minimize bias from pre-PSA era screening regimens) and/or lacking staging information, clinicopathologic data among BRCA2*mut* cases were compared to SEER-18 population data (Table III) [5,6,13-15]. This analysis confirmed a statistically significant earlier median age of disease onset (62 years in BRCA2*mut* vs. 66 years from SEER, $P < 0.001$) and significantly higher

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stage presentation with cT3/T4 disease in 40% of BRCA2*mut* carriers versus 9% of SEER prostate cancer cases ($P < 0.001$). Similarly, metastatic presentation was noted in 18% of BRCA2*mut* carriers versus 4% of prostate cancer cases from the SEER database ($P < 0.001$).

To assess the impact of formal screening protocols, clinicopathologic data from Bancroft et al.'s prospective trial was compared to retrospective studies [3,5-9,13,15-17]. Significantly fewer cases of GS ≥ 7, stage T3/T4, and M1 disease were seen among subjects undergoing systematic screening ($P < 0.05$) (Fig. 1a). To assess if age of diagnosis impacted how disease presented, we compared studies with an average age >65 years [3,5,7,8,14,15] against those with an average age <65 years [6,13,16,17]. The older populations had significantly more GS ≥ 7, stage T3/T4, and M1 disease ($P < 0.05$) (Fig. 1b).

Survival Outcomes

Overall survival (OS) hazard ratios were reported in three studies, while cause-specific survival (CSS) outcomes were reported in four studies. For all BRCA2*mut* carriers, the OS random effect hazard ratio is 3.30 (95%CI, 1.56–6.95) with a Q-score of 9.24 (*P*-value=0.01), an I^2 statistic of 78%, and a Tau^2 of 0.34 which suggests increased heterogeneity among studies (Fig. 2a). The CSS random effect hazard ratio is 3.00 (95%CI, 2.20–4.09) with a Q-score of 3.30 (*P*-value = 0.35), an I^2 statistic of 9.22%, and a Tau^2 of 0.01 which implies decreased heterogeneity among studies (Fig. 2b).

DISCUSSION

This systematic review allows a comprehensive overview of the clinical features of BRCA2*mut* prostate cancer. At diagnosis, greater than two-thirds of carriers have GS ≥ 7 disease and nearly half have cT3/T4 disease. Most concerning, over one quarter had metastatic disease at presentation. When comparing disease in BRCA2*mut* cases to the general population, carriers are four times more likely to present with both metastatic and higher stage (T3/T4) disease. When compared to non-carrier men from similar geographical and/or higher risk backgrounds, they are three times more likely to develop metastatic disease. They also have worse overall survival and are three times more likely to die from their prostate cancer than their counterparts. Recent genetic testing of patients with mCRPC has revealed high rates of mutations to DNA repair genes, including *BRCA2* [2,23]. This suggests that BRCA2*mut* disease has a tendency for early spread and therapeutic resistance so early detection of mutations is believed to be important. The NCCN recommends genetic testing in men with advanced prostate cancer (GS ≥ 7) in the context of a family history of breast, ovarian, pancreatic, or aggressive prostate cancer (GS ≥ 7), or a similar family history even without a personal history of prostate cancer [24]. Integration of genetic testing into the screening paradigm should be considered [25].

Upon identification of BRCA2*mut*, specific surveillance strategies have not been established. In the Identification of Men with a genetic predisposition to ProstAte Cancer Trial (IMPACT) screening protocol, men aged 40–59 years from families with known BRCA mutations were recruited and underwent an annual PSA assay that utilized a biopsy threshold of 3 ng/dl [14]. The trial showed that a PSA level of 3 ng/dl had a 48% positive

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predictive value (PPV) in BRCA2*mut* patients versus 33% in controls. Ongoing follow-up analyses from IMPACT, including an optional end of study biopsy in men with PSA levels < 3 ng/dl, will offer insights regarding negative predictive values (NPV) and optimal PSA thresholds.

Other markers, such as PCA3, Ki-67, and microseminoprotein (MSP), have been explored but have not been shown to provide additional diagnostic value in BRCA2*mut* men [14,18,26]. Newer strategies of prognostication, such as prostate multiparametric MRI (mpMRI), with a reported PPV of 65% for detection and localization of cancer in a non-BRCA2*mut* specific population, offers potential improved diagnostic certainty with a greater confidence of disease exclusion among BRCA2*mut* men [27]. Further studies to specifically compare diagnostic performance of mpMRI among BRCA2*mut* men are currently underway [28,29].

The median age of prostate cancer onset among BRCA2*mut* men was found to be 61.7 years, which is 5 years less than the general population (per SEER data). Interestingly, no significant difference in age was found between BRCA2*mut* and non-carrier controls. Given that most studies were retrospective in nature, this allowed for age-matched controls [17,21], a focus on study populations comprised of early-onset disease [5], or populations with a known or suspected oncogenic predisposition [6]. Based on this information, we consider age to be mostly a controlled variable when comparing carriers versus non-carriers. This is further supported by the IMPACT trial findings of an average age of onset among BRCA2*mut* men of 58.5 versus 65 years in non-carriers. Limited by a small sample size, a second prospective study, among BRCA2*mut* male carriers aged 40–70 in Israel, is being conducted to assess screening methods and will offer more data regarding average age of onset [30]. Ideally, these prospective studies may also assess optimal PSA dynamics and thresholds for diagnosis. These prospective studies will offer greater insights on how best to design and when to initiate screening algorithms.

Kote-Jarai et al. showed worse 5 year outcomes (as assessed by metastatic free survival [MFS] and CSS) in similarly treated BRCA2*mut* patients with M0 disease versus controls with M0 disease [5]. Given the strong metastatic potential of BRCA2*mut* disease, this suggests a need for alternative treatment algorithms. Castro et al. showed significantly better outcomes (as assessed by MFS and CSS) among men who underwent radical prostatectomy versus radiation (± androgen deprivation therapy [ADT]) for localized disease [5,31]. This study was confounded by the fact that subjects who received radiation had more advanced localized disease. Nevertheless, these findings mimic the pattern seen among women with BRCA*mut* associated breast cancer who do significantly better with mastectomy versus lumpectomy with radiation [32]. Interestingly, outcomes are equalized when women undergoing lumpectomy with radiation also receive chemotherapy [32]. There is a need to explore the optimal initial radical therapy for localized disease, as well as the potential for adjuvant or neoadjuvant chemotherapy [33].

Currently, alternative therapies are being explored within the sub-population of mCRPC BRCA2*mut* disease. The poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors, acting via synthetic lethality with possible BRCA2*mut* cell targeting, were

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recently granted breakthrough therapy designation for mCRPC in the setting of BRCA1/2 or ATM mutations [34]. Among eight of the nine BRCA2*mut* mCRPC men, PARP inhibitors decreased PSA by at least 50% from baseline; all seven BRCA2*mut* men with complete BRCA2 loss had a noted decrease in PSA [4]. Among the six BRCA2*mut* subjects with measurable disease at baseline, a radiologic partial response was elicited [4]. A recently published case report described the first patient with BRCA2*mut* mCRPC disease to have a complete response with PARP therapy [35]. In addition to PARP inhibitors, alkylating platinum therapy is being explored in mCRPC due to its efficacy in BRCA*mut* associated epithelial ovarian cancer [36]. A recent study showed a partial to complete response for at least 6 months among three men with mCRPC BRCA2*mut* disease, of whom two previously had biochemical recurrence in the setting of ADT with taxanes [37]. Given the tendency for metastatic disease and the possibility for more efficacious therapeutics, the significance of genetic testing and earlier detection on BRCA2*mut* status is further emphasized.

Limitations of this study include a reliance on retrospective studies that comprised disparate cohorts. Our literature search limitation to the MEDLINE database may have missed relevant studies in other aggregate databases. Our inclusion criteria requirement to report data for at least two clinical parameters and a sample of five subjects may have prevented identification of some BRCA2*mut* cases. Study samples may be geographically or ethnically biased (i.e., Gallagher et al. with Ashkenazi Jewish patients, Tryggvadottir et al. and Sigurdsson et al. with the 999del5 Icelandic mutation) which could influence screening paradigms, access to healthcare, and the manner in which particular germline mutations manifest clinically. Another limitation, common to all systematic reviews, is the lack of access to full data sets, which led to several unreported values in our analysis. With regard to our meta-analysis, a small number of studies were included which limits the reliability of our outcomes and leads to increased sampling error. Given the significant heterogeneity for the overall survival model, it is unclear if the included studies are truly representative of the BRCA2*mut* population. A more robust analysis is needed to assess survival outcomes among BRCA2-*mut* carriers. While the SEER population highlighted a deviation from more typical disease presentation, it is important to consider the likely earlier and more vigorous screening regimens among study candidates representing BRCA2*mut* carriers which limits a direct comparison. The comparison with non-carrier control subjects with similar high risk features (family history, early onset disease, overlap in geography), however, controls for some ascertainment bias allowing us to better appreciate our findings. Additionally, it is important to note that the SEER data may contain BRCA2*mut* men.

CONCLUSION

This systematic review quantitatively characterizes the clinical characteristics of prostate cancer among BRCA2*mut* men. Prostate disease in BRCA2*mut* carriers is more aggressive with early systemic spread and poorer survival outcomes. Given that no formal screening recommendations exist for this high-risk subset of men, ongoing studies exploring various screening tools and survival outcomes from earlier detection will be highly beneficial. Additionally, ongoing studies to explore the impact of alternative treatment regimens and innovative therapeutics hold much promise.

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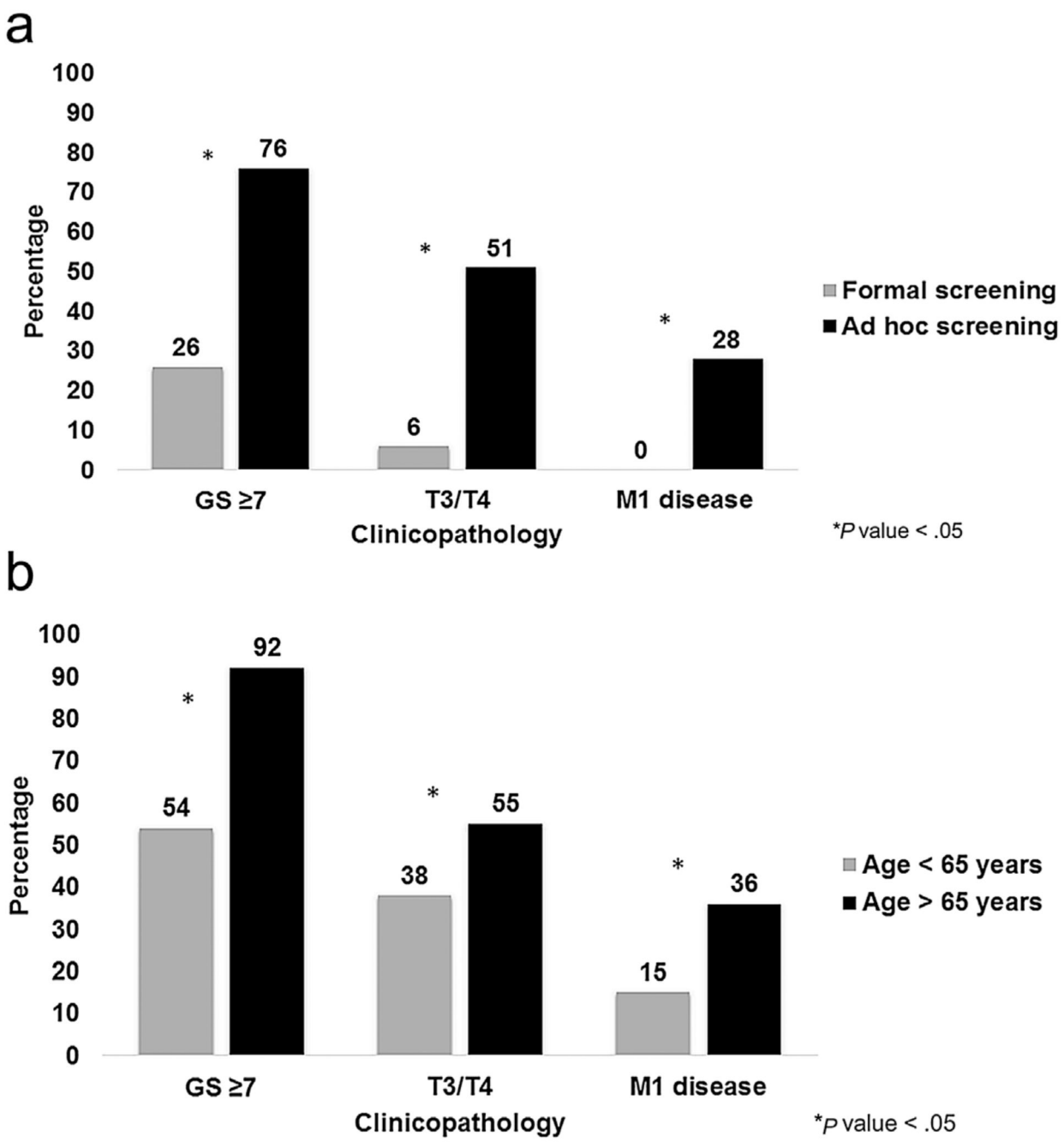

Fig. 1.

a: Comparison of GS ≥ 7, T3/T4 stage, and metastasis for subjects from prospective versus retrospective studies. **b**: Comparison of GS ≥ 7, T3/T4 stage, and metastasis for subjects aged <65 versus >65 years.

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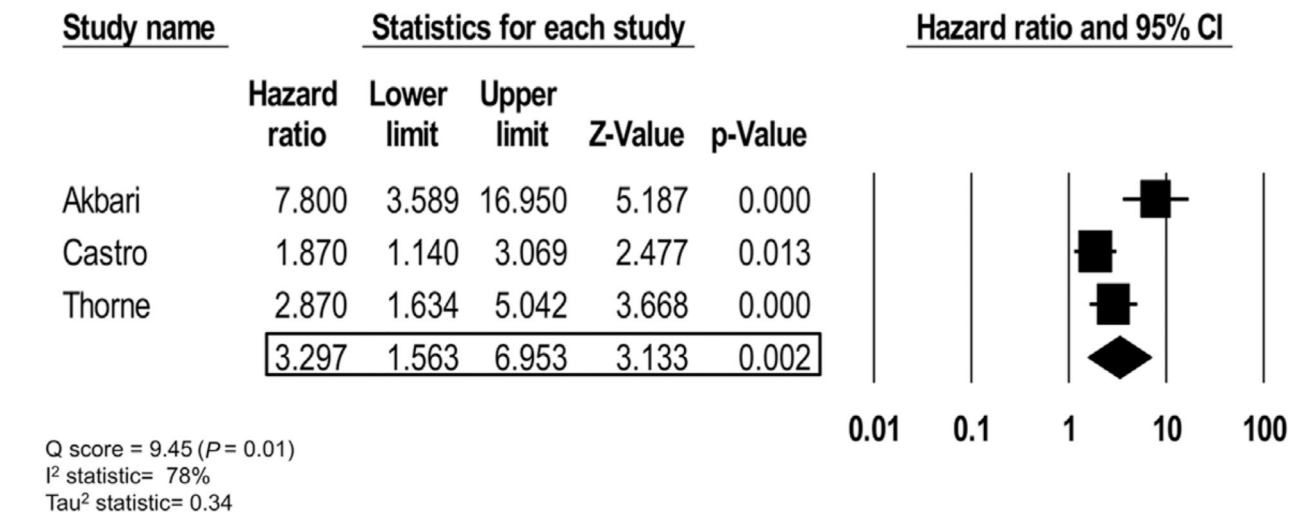
a



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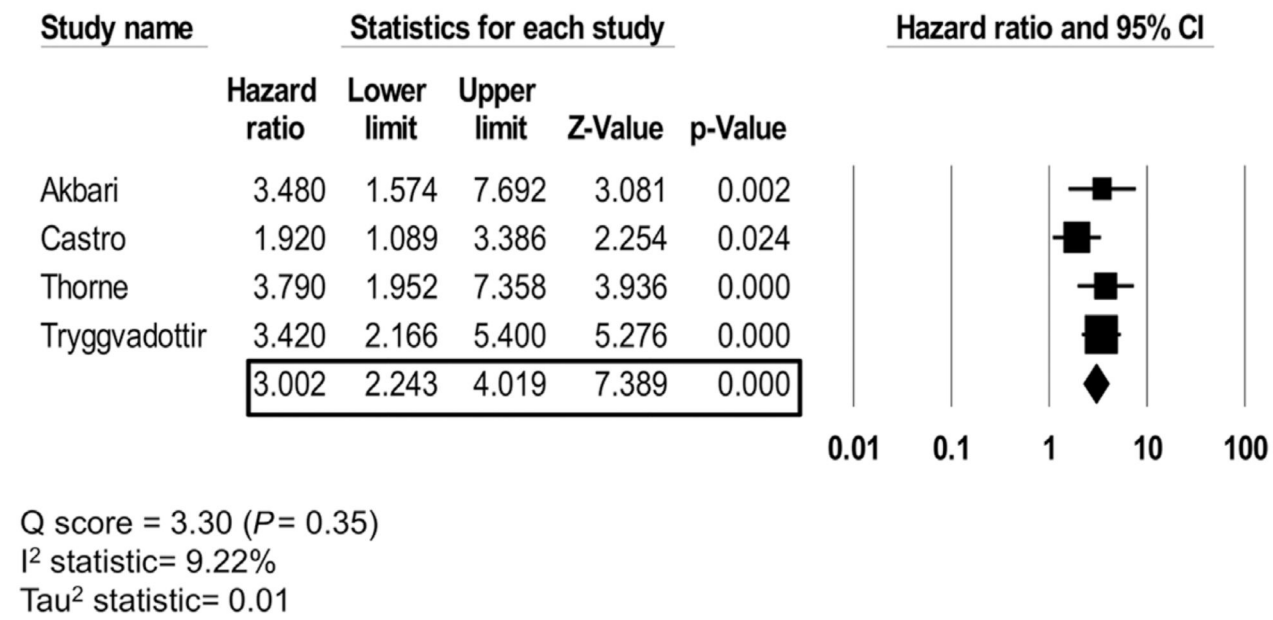

Fig. 2.

a: Random effect model meta-analysis for OS hazard ratio with measures of heterogeneity (Q score, I^2 statistic, and Tau^2 statistic). **b**: Random effect model meta-analysis for CSS hazard ratio with measures of heterogeneity (Q score, I^2 statistic, and Tau^2 statistic).

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TABLE I

Summary of Studies by Author, Country, Rear, Design, Population, Participants, Mutations, and Sample Size

Study	Country	Year	Design	n	Population	Participants	BRCA2+ mutations
Maia et al.	Portugal	2015	Retrospective cohort	6	460 early-onset (≤55 years) and/or familial/hereditary prostate cancer (PrCa) Portuguese probands from a regional cancer registry; 288 male blood donors with no history of PrCa as controls	n = 6 BRCA2*mut*, n = 288 men with no history cancer	c.l56_157insAlu × 6
Maier et al.	Germany	2014	Retrospective cohort	5	474 PrCa cases: 382 with FHx from the Prostate Cancer Genetics Project; 92 sporadic, early onset from University Hospital	n = 5 BRCA2*mut*, all with FHx, n = 474 all PrCa cases (including BRCA2*mut*)	Three frameshifts (1605 fs, V128 fs, T1483 fs, two nonsense (K2013X, Q2499X); VUS excluded
Walker et al.	Canada	2014	Retrospective cohort	6	106 PrCa naïve men from Prostate Cancer Prevention Clinic (23 with BRCA2*mut*, 29 with BRCAl*mut*, and 53 with PrCa FHx)	n = 6/23 with BRCA2*mut* and PrCa, n = 11 /53 with FHx of PrCa and PrCa	c.6137C>A, c.6174delT (×2), c.7757G>A, unknown (×2)
Bancroft et al.	Global (≥20 countries)	2014	Prospective cohort	24	2,481 PrCa naïve men from IMPACT trial; 731 BRCA2mut carriers and 428 BRCA2 controls, as well as 791 BRCA1 *mut* carriers and 531 BRCA1 controls	n = 24/731BRCA2*mut* carriers and PrCa, n = 7/ 428 non-carriers and PrCa	Unknown
Akbari et al.	Canada	2014	Retrospective cohort	26	1,904 men with PrCa from two tertiary care centers	n = 26 with BRCA2*mut*, n = 1,878 non-carriers	Unknown
Castro et al.	United Kingdom, Ireland	2013	Retrospective cohort	61	2,019 eligible patients from EMBRACE, UKGPC study	n = 61 BRCA2*mut*; n = 1,940 non-carrier (n = 18 BRCA1*mut*)	Unknown
Kote-Jarai et al.	United Kingdom	2011	Retrospective cohort	19	1,621 PrCa cases ≤65 years, 243 PrCa cases >65 with FHx of first degree relative with PrCa from UKGPC study; of which 32 were excluded from the analysis	n = 19 BRCA2*mut*, n = 1,813 non-carriers	1231delA, 1265delA, 1787delATGAAACATCTTA, 1813insA, 2807delAACA, 2836delGA, 3158T>G, 3405C>A, 3847delGT, 4478delAAAG, 4877delAA (×2), 4981delT, 5303delTT< 5645C>A, 6405delCTTAA (×2), 8904delC, 9253insA
Thorne et al.	Australia, New Zealand	2011	Retrospective cohort	40	137 men with PrCa from kCONFAB cohort	n = 40 BRCA2*mut*, n = 97 non-carriers	24 frameshift, nonsense, missense mutations and 2 Large genomic rearrangements
Gallagher et al.	USA	2010	Retrospective cohort	20	832 PrCa cases with localized disease of Ashkenazi Jewish descent at Memorial Sloan Kettering	n = 20 BRCA2*mut*, n = 806 non-carriers (n = 6 BRCAl*mut*)	BRCA2* 6174delT
Mitra et al.	United Kingdom, Ireland	2008	Retrospective cohort with nested case control	16	PrCa cases from EMBRACE study, IMPACT, cancer genetics outpatient clinic, series of young onset PrCA cases	n = 16 BRCA2*mut*, n = 16 controls matched by age, PSA, disease stage of which two were	6819delTG, 6174delT, 5910C>G, 7771ins A, 6503delTT, 3386T>G (×2) 6503delTT, 7084delAAAAG, 2558insA, 7772insA, 6710delCAA,

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Study	Country	Year	Design	n	Population	Participants	BRCA2+ mutations
						confirmed non-carriers	5531delTT, 8395G>C, 8205-lG>C, nucleotide variation 2
Tryggvadottir et al.	Iceland	2007	Retrospective cohort with nested case control	29	527 PrCa cases in Icelandic Cancer Registry with female breast cancer relatives	n = 30 BRCA2*mut*, n = 497 non-carriers with n = 57 matched controls	999del5
Sigurdsson et al.	Iceland	1997	Case series	9	12 PrCa cases from BRCA2*mut* Icelandic families and 77 PrCa diagnosed in 1983	n = 9 BRCA2*mut*, n = 4 non-carriers from BRCA2*mut* families	999del5

PrCa, prostate cancer; FHx, family history; BRCA2*mut*, BRCA2 mutation carrier; BRCA1*mut*, BRCA1 mutation carrier; IMPACT, identification of men with a genetic predisposition to prostate cancer; EMBRACE, epidemiological study of BRCA1/2 Mutation Carrier; UKGPC, United Kingdom Genetic Prostate Cancer study; kCONFAB, Kathleen Cunningham Consortium for Research info Familial Breast Cancer.

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TABLE II

Summary of Clinical Features of Prostate Cancer in BRCA2*mut* Men by Age, PSA (ng/mL), Gleason's Score, and Tumor Stage

				PSA (ng/ml)						Gleason's score			Local tumor stage					Localized versus non-localized	
Study	**Year**	**n**	**Age (years)**	**≤3, n (%)**	**>3, n (%)**	**Unknown, n (%)**	**>10, n (%)**	**>100, n (%)**	**Average**	**<7, n (%)**	**≥7, n (%)**	**Unknown, n (%)**	**≤cT2, n (%)**	**cT3/T4, n (%)**	**≤pT2, n (%)**	**pT3/T4, n (%)**	**Unknown, n (%)**	**M0, n (%)**	**M1, n (%)**
Maia et al.	2015	6	61.6	1 (17)	3 (50)	2 (33)	1 (17)	0	7.8	2 (33)	3 (50)	1 (17)	1 (17)	1 (17)	1 (17)	2 (32)	1 (17)	6 (100)	0
Maier et al.	2014	5	–	0	5 (100)	0	–	–	–	1 (20)	4 (80)	–	–	–	2 (40)	3 (60)	0	–	–
Walker et al.	2014	6	58.1	0	5 (83)	1 (17)	1 (17)	0	5.9	3 (50)	3 (50)	–	–	–	3 (50)	2 (33)	1 (17)	–	–
Bancroft et al.	2014	24	58.5	1 (4)	23 (96)	0	2 (8)	0	4.4	17 (71)	6 (25)	1 (4)	13 (54)	3 (12)	5 (21)	3 (13)	0	17 (100)	0
Akbari et al.	2014	26	67	–	–	–	–	–	56.3	1 (4)	25 (96)	0	13 (50)	11 (42)	–	–	2 (8)	18 (75)	6 (25)
Castro et al.	2013	61	57.6	–	–	–	–	–	15.1	14 (23)	38 (62)	9 (15)	26 (43)	23 (37)	–	–	12 (20)	38 (78)	11 (22)
Kote-Jarai et al.	2011	19	56	–	–	–	–	–	–	3 (16)	13 (68)	3 (16)	10 (53)[a]	7 (37)[a]	10 (53)[a]	7 (37)[a]	2 (10)	15 (88)	2 (12)
Thorne et al.	2011	40	66	1 (3)	28 (70)	11 (27)	18 (45)	4 (10)	–	2 (5)	36 (90)	2 (5)	21 (52)	15 (37)	–	–	2 (5)	29 (81)	7 (19)
Gallagher et al.	2010	20	62	–	–	–	–	–	7.0	17 (85)	2 (10)	1 (5)	–	–	–	–	–	–	–
Mitra et al.	2008	16	52.5	1 (6)	12 (75)	3 (19)	7 (44)	5 (31)	24.3	–	–	–	–	–	–	–	–	–	–
Tryggvadottir et al.	2007	29	69	–	–	–			–	4 (14)	21 (72)	4 (14)	–	–	6 (21)	23 (79)	0	13 (45)	16 (55)
Sigurdsson et al.	1997	9	71	–	–	–			–	1 (11)	6 (67)	2 (22)	–	–	–	–	–	3 (33)	6 (67)
Averages			61.6[b]	4%	78%	18%	39%[c]	12%[c]	15.1[b]	27%	64%	9%	58%[c]	42%[c]	40%[c]	60%[c]	9%	74%[c]	26%[c]
			61.7[c]	5%[c]	95%[c]				19.6[d]	29%[c]	71%[c]								

[a] Combined clinical and pathologic staging data.

[b] Median average.

[c] Unknowns removed from denominator.

[d] Weighted mean average.

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TABLE III

Summary of Clinical Features Among BRCA2*mut* Men, Study Control Subjects ("Non-Carrier Controls"), and the General Population ("SEER Population")

	BRCA2*mut* cases, n (%)	Non-carriers controls, n (%)	*P*-value	SEER population, n (%)	*P*-value
n	261	7,109		494,739	
Median age in years (mean)	61.6 (61.7)	65 (62.2)	0.12	66 (66.5)	<0.001[a]
PSA			0.95		
≤3ng/dl	4 (5)	10 (10)		–	
>3ng/dl	76 (95)	89 (90)		–	
Unknown	181	7,010		–	
Median PSA ng/dl (mean)	15.1 (19.5)	11 (11.1)	<0.001[b]	–	
Gleason's score			<0.001[b]		
<7	65 (29)	1,972 (46)		–	
≥7	157 (71)	2,366 (54)		–	
Unknown	39	2,771		–	
Stage overall			0.006[b]		<0.001[a]
≤T2	100 (53)	1,385 (65)		429,531 (90)	
T3/T4	88 (47)	750 (35)		45,936 (10)	
Unknown	73	4974		19,272	
Localized			<0.001[b]		<0.001[a]
M0	139 (74)	2,322 (92)		452,296 (96)	
M1	48 (26)	191 (8)		18,341 (4)	

[a]Statistically significant difference between BRCA2*mut* and SEER control subjects.

[b]Statistically significant difference between BRCA2*mut* and non-carrier control subjects.