A systematic review of the prevalence of DNA damage response gene mutations in prostate cancer

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Abstract. Several ongoing international prostate cancer (PC) clinical trials are exploring therapies that target the DNA damage response (DDR) pathway. This systematic review summarizes the prevalence of DDR mutation carriers in the unselected (general) PC and familial PC populations. A total of 11 electronic databases, 10 conference proceedings, and grey literature sources were searched from their inception to December 2017. Studies reporting the prevalence of somatic and/or germline DDR mutations were summarized. Metastatic PC (mPC), castration-resistant PC (CRPC) and metastatic CRPC (mCRPC) subgroups were included. A total of 11,648 records were retrieved, and 80 studies (103 records) across all PC populations were included; 59 records were of unselected PC and 13 records of familial PC. Most data were available for DDR panels (n=12 studies), ataxia telangiectasia mutated (*ATM*; n=13), breast cancer susceptibility gene (*BRCA)1* (n=14) and *BRCA2* (n=20). *ATM*, *BRCA2* and partner and localizer of *BRCA2 (PALB2)* had the highest mutation rates (≥4%). Median prevalence rates for DDR germline mutations were 18.6% in PC (range, 17.2-19%; three studies, n=1,712), 11.6% in mPC (range, 11.4-11.8%; two studies, n=1,261) and 8.3% in mCRPC (range, 7.5-9.1%; two studies, n=738). Median prevalence rates for DDR somatic mutations were 10.7% in PC (range, 4.9-22%; three studies, n=680), 13.2% in mPC (range, 10-16.4%; two studies, n=105) and not reported (NR) in mCRPC. The prevalence of DDR germline and/or somatic mutations was 27% in PC (one study, n=221), 22.67% in mCRPC (one study, n=150) and NR in mPC. In familial PC, median mutation prevalence was 12.1% (range, 7.3-16.9%) for germline DDR (two studies, n=315) and 3.7% (range, 1.3-7.9%) for *BRCA2* (six studies, n=945). In total, 88% of studies were at a high risk of bias. The prevalence of DDR gene mutations in PC varied widely within somatic subgroups depending on study size, genetic screening techniques, DDR mutation definition and PC diagnosis; somatic and/or germline DDR mutation prevalence was in the range of 23-27% in PC. These findings support DDR mutation testing for all patients with PC (including those with mCRPC). With the advent of the latest clinical practice PC guidelines highlighting the importance of DDR mutation screening, and ongoing mCRPC clinical trials evaluating DDR mutation-targeted drugs, future larger epidemiological studies are warranted to further quantify the international burden of DDR mutations in PC.

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Abbreviations: *ATM*, ataxia telangiectasia mutated; *ATR*, ataxia telangiectasia and Rad3-related protein; *BRCA*, breast cancer susceptibility gene; BRISQ, Biospecimen Reporting for Improved Study Quality; *CHEK2*, checkpoint kinase 2; CRPC, castration-resistant prostate cancer; DDR, DNA damage response; ESMO, European Society for Medical Oncology; *FANCA,* Fanconi anemia complementation group A; FISH, fluorescence *in situ* hybridization; mCRPC, metastatic castration-resistant prostate cancer; *MLH1*, MutL homolog 1; mPC, metastatic prostate cancer; *MRE11A*, *MRE11* homolog A, double-strand break repair nuclease; *NBN*, nibrin; NCCN, National Comprehensive Cancer Network; NR, not reported; *PALB2*, partner and localizer of *BRCA2*; PARP, poly (ADP)-ribose polymerase; PC, prostate cancer; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; *RAD51C*, *RAD51* paralog C; STREGA, Strengthening the Reporting of Genetic Association Studies; SUO, Society of Urologic Oncology

Key words: DNA damage response, genes, germline, mutations, prostate cancer, somatic

Introduction

Prostate cancer (PC) is a major global health burden, with a worldwide incidence of 1.1 million in 2012 (1). While typical active treatments may involve surgery, chemotherapy, brachytherapy and/or androgen-deprivation therapy, these often fail to be curative, with many patients developing metastatic disease or therapeutic resistance. Aggressive prostate disease, such as metastatic castration-resistant PC (mCRPC), is usually lethal.

The DNA damage response (DDR) is an essential pathway that ensures the survival of both normal and malignant prostate cells and includes many important genes, such as breast cancer susceptibility gene (*BRCA*)1/2, ataxia telangiectasia mutated (*ATM*) and partner and localizer of *BRCA2* (*PALB2*) (2). Efficient and specific repair of DNA damage maintains the genomic integrity of the cell and ensures its ability to persist and proliferate. Mutations in DDR genes contribute to destabilizing PC cells, often making them more susceptible to cell death (3). Poly (ADP)-ribose polymerase (PARP) inhibitors represent an emerging therapeutic approach to target the DDR pathway in malignant cells (3). In cancer cells that already harbor multiple other genetic mutations (e.g. *BRCA1/2* mutations), PARP inhibition can render the cell unable to repair DNA damage, leading to cell death (3).

In PC, mutations in genes involved in the DDR pathway are relatively common, particularly in the advanced stages of the disease (4). Several ongoing international PC clinical trials are exploring PARP inhibitors that target the DDR pathway, and the contribution of DDR gene mutations to improving therapeutic outcomes in the context of PARP inhibitor therapy is becoming more evident (Swift *et al*, unpublished data).

Treatment guidelines and consensus statements from international clinical organizations have recently been published to reflect the importance of DDR mutation screening for the management of PC, although the precise genes or gene panels are not always in accordance. The National Comprehensive Cancer Network (NCCN) 2018 guidelines for PC state that a strong family history consists of: Brother, father or multiple family members diagnosed with prostate cancer by at least 60 years of age; and known germline DNA repair gene abnormalities, especially *BRCA2* mutation. These guidelines advise clinicians as follows: 'Consider testing for mutations in these genes (germline and somatic): *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*; refer to genetic counseling if positive. At present, this information may be useful for genetic counseling, early use of platinum chemotherapy, or eligibility for clinical trials (e.g. PARP inhibitors)' (5). The Philadelphia Prostate Cancer Consensus Conference 2017 recommended that all patients with familial and metastatic PC (mPC) consider genetic testing [encompassing *ATM*, *BRCA1*, *BRCA2*, nibrin (*NBN*) and DNA mismatch repair genes] (6): 'There was strong consensus to factor *BRCA2* mutations into [prostate cancer] screening discussions. *BRCA2* achieved moderate consensus for factoring into early stage management discussion, with stronger consensus in high-risk/advanced and metastatic setting[s]' (6). The St Gallen Advanced Prostate Cancer Consensus Conference 2017 reported 'that *BRCA1*, *BRCA2* and *ATM* mutations should be reported [for mCRPC] because that knowledge will likely influence management decisions' (7). It is important that national/regional healthcare providers and decision makers be kept informed of the burden of DDR mutations in PC.

The authors of the present study undertook a systematic review of data to identify and summarize the prevalence of DDR mutations in the unselected (general) population of patients with PC (including mPC, mCRPC and CRPC). Selected subgroup data for familial PC were also presented, since this population is currently considered a key focus for genetic testing guidelines. Studies that reported on other selected subgroups (including young-onset PC, lethal PC, ductal PC, patients receiving pre-specified treatment regimens, and Ashkenazi Jewish and African-American populations) were identified but were not the focus of the review. Methodological factors and limitations of the included studies that may have led to variation in the prevalence rates reported are noted and discussed.

Materials and methods

Inclusion criteria. This systematic review was carried out in accordance with the methodologies recommended by the Cochrane Collaboration (8) and the Centre for Reviews and Dissemination (9). The review adhered to a pre-defined protocol, which stipulated the methodology provided below. Studies that reported the prevalence of mutated DDR genes in men with PC, castration-resistant PC (CRPC), mPC or mCRPC were included. Detailed inclusion criteria (including DDR definition) are provided in Data S1, Appendix S1.

Search methods. In order to identify relevant studies, a range of electronic databases (n=11) were searched from their inception to December 2017, including Medline (Ovid), Embase (Ovid), CINAHL (EBSCO) and the Cochrane Database of Systematic Reviews (Wiley). Searches used a combination of text and database thesaurus terms. No restrictions on language or publication status were applied. Searches of conference abstracts and reference lists of articles were conducted. Full details of the search methods employed, the databases searched, and the Embase search strategy are provided in Data S1, Appendix S2. Titles and abstracts were independently screened by two reviewers. Full paper copies were independently examined in detail by two reviewers to determine whether or not they met the inclusion criteria. Data were extracted from the included studies using a specifically designed and piloted data extraction sheet developed using Microsoft Excel 2016 (Microsoft Corporation). Details of the study methods, population characteristics, risk of bias, and outcome data were extracted from each study by one reviewer and checked for accuracy against the original publication by a second reviewer. Criteria used to assess the risk of bias were taken from the Joanna Briggs Institute Critical Appraisal Checklist for studies reporting prevalence data (10). Any disagreements or discrepancies in study selection or data extraction were resolved by consensus or through consultation with a third reviewer.

Data synthesis. A narrative summary of all included studies was produced. The results prioritized the following countries: Australia, Canada, France, Germany, Israel, Italy, Japan, Korea, Russia, Spain, the UK and the USA. Multinational studies were summarized separately. Analysis of prevalence was primarily conducted for the unselected PC population and familial PC subgroups only; data for additional subgroups identified during screening (including young-onset PC, ductal PC, lethal PC, African-American with PC, Ashkenazi Jewish with PC or patients receiving pre-specified treatment regimens) were also extracted. Studies were excluded from the analysis of prevalence if they involved: i) Specific mutation(s) in a given gene

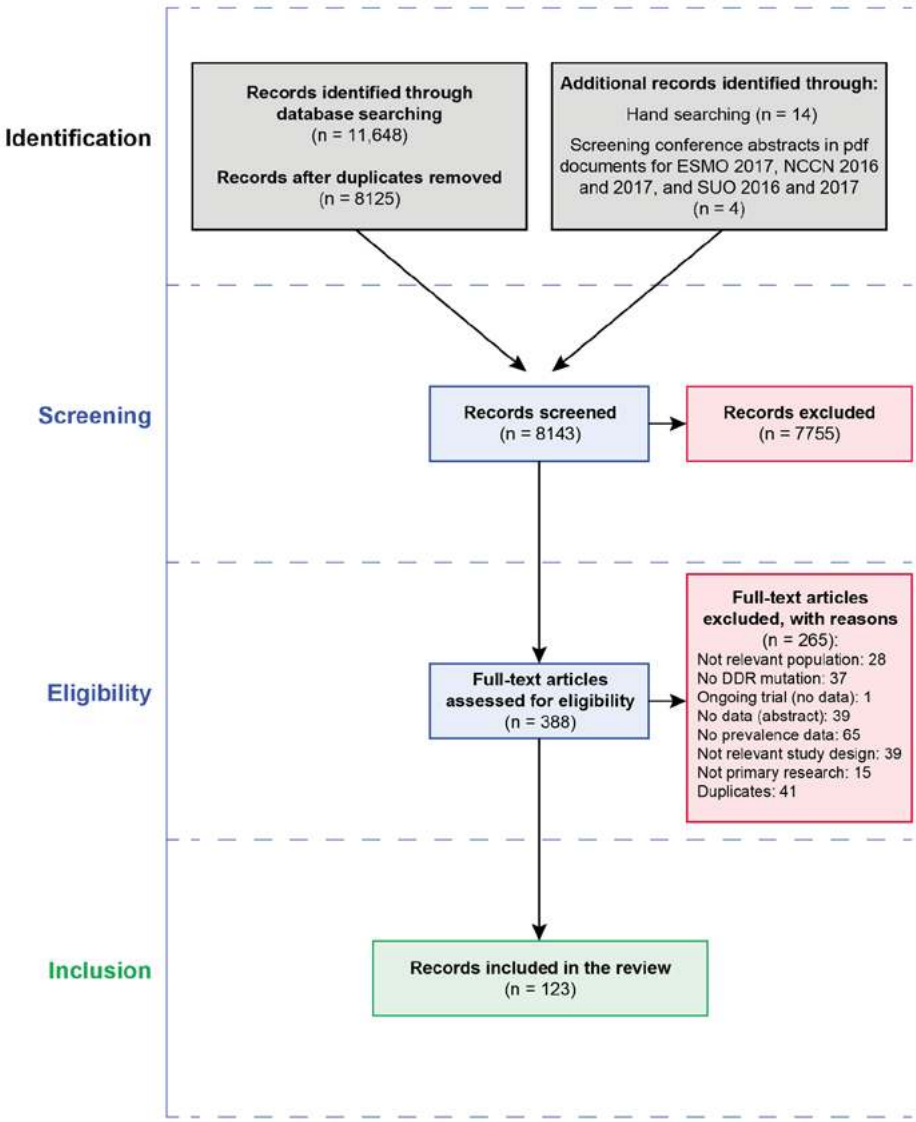

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses study flow diagram. DDR, DNA damage response; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Care Network; SUO, Society of Urologic Oncology.

rather than all mutations for a given gene (unless the study was familial); ii) <50 participants (unless the study was familial), to focus on well powered studies (11,12); or iii) did not clearly report whether a mutation was germline or somatic. Such studies are summarized in Data S1, Appendix S3, together with reported prevalence values. The median prevalence and range were reported for each gene of interest or combination of genes (DDR). If multiple definitions were available for a given gene mutation, then the broadest definition was included where possible. The median prevalence rates were compared between germline and somatic mutations or between prostate subgroups if the dataset was greater than 500 combined participants, to focus on data with a large sample size.

Results

Search methods and inclusion assessment. In total, 11,648 titles were retrieved from the database searches. A total of 14 articles were identified from hand and citation searching. Four articles were identified from conference abstracts. Fig. 1 summarizes the flow of studies through the search and screening process. A total of 265 articles were excluded after the full records were read (Fig. 1 and Data S1, Appendix S3). There were 123 records identified for inclusion in the review, though 20 records were not from countries of interest and were not considered further (Data S1, Appendix S3). For the prioritized countries, 103 records from 80 studies (some of which had multiple records or publications) were identified for inclusion in the present review. A total of 59 records focused on unselected patient populations, and 13 records focused on familial PC patients.

Several records reporting on additional selected subgroups were identified, including 11 for Ashkenazi Jewish patients, 10 for patients receiving pre-specified treatment regimens, five for young-onset (≤55 or 65 years) PC, five for lethal PC, two for ductal PC and one for African-American patients with PC. The results for these subgroups are presented in Data S1, Appendices S3 and S4, together with reported prevalence values.

Unselected populations. A total of 47 studies (59 records) were identified for the unselected population. Out of the 47 studies, the majority (22 studies) were conducted exclusively in the USA (Table I). A total of five studies were conducted in the UK, three in Canada and two in Japan. Denmark, Germany, Israel and Spain each provided a single study. A total of nine studies recruited patients from multiple locations; the country of recruitment was not reported for two studies (both abstracts).

In total, 37 of the 47 primary studies reported results for patients with unselected PC, five of which focused on primary or localized PC (the authors' descriptions are reported where the definitions of disease terms were not made more explicit). Four studies focused on mPC and six studies focused on mCRPC.

The numbers of patients in the studies varied considerably, ranging from 8 to 39,014. A total of 10 studies included <50 patients in their cohort, 23 studies included between 50 and 500 patients, and 14 studies included >500 patients. The majority of studies failed to report recruitment or enrollment dates (32 studies). Of the remaining studies, 11 commenced recruitment between 1990 and 1998, and only four recruited patients after the year 2000.

Detailed patient baseline details are presented in Data S1, Appendix S5. Generally, studies provided limited baseline details and inclusion criteria.

Familial prostate cancer. A total of 11 primary studies (and two related publications) focused on patients with familial PC (Table II). As with the studies targeting unselected populations, the majority included patients from the USA (six studies, including one multinational study) and the UK (two studies). Two studies were identified for Germany (including the single multinational study), and one study each included patients from Australia and Japan. All 11 studies exclusively reported results for patients with unselected PC. For the selected familial PC subgroup, specific DDR mutations are described in Data S1, Appendix S4.

DNA damage response gene definition and reported methodology. The DDR genes reported and analyzed are presented in Table III. In total, 40 studies (50%) and 25 studies (31%) analyzed germline and somatic mutations, respectively. Six studies (7.5%) considered both germline and somatic mutations, and nine studies (11%) did not specify the nature of the mutation.

The source of DNA and the methods of genetic analysis varied considerably among studies (Data S1, Appendix S6). The major sources of DNA were blood (39 studies, 48.1%) and tumor tissue (28 studies, 34.6%). Six samples were sourced from cell-free DNA (7.4%), five from paraffin-embedded tumor tissue (6.2%), and four from buccal swabs/saliva (4.9%). One study sourced DNA from a single-cell suspension of a primary tumor (1.2%). Nine studies did not report the source of the DNA analyzed (11.1%).

The two most frequently used methods of mutational analysis were PCR (29 studies, 35.8%) and next-generation sequencing (19 studies, 23.5%). Seven studies performed whole-exome sequencing (8.6%), three used Sanger sequencing (3.7%), three used capture sequencing (3.7%) and two used fluorescence *in situ* hybridization (FISH; 2.5%). A total of 10 studies used methods other than those specified within this report (12.3%), whereas six studies (7.4%) did not report which methods were used.

DDR genes could be separated into three general categories: Those that focused on specific mutations in a specific gene (21 studies, 25.9%); those that focused on all, or undefined, mutations in a specific gene (22 studies, 27.1%); and those that focused on undefined mutations in multiple DDR genes (38 studies, 46.9%). Definitions for individual gene mutations or DDR combinations varied considerably from study to study.

Risk of bias of included studies. None of the studies were free from the risk of bias based on the Joanna Briggs Institute Critical Appraisal Checklist; 88% (of the 80 included studies) had at least one domain judged to be high risk (Data S1, Appendix S7 and Fig. S1). The majority of studies had a sample size of >50 participants (79% of studies), an analysis with sufficient coverage/clearly described mutations (84%), and appropriate statistical analysis with a clear prevalence calculation (74%). Overall, however, the quality of reporting was poor and did not allow for judgment of how well participants were recruited or how data were acquired; consequently, 76% of studies were judged to have an unclear risk of bias. Likewise, the criteria for the diagnosis of PC (e.g. the Gleason score) were unreported in the majority of studies (74%), and it was unclear in most studies (91%) whether a pathologist had performed the diagnosis. Confounding factors were not taken into consideration for prevalence reporting in the majority of studies (71%). In addition, the majority of studies (73%) did not describe one or more of the participant baseline characteristics for this review.

Results for prevalence in the unselected population. All studies excluded at the analysis stage are summarized in Data S1, Appendix S3, together with prevalence calculations. To establish if there were patterns of prevalence between somatic and germline mutations, between different genes, and between different PC types, all median prevalence values for all gene datasets were compared (Fig. 2 and Data S1, Appendix S8). Patients identified as having primary PC were grouped under unselected PC; thus, unselected PC was a mixed group in terms of overall diagnosis.

The most evidence was available for DDR gene panels [14 datasets; 11 studies (13-23)], ATM [17 datasets; 13 studies (13,17,18,20-22,24-29)], *BRCA1* [19 datasets; 14 studies (17,18, 20-22,24,25,28,30-35)] and *BRCA2* [27 datasets; 19 studies (17,18,20-26,28,30,31,33-38)]. Other genes had between four and 11 datasets. For individual genes, the most common mutations were in *ATM* [median, 1.5-6% across prostate groups (general PC, mPC and mCRPC); full reported range, 0-12%], *BRCA2* (median, 1.1-5.2% across prostate groups; full reported range, 0-11.8%), and *PALB2* (median, 0-4% across prostate groups; full reported range, 0-4%). The median prevalence of all MutL homolog 1 (*MLH1*), *BRCA1* and Fanconi anemia complementation group A (*FANCA*) mutations was <4%, and the median prevalence of all checkpoint kinase 2 (*CHEK2*), *NBN*, *RAD51* paralog C (*RAD51C*), ataxia telangiectasia and Rad3-related protein (*ATR*) and *MRE11* homolog A, double-strand break repair nuclease (*MRE11A*) mutations was <2%.

Table I. Study characteristics: Unselected populations.

PC group	Study ID	Other related publications	No. analyzed	Recruitment/ enrollment dates	Place(s) of recruitment
A, Canada					
PC	Akbari *et al*, 2014 (36)	NR	1904	June 1998-February 2010	Sunnybrook Health Sciences Center, Toronto, Canada; Princess Margaret Hospital, Toronto, Canada
	Nam *et al*, 2005 (57)	NR	996	June 1998-January 2003	Two prostate centers at the University of Toronto (University Health Network and Sunnybrook and Women's College Health Sciences Center)
mCRPC	Struss *et al*, 2017[a],(23)	NR	319	NR	NR
B, Denmark					
PC	Naslund-Koch *et al*, 2016 (58)	NR	39014	2003-2010	Copenhagen General Population Study
C, Germany					
PC	Maier *et al*, 2014 (37)	Maier 2010 (59)	382; 92	1998-2007	Ulm, Germany
D, Israel					
PC	Vazina *et al*, 2000 (60)	NR	174	1998	Rabin Medical Center, Sheba Medical Center or Wolfson Medical Center
E, Japan					
PC	Tanaka *et al*, 2009 (61)	NR	177	1997-2003	Shimane Medical University, Izumo, Japan
	Uchida *et al*, 1999 (62)	NR	24	NR	University of Kitasato Hospital, Sagamihara, Kanagawa, Japan
F, Spain					
mCRPC	Romero Laorden *et al*, 2017[a] (22) NCT03075735 (PROREPAIR-B)	Cendón Flórez *et al*, 2017 (63); NCT3075735 (64)	419	NR	38 centers across Spain
G, UK					
PC	Castro *et al*, 2011[a] (31) UKGPCS	NR	2181	1990-2005	UK Genetic Prostate Cancer Study (UKGPCS)
PC	Manson-Bahr *et al*, 2015 (27)	NR	63	NR	NR
PC	Leongamornlert *et al*, 2012 (32) UKGPCS	NR	886	NR	UK Genetic Prostate Cancer Study (UKGPCS)
PC	Angele *et al*, 2004 (65)	NR	637	1993-2002	Royal Marsden NHS Trust
PC	Jefferies *et al*, 2017[a] (14)	NR	61	NR	Welsh Cancer Bank
H, USA					
PC	Dawson *et al*, 2016[a] (66)	NR	437	NR	NR
PC	Nicolosi *et al*, 2017[a] (19)	NR	1158	2013-2016	

Table I. Continued.

PC group	Study ID	Other related publications	No. analyzed	Recruitment/ enrollment dates	Place(s) of recruitment
PC	Xia *et al*, 2015 (67)	NR	20	NR	NR; hospital-based registry
PC	Abida *et al*, 2017 (17)	Abida *et al*, 2015 (68); Abida *et al*, 2016 (69); Abida *et al*, 2016 (70); Cheng *et al*, 2017 (71)	451	May 2015-unknown	Memorial Sloan Kettering Cancer Center, New York, USA
PC	Feldman *et al*, 2014[a] (72)	NR	330	NR	Large referral laboratory
PC	Myers *et al*, 2016[a] (35)	NR	85	NR	NR
PC	Palapattu *et al*, 2015[a] (73)	NR	9	NR	NR
PC	Browning *et al*, 2006 (74)	NR	98	1997	Vanderbilt Hospital, USA
PC	Patel *et al*, 2016[a] (29)	Patel *et al*, 2017 (75)	327	NR	Dana Farber Cancer Institute
PC	Lara *et al*, 2017[a] (34)	NR	207; 936	NR	NR
PC	Evans *et al*, 2016 (28)	NR	1090	NR	Mayo Clinic, Cleveland Clinic, Thomas Jefferson University
PC	Wu *et al*, 2006 (76)	NR	84	1997-1998	Mayo Clinic, USA
PC	Williams *et al*, 1996 (47)	Gao *et al*, 1995 (48)	23	NR	University of Utah
Primary PC; mCRPC	Grasso *et al*, 2012 (26)	NR	11; 50	NR	University of Michigan and from the Rapid Autopsy Program
Primary PC; mPC	Dall'Era *et al*, 2017[a] (77)	Glass *et al*, 2017 (78)	936	NR	NR
Primary PC; mPC	Beltran *et al*, 2015 (79)	Beltran *et al*, 2015 (80)	69; 29	February 2013-September 2014	Weill Cornell Medical College–New York Presbyterian Hospital
Primary PC; mPC; CRPC	Beltran *et al*, 2013 (81)	NR	16; 4; 25	NR	Weill Cornell Medical College
mCRPC	Gambhira *et al*, 2016[a] (82)	NR	13	NR	NR
mCRPC	Daniel *et al*, 2017[a] (83)	NR	1911	NR	NR
mPC	Pritchard *et al*, 2014 (16)	NR	60	NR	University of Washington Prostate Cancer Biorepository
mPC	Gourdin and Lilly 2016[a] (15)	NR	55	NR	NR
mPC	Robbins *et al*, 2011 (84)	NR	8	NR	Rapid Autopsy Program at the University of Michigan
I, Multi-national					
PC	Fontugne *et al*, 2015[a] (38)	NR	51	NR	UK and USA
PC	Cancer Genome Atlas 2015 (18)	NR	333	NR	Multiple institutions (including Australia, Brazil, Israel, UK, USA)
PC	Lu *et al*, 2015 (24) Cancer Genome Atlas	NR	178	NR	NR, but presumed to be multiple institutions (including Australia, Brazil, Israel, UK, USA) (18)
PC	Timms *et al*, 2016[c] (13)	NR	84	1990-2011	Transatlantic Prostate Group Cohort and commercial databank

Table I. Continued.

PC group	Study ID	Other related publications	No. analyzed	Recruitment/ enrollment dates	Place(s) of recruitment
PC	Hebbring *et al*, 2006 (85)	NR	1819; 1218	NR	USA (Johns Hopkins, Tampere University Hospital, University of Michigan, Mayo Clinic); Germany (Universitätsklinikum Ulm)
PC; mCRPC	Decker *et al*, 2016 (30)	Baca *et al*, 2013 (86)	60; 150	NR	Multiple institutions (including Australia, Brazil, Israel, UK, and USA); unclear for some institutions
Primary PC; mPC	Pritchard *et al*, 2016 (21) Stand Up to Cancer-Prostate Cancer Foundation (SU2C-PCF) International Prostate Cancer Dream Team discovery series; MSK-IMPACT	NR	499; 692	1997-2015 (multiple case series)	Royal Marsden Hospital (London, UK), University of Washington Rapid Autopsy Program (District of Columbia, USA), Weill Cornell Medical College (New York, USA), University of Michigan Rapid Autopsy Program (Michigan, USA), Memorial Sloan Kettering Cancer Center (New York, USA); 144 international centers (SU2C-PCF)
mCRPC	Robinson *et al*, 2015 (4)	NR	150	NR	8 centers, including University of Michigan Medical School, University of Washington, Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center, Royal Marsden Institute of Cancer Research (London). Karmanos Cancer Institute, Beth Israel Deaconess Medical Center, Harvard Medical School, and Weill-Cornell
mPC	Nelson *et al*, 2016[a] (20)	NR	569	NR	NR but includes UK and USA
J, Country not reported					
PC	Liu *et al*, 2016[a] (87)	NR	36	NR	NR
mCRPC	Sonpavde *et al*, 2017[a] (33)	NR	514	NR	NR

[a]Abstract; [b]letter; [c]poster. Note that some unselected populations could also present data for the selected populations. CRPC, castration resistant prostate cancer; mCRPC, metastatic castration resistant prostate cancer; mPC, metastatic prostate cancer; NR, not reported; PC, prostate cancer.

Table II. Study characteristics: Selected familial subgroups.

PC group	Study ID	Other related publications	No. analyzed	Recruitment/ enrollment dates	Place(s) of recruitment
A, Australia					
PC	Cheng *et al*, 2011[a] (88)	NR	147	NR	NR
B, Germany					
PC	Maier *et al*, 2014 (37)	Maier *et al*, 2010 (59)	382; 92	1998-2007	Ulm, Germany
C, Japan					
PC	Hayano *et al*, 2016 (42)	NR	140	NR	Gunma University Hospital and its affiliated hospitals, Japan
D, UK					
PC	Gayther *et al*, 2000 (89)	NR	38	NR	UK
PC	Leongamornlert *et al*, 2014 (41)	NR	191	NR	UK Genetic Prostate Cancer Study (UKGPCS)
E, USA					
PC	Zuhlke *et al*, 2012 (90)	NR	94	NR	University of Michigan Prostate Cancer Genetics Project and Johns Hopkins University
PC	LaDuca *et al*, 2017[a] (91)	NR	NR	NR	Not clear-patients referred from unknown centers
PC	Ledet *et al*, 2017[a] (92)	Lin *et al*, 2017 (93)	124	2015-2016	Tulane Cancer Center
PC	Nicolas *et al*, 2015 (39)	NR	12	NR	Fox Chase Cancer Center
PC	Marshall *et al*, 2017[a] (94)	NR	92	August 2013-September 2016	NR
F, Multi-national					
PC	Hebbring *et al*, 2006 (85)	NR	1819; 1218	NR	USA (Johns Hopkins, Tampere University Hospital, University of Michigan, Mayo Clinic); Germany (Universitätsklinikum Ulm)

[a]Abstract. NR, not reported; PC, prostate cancer.

Table III. DDR genes of interest analyzed.

Author, year	Germline or somatic mutation	*ATM*	*ATR*	*BRCA1*	*BRCA2*	*CHEK2*	*FANCA*	*MLH1*	*MRE11A*	*NBN*	*PALB2*	*RAD51C*	Other DDR genes	Refs.
A, Australia														
Cheng *et al*, 2011	NR/unclear	No	No	Yes	Yes	No	No	No	No	No	No	No	No	(88)
B, Canada														
Nam *et al*, 2005	Germline	No	No	No	No	Yes	No	No	No	No	No	No	No	(57)
Tischkowitz *et al*, 2008	Germline	No	No	No	No	Yes	No	No	No	No	No	No	No	(95)
Akbari *et al*, 2014	Germline	No	No	No	Yes	No	No	No	No	No	No	No	No	(36)
Hamel *et al*, 2003	Germline	No	No	Yes	Yes	No	No	No	No	No	No	No	No	(96)
Struss *et al*, 2017	Germline	?	?	?	Yes	?	?	?	?	?	Yes	?	?	(23)
Damaraju *et al*, 2006	Germline	Yes	No	Yes	Yes	No	No	No	Yes	No	No	Yes	Yes	(97)
C, Denmark														
Naslund Koch *et al*, 2016	Germline	No	No	No	No	Yes	No	No	No	No	No	No	No	(58)
D, Germany														
Maier *et al*, 2014	Germline	No	No	No	Yes	No	No	No	No	No	No	No	No	(37)
Meyer *et al*, 2007	Germline	Yes	No	No	No	No	No	No	No	No	No	No	No	(98)
Nientiedt *et al*, 2017	Somatic	No	No	Yes	Yes	No	No	No	No	No	No	No	No	(99)
E, Israel														
Vazina *et al*, 2000	Germline	No	No	Yes	Yes	No	No	No	No	No	No	No	No	(60)
Hubert *et al*, 1999	Germline	No	No	Yes	Yes	No	No	No	No	No	No	No	No	(100)
Giusti *et al*, 2003	Somatic	No	No	Yes	Yes	No	No	No	No	No	No	No	No	(101)
F, Japan														
Hayano *et al*, 2016	Germline	Yes	?	?	?	?	Yes	?	?	?	Yes	?	Yes	(42)
Tanaka *et al*, 2009	Somatic	No	No	No	No	No	No	Yes	No	No	No	No	No	(61)
Uchida *et al*, 1999	NR/unclear	No	No	Yes	No	No	No	No	No	No	No	No	No	(62)
G, Spain														
Romero *et al*, 2017	Germline	Yes	?	Yes	Yes	Yes	?	?	?	?	Yes	?	Yes	(22)
H, UK														
Kote-Jarai *et al*, 2011	Germline	No	No	No	Yes	No	No	No	No	No	No	No	No	(102)
Edwards *et al*, 2003	Germline	No	No	No	Yes	No	No	No	No	No	No	No	No	(103)
Leongamornlert *et al*, 2012	Germline	No	No	Yes	No	No	No	No	No	No	No	No	No	(32)
Castro *et al*, 2011	Germline	No	No	Yes	Yes	No	No	No	No	No	No	No	No	(31)
Gayther *et al*, 2000	Germline	No	No	Yes	Yes	No	No	No	No	No	No	No	No	(89)
Angele *et al*, 2004	Germline	Yes	No	No	No	No	No	No	No	No	No	No	No	(65)
Leongamornlert *et al*, 2014	Germline	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	(41)
Jefferies *et al*, 2017	Somatic	Yes	?	?	?	?	?	?	?	?	?	?	?	(14)
Manson-Bahr *et al*, 2015	Somatic	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	(27)

Table III. Continued.

Author, year	Germline or somatic mutation	*ATM*	*ATR*	*BRCA1*	*BRCA2*	*CHEK2*	*FANCA*	*MLH1*	*MRE11A*	*NBN*	*PALB2*	*RAD51C*	Other DDR genes	Refs.
I, USA														
Agalliu *et al*, 2007	Germline	No	No	No	Yes	No	No	No	No	No	No	No	No	(104)
Gallagher *et al*, 2012	Germline	No	No	Yes	Yes	No	No	No	No	No	No	No	No	(105)
Agalliu *et al*, 2009	Germline	No	No	Yes	Yes	No	No	No	No	No	No	No	No	(106)
Kirchoff *et al*, 2004	Germline	No	No	Yes	Yes	No	No	No	No	No	No	No	No	(107)
Lehrer *et al*, 1998	Germline	No	No	Yes	Yes	No	No	No	No	No	No	No	No	(108)
Petrovics *et al*, 2016	Germline	No	No	Yes	Yes	No	No	No	No	No	No	No	No	(46)
Nicolosi *et al*, 2017	Germline	?	?	Yes	Yes	?	?	?	?	?	?	?	?	(19)
Cesaretti *et al*, 2007	Germline	Yes	No	No	No	No	No	No	No	No	No	No	No	(109)
Browning *et al*, 2006	Germline	Yes	No	No	No	No	No	No	No	No	No	No	No	(74)
Zhu *et al*, 2010	Germline	Yes	No	No	No	No	No	No	No	No	No	No	Yes	(110)
Pomerantz *et al*, 2017	Germline	Yes	?	?	Yes	?	Yes	?	?	?	?	?	Yes	(111)
Marshall *et al*, 2017	Germline	Yes	?	Yes	Yes	Yes	?	?	?	?	?	?	Yes	(94)
Ledet *et al*, 2017	Germline	Yes	?	Yes	Yes	Yes	?	?	?	Yes	?	?	Yes	(92)
LaDuca *et al*, 2017	Germline	Yes	?	Yes	Yes	Yes	Yes	?	?	?	Yes	?	Yes	(91)
Hart *et al*, 2016	Germline	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	(112)
Antonarakis *et al*, 2018	Germline	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	(113)
Nicolas *et al*, 2015	Germline	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	(39)
Beltran *et al*, 2015	Germline and somatic (mixed)	No	No	No	No	No	Yes	No	No	No	No	No	No	(79)
Wu *et al*, 2006	Germline and somatic (mixed)	No	No	No	No	Yes	No	No	No	No	No	No	No	(76)
Abida *et al*, 2017	Germline and somatic (mixed)	Yes	?	Yes	Yes	Yes	Yes	Yes	?	Yes	Yes	?	Yes	(17)
Zuhlke *et al*, 2012	NR/unclear	No	No	No	No	No	No	No	No	Yes	No	No	No	(90)
Nastiuk *et al*, 1999	NR/unclear	No	No	Yes	Yes	No	No	No	No	No	No	No	No	(114)
Daniel *et al*, 2017	NR/unclear	?	?	Yes	Yes	?	?	?	?	?	?	?	?	(83)
Feldman *et al*, 2014	NR/unclear	Yes	?	?	?	?	?	?	?	?	?	?	?	(72)
Dawson *et al*, 2016	NR/unclear	Yes	?	?	Yes	?	?	?	?	?	?	?	Yes	(66)
Dall'Era *et al*, 2017	NR/unclear	Yes	Yes	Yes	Yes	?	?	Yes	?	?	?	?	Yes	(77)
Williams *et al*, 1996	Somatic	No	No	Yes	No	No	No	No	No	No	No	No	No	(47)
Myers *et al*, 2016	Somatic	No	No	Yes	Yes	No	No	No	No	No	No	No	No	(35)
Palapattu *et al*, 2015	Somatic	?	?	?	Yes	?	?	?	?	?	?	?	?	(73)
Robbins *et al*, 2011	Somatic	?	?	?	Yes	?	?	?	?	?	?	?	Yes	(84)
Pritchard *et al*, 2014	Somatic	?	?	?	?	?	?	Yes	?	?	?	?	Yes	(16)

Table III. Continued.

Author, year	Germline or somatic mutation	*ATM*	*ATR*	*BRCA1*	*BRCA2*	*CHEK2*	*FANCA*	*MLH1*	*MRE11A*	*NBN*	*PALB2*	*RAD51C*	Other DDR genes	Refs.
Evans *et al*, 2016	Somatic	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	(28)
Schweizer *et al*, 2016	Somatic	?	?	?	Yes	Yes	?	Yes	?	?	?	?	Yes	(115)
Lara *et al*, 2017	Somatic	?	?	Yes	Yes	?	?	?	?	?	?	?	?	(34)
Grasso *et al*, 2012	Somatic	Yes	No	No	Yes	No	No	No	No	No	No	No	Yes	(26)
Gourdin *et al*, 2016	Somatic	Yes	No	Yes	Yes	No	No	No	No	No	No	No	?	(15)
Gambhira *et al*, 2016	Somatic	Yes	No	Yes	Yes	No	No	Yes	No	No	No	No	Yes	(82)
Patel *et al*, 2016	Somatic	Yes	?	Yes	Yes	?	?	?	?	?	Yes	?	Yes	(29)
Xia *et al*, 2015	Somatic	Yes	Yes	?	?	Yes	Yes	Yes	?	Yes	?	?	Yes	(67)
Beltran *et al*, 2013	Somatic	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	(81)
J, Multi-national														
Na *et al*, 2017	Germline	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No	(25)
Pritchard *et al*, 2016	Germline	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	(21)
Nelson *et al*, 2016	Germline	Yes	Yes	Yes	Yes	Yes	?	?	Yes	Yes	Yes	Yes	Yes	(20)
Decker *et al*, 2016	Germline and somatic (mixed)	?	?	?	Yes	?	?	?	?	?	?	?	Yes	(30)
Robinson *et al*, 2015	Germline and somatic (mixed)	Yes	?	Yes	Yes	Yes	?	Yes	?	?	Yes	?	Yes	(4)
Lu *et al*, 2015	Germline and somatic (mixed)	Yes	Yes	Yes	Yes	?	Yes	?	?	?	Yes	?	Yes	(24)
Hebbring *et al*, 2006	NR/unclear	No	No	No	No	No	No	No	No	Yes	No	No	No	(85)
Fontugne *et al*, 2015	Somatic	?	?	?	Yes	?	?	?	?	Yes	?	?	Yes	(38)
The Cancer Genome Atlas, 2015	Somatic	Yes	?	Yes	Yes	?	?	Yes	?	?	?	Yes	Yes	(18)
Timms *et al*, 2016	Somatic	Yes	Yes	Yes	Yes	Yes	Yes	?	?	Yes	Yes	Yes	Yes	(13)
K, NR														
Stephens *et al*, 2016	Somatic	?	?	?	Yes	?	?	?	?	?	?	?	?	(116)
Sonpavde *et al*, 2017	Somatic	?	?	Yes	Yes	?	?	?	?	?	?	?	?	(33)
Liu *et al*, 2016	Somatic	Yes	?	?	?	?	?	Yes	?	?	?	?	?	(87)

?, unclear; *ATM*, ataxia telangiectasia mutated; *ATR*, ataxia telangiectasia and Rad3-related protein; *BRCA*, breast cancer susceptibility gene; *CHEK2*, checkpoint kinase 2; DDR, DNA damage repair; *FANCA*, Fanconi anemia complementation group A; *MLH1*, MutL homolog 1, *MRE11A, MRE11* homolog A, double-strand break repair nuclease; *NBN*, nibrin; NR, not reported; *PALB2*, partner and localizer of *BRCA2; RAD51C, RAD51* paralog C.

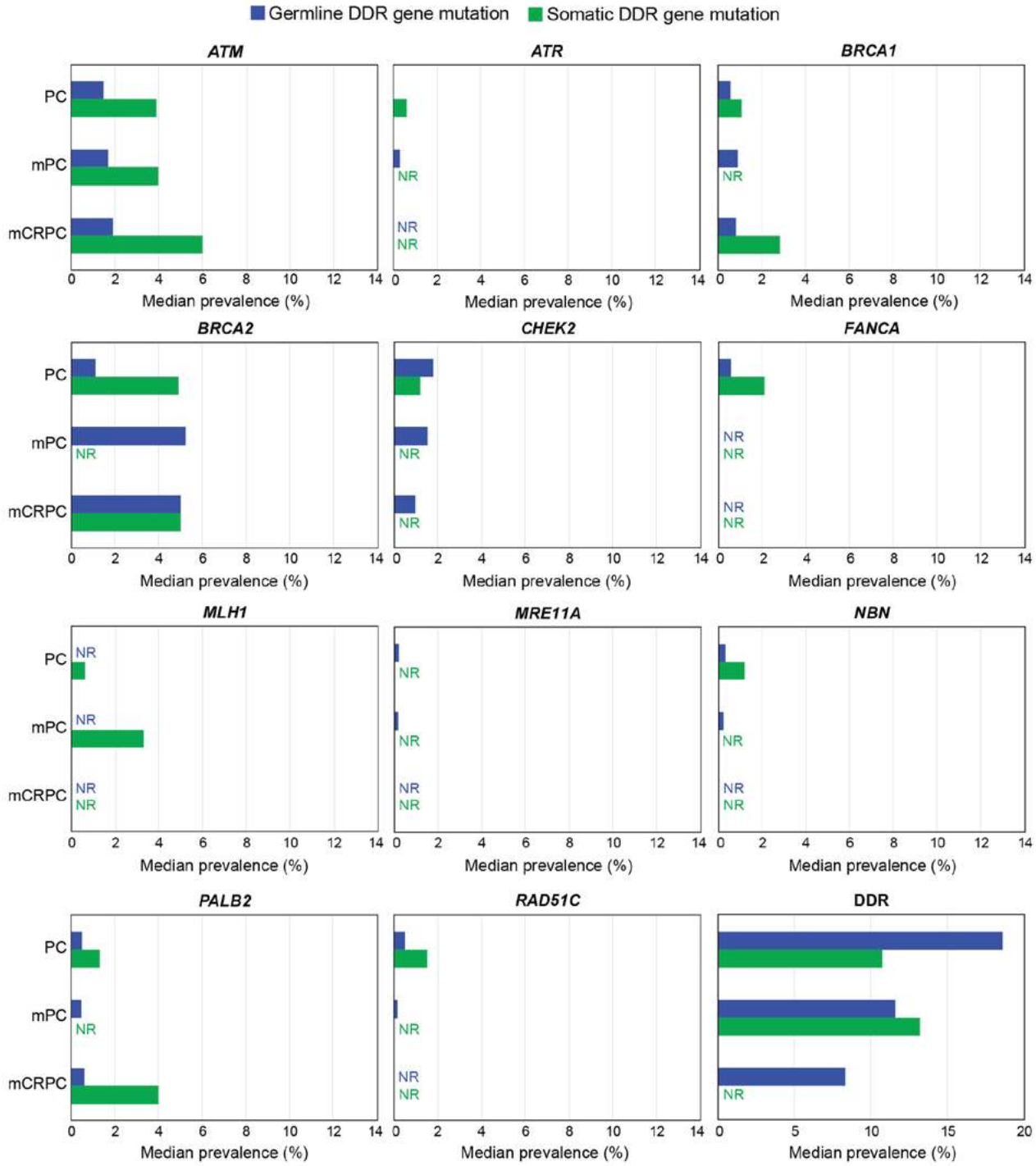

Figure 2. Summary of median prevalence for germline (blue) and somatic (green) DDR gene mutations in unselected populations. Study numbers, median prevalence, range and original data are reported in Data S1, Appendix S8. Data from studies with >50 patients are included. *ATM*, ataxia telangiectasia mutated; *ATR*, ataxia telangiectasia and Rad3-related protein; *BRCA*, breast cancer susceptibility gene; *CHEK2*, checkpoint kinase 2; DDR, DNA damage repair; *FANCA*, Fanconi anemia complementation group A; *MLH1*, MutL homolog 1; *MRE11A*, *MRE11* homolog A, double-strand break repair nuclease; *NBN*, nibrin; NR, not reported; *PALB2*, partner and localizer of *BRCA2*; *RAD51C*, *RAD51* paralog C; PC, prostate cancer; mPC, metastatic prostate cancer; mCRPC, metastatic castration-resistant prostate cancer.

In unselected PC populations and datasets including >500 patients, the frequency of somatic mutations was higher than that of germline mutations in ATM (3.9% vs. 1.5%, respectively), *ATR* (0.6% vs. 0%), *BRCA1* (1.1% vs. 0.6%), *BRCA2* (4.9% vs. 1.1%), *MLH1* (0.6% vs. 0%), *NBN* (1.2% vs. 0.3%), *PALB2* (1.3% vs. 0.5%) and *RAD51C* (1.5% vs. 0.5%). By contrast, germline mutations were more common than somatic mutations in *CHEK2* (1.8% vs. 1.2%, respectively) and *MRE11A* (0.2% vs. 0%). In mCRPC, somatic mutations were more common than germline mutations for *BRCA1* (2.8% vs. 0.8%, respectively), whereas somatic and germline mutations were equally common for *BRCA2* (5% for each group). The prevalence rates for other prostate subgroups were based on <500 patients and were not summarized.

Germline mutations were more common in patients with mPC (based on datasets that included >500 patients) than in patients with general PC for *ATM* (1.7% vs. 1.5%, respectively), *ATR* (0.3% vs. 0%), *BRCA1* (0.9% vs. 0.6%) and *BRCA2* (5.2% vs. 1.1%), but not for *CHEK2* (1.5% vs. 1.8%), *NBN* (0.2% vs. 0.3%), *PALB2* (0.5% for both groups) or *RAD51c* (0.2% vs. 0.5%). Germline mutations were more common in mCRPC than in general PC for *BRCA1* (0.8% vs. 0.6%) and *BRCA2* (5.0% vs. 1.1%). Fewer than 500 patients were available for other prostate subgroups, and prevalence in those groups was therefore not summarized.

Somatic mutations were more common in the mCRPC population (based on datasets including >500 patients) than in the unselected PC population for *BRCA1* (2.8% vs. 1.1%), whereas similar rates of somatic mutations were seen in the two populations for *BRCA2* (5.0% vs. 4.9%).

The prevalence for DDR genes as a combined term was much higher than for the individual genes. This was expected, as the definition was based on the presence of multiple gene mutations (Table III and Data S1, Appendix S8). In general PC, the prevalence of somatic DDR gene mutations was in the range of 4.9-22%, while germline DDR mutation rates ranged between 17.2 and 19%. In mPC, the prevalence of somatic DDR mutations ranged between 10 and 16.4%, while germline mutation rates ranged between 11.4 and 11.8%. In mCRPC, the prevalence of germline DDR mutations was in the range of 7.5-9.1%; no somatic mutations were reported. In general PC, based on datasets including >500 patients, germline mutations had a higher prevalence than somatic mutations (18.6% vs. 10.7%, respectively); other somatic subgroups included <500 patients, and so prevalence rates were not analyzed. Germline DDR mutation rates were higher in patients with general PC (18.6%) than in those with mPC (11.6%) or mCRPC (8.3%).

Two multinational studies (4,30) and one US study (17) reported the prevalence of mutations using definitions that combined germline and somatic variants (Table IV). These studies used different sequencing methods to investigate mutation rates in mCRPC (4,30) and general PC (17). Decker *et al* (30) reported the prevalence for patients who had both somatic and germline mutations, whereas Robinson *et al* (4) and Abida *et al* (17) reported the prevalence for patients who had either a somatic or a germline mutation (or both). Thus, the rates in the study of Robinson *et al* (4) for *BRCA1* (2.67%) and *BRCA2* (12.67%) are approximately double those in the study of Decker *et al* (30) (0.66 and 6%, respectively). The combined prevalence of germline and/or somatic DDR gene mutations was 22.67% in mCRPC (4) and 27% in general PC (17).

Results for prevalence in the familial subgroup. The prevalence of *BRCA2* and DDR mutations in familial PC is summarized in Fig. 3 and Data S1, Appendix S4. The median prevalence of germline *BRCA2* mutations in the familial PC subgroup was 3.7% (range, 1.3-7.9%), based on six studies (n=945). While these studies reported variable definitions for familial PC, they generally required more than two family members with PC. Only one-half of the studies reported baseline characteristics (Data S1, Appendix S5); therefore, further analysis of the influence of baseline details was not possible. The median prevalence of germline *BRCA2* mutations (3.7%) was notably higher than that in the unselected population (1.1%).

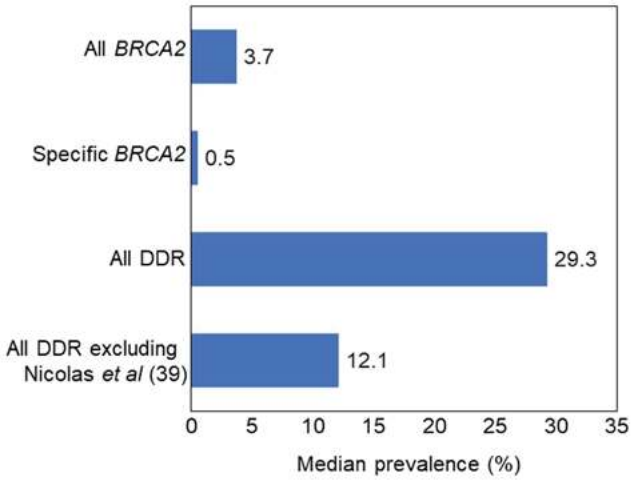

Figure 3. Summary of median prevalences for DDR and *BRCA2* gene mutations in patients with familial prostate cancer. 'All *BRCA2*' and 'All DDR' signify all mutations identified for each gene, whereas 'specific *BRCA2*' signifies one specific mutation (e.g. a specific deletion) in the gene. Study numbers and *BRCA2*/DDR definitions are reported in Data S1, Appendix S4. BRCA, breast cancer susceptibility gene; DDR, DNA damage repair.

The median prevalence of germline DDR mutations in familial PC was 29.3% (range, 7.3-91.67%), based on three studies (n=327). It is noteworthy that one other study (39) provided two definitions for 'DNA damage response or androgen-signaling gene variants' (Data S1, Appendix S6); one definition referred to any affected gene (91.7%), whereas the other referred to two or more affected genes (41.7%). The inclusion of 'androgen-signaling gene variants' in the definition of DDR was inconsistent with the definitions of DDR in the other studies, and therefore this study was excluded from a sensitivity analysis, leading to a median prevalence of 12.1% (range, 7.3-16.9%).

Discussion

To the best of our knowledge, this is the first review that has used rigorous systematic review methods (8,9) to report a comprehensive summary of recently published data on the prevalence of DDR genes in PC (including in mPC, mCRPC and selected subgroups).

The most common mutations (measured by median prevalence) in all unselected populations were *ATM*, *BRCA2* and *PALB2*. The highest median reported rates for germline mutations in *BRCA2* were found in mPC and mCRPC. The highest median reported rates for somatic mutations in mCRPC were found for *ATM* and *BRCA2*.

Overall, the median prevalence for DDR germline mutations was 18.6% in general PC (range, 17.2-19%; n=1,712), 11.6% in mPC (range, 11.4-11.8%; n=1,261), and 8.3% in mCRPC (range, 7.5-9.1%; n=738). The median prevalence for DDR somatic mutations was 10.7% in general PC (range, 4.9-22%; n=1,537) and 13.2% in mPC (range, 10-16.4%; n=105).

The prevalence for DDR germline and/or somatic mutations was 27% in general PC (17) and 22.67% in mCRPC (4). The higher rate of 27% (17) for germline and/or somatic mutations

Table IV. Summary of DDR gene mutation prevalence in combined definitions for germline and/or somatic tissues.

Author, year	Study information	Definition of combined germline and somatic	Method of mutation identification	Inclusion criteria	Gene	Gene definition	No. of patients	% prevalence	Refs.
Decker *et al*, 2016	mCRPC; Multi-national	Patients who had both germline and somatic mutations	Whole-genome sequencing	Discovery set PC patients were selected based on high Gleason score and availability of both peripheral blood DNA and fresh frozen prostatectomy samples. 150 samples from Robinson 2015 (4).	*BRCA2*	Biallelic mutation	150	6	(30)
					BRCA1	Ballelic loss	150	0.66	
Abida *et al*, 2017	PC; USA	Patients who had either germline or somatic or both mutations	Next-generation sequencing	Mixed population of locoregional (n=50), biochemically recurrent (n=53), and metastatic (n=348). 221 samples were included of unclear pathology, including 124 samples from Pritchard 2016 (21).	DDR	Alterations of *BRCA2, BRCA1, ATM, CHEK2*	221	27	(17)
Robinson *et al*, 2015	mCRPC; Multi-national	Patients who had either germline or somatic or both mutations	Whole-exome sequencing	Affected individuals who had metastatic disease accessible by image-guided biopsy and were being considered for abiraterone acetate or enzalutamide as standard of care or as part of a clinical trial were considered for enrollment	*ATM*	*ATM* mutations (total)	150	5.33	(4)
					BRCA2	Loss of *BRCA2*	150	12.67	
					BRCA1	*BRCA1* mutations (total)	150	2.67	
					CHEK2	*CHEK2* mutations (total)	150	3.33	
					FANCA	*FANCA* mutations (total)	150	0.67	
					MLH1	*MLH1* mutations (total)	150	2.00	
					PALB2	*PALB2* mutations (total)	150	2.00	
					DDR	Aberrations in DNA repair/recombination	150	22.67	

All studies were in unselected populations from multi-national countries. *ATM*, ataxia telangiectasia mutated; *BRCA*, breast cancer susceptibility gene; *CHEK2*, checkpoint kinase 2; DDR, DNA damage repair; *FANCA*, Fanconi anemia complementation group A; mCRPC, metastatic castration resistant prostate cancer; *MLH1*, MutL homolog 1; *PALB2*, partner and localizer of *BRCA2*; PC, prostate cancer.

in general PC may reflect the mixed population of the sample, which was predominantly metastatic rather than localized; it may also reflect differences in the genes included in the definition of 'DDR.' A recent study by Armenia *et al* (40) (after the search dates of this review) reported a combined germline and somatic mutation rate of 27% for DDR genes in mCRPC. This rate is similar to those reported here. Differences in the precise rates for mCRPC reported by Armenia *et al* (40) and Robinson *et al* (4) could be due to variations in the genes included in the definition of 'DDR' or the use of different sequencing methods (next-generation sequencing vs. whole-exome sequencing). The median rate of germline *BRCA2* mutations in patients with familial PC history was 3.7%, higher than that in the equivalent unselected population (1.1%). Studies report that DDR pathways are good candidates for PC predisposition and that, although *BRCA2* is the most frequently mutated gene, a wider range of DDR genes are likely to predispose to PC (41,42).

These results should be interpreted with caution given the limited reporting of baseline characteristics and the heterogeneity of sequencing methods and mutational definitions. In particular, the patients included in the 'unselected PC' population varied widely. For example, unselected PC cases in Abida *et al* (17) represented a mixed population of cancer types (local and metastatic) dominated by metastatic samples (77%), whereas patients from the Cancer Genome Atlas (18) were described as primary since they were derived from prostatectomies, but in fact included many high-grade cancers that were likely to be metastatic.

No other systematic reviews on the prevalence of DNA repair gene mutations and PC were identified. Two recent papers by Isaacsson Velho *et al* (43) and Quigley *et al* (44) identified similar mutational rates to those reported in this review. Isaacsson Velho *et al* (43) found a germline mutational rate of *BRCA2* in mPC of 6%, compared with the median prevalence of 5.2% reported here. Quigley *et al* (44) found germline and/or somatic *BRCA2* rates in mCRPC of 10%, compared with the rate of 12.7% (4) reported here. It is likely that the differences in rates may be explained by differences in sequencing methodology, precise definitions of mutations, and/or differences in populations. Another recent paper (45) used The Cancer Genome Atlas (18) tissues and those reported by Armenia *et al* (40) to investigate the influence of Gleason score and tumor stage. The overall prevalence of somatic DDR gene mutations in localized tumors was 8%, which is within the range reported here (4.9-22%). Marshall *et al* (45) identified an increase in DDR mutation prevalence in patients with Gleason grade ≥3 and clinical stage ≥cT3 disease.

The findings of the present review provide evidence in support of the testing of DDR germline mutations in advanced disease, in line with NCCN and Philadelphia Prostate Cancer Consensus recommendations, and the St Gallen Advanced Prostate Cancer Consensus Conference 2017 (5-7). Some germline DDR mutations may present an increased healthcare burden, since family members may also be at risk of PC. Depending on which DDR gene mutations are present, family members may also have an increased risk of breast, ovarian, pancreatic and colorectal cancer, melanoma and other cancer types (5). Given that somatic mutations were found to have a higher or similar prevalence compared with germline mutations in patients with mCRPC, somatic mutations may provide useful genetic information to guide participation in clinical trials or additional mutation testing. These findings support the testing of all patients with metastatic disease and not just those with familial disease. *BRCA2* was identified as having the highest mutation rate of any individual DDR gene, supporting the use *BRCA2* screening as recommended across all consensus conferences and NCCN (5-7).

Of note, some of the included studies provided limited baseline details. Where reported, there was evident heterogeneity in terms of the period of data collection, data sources, previous treatments, sequencing/screening methods and the risk of bias. Prevalence data based on low patient/study numbers combined with limited information about and/or variation in study characteristics prevented a thorough interrogation of the results, and the reasons for variation in prevalence could not always be determined. The repository data in many of the studies included in this review were unaccompanied by baseline patient details (13), and the source of the samples was often mentioned only incidentally within the results. This hampered data extraction and increased the risk of double counting (using the same data source twice). For example, among the three sets of tissues analyzed in the 2016 report of Decker *et al* (30), one was the same tumors used in the 2015 study of Robinson *et al* (4). Despite this apparent overlap, the data presented in the two papers do not double count for any result presented. To avoid double counting, only original data were extracted from each paper. Study sizes were limited, and only eight studies included >500 participants (20,21,25,31,32,34,36,46).

Definitions for individual gene mutations or DDR combinations varied considerably from study to study. Sources of tissue varied (being either fresh or paraffin-embedded), as did methods of mutational analysis. Different DNA sequencing/screening methods used for the detection of DDR mutation may explain the variations observed in the prevalences reported; this was demonstrated by the two linked publications of Williams *et al* (47) and Gao *et al* (48). Both publications used the same 23 patients with PC, but reported using different techniques to identify *BRCA1* mutations. The first (48) detected loss of heterozygosity, using PCR, at the *BRCA1* locus in 22% of samples, whereas the second paper (47), using FISH, found that the loss was not in the *BRCA1* gene but was distal, and therefore reported a 0% prevalence. Small gene panels and circulating DNA analysis may have lower coverage of large tumor suppressor genes such as *ATM*, *BRCA1* and *BRCA2* compared to whole genome or whole exome sequencing.

Differences in the definitions of what is considered a mutation can also arise, such as the use of monoallelic versus biallelic approaches to categorizing DDR mutations compared with non-mutations. One study (49) reported a comparison between DDR mutations (defined as biallelic mutations in DDR genes) compared with non-mutations (defined as wild-type or monoallelic mutations in DDR genes, which the authors considered non-deleterious). By contrast, all other studies (with one partial exception) reported any mutation in a DDR gene (whether it affected one or both alleles) as a *bona fide* DDR mutation. The exception involved a study (13) that provided two definitions for DDR, alternately based on one or both alleles being defective.

The use of different reference genome builds as comparator sequences introduces uncertainty. It is standard practice to use such builds as normal comparator sequences in order to identify mutations, but these reference sequences may change over time (with improved methodologies), which may influence what is defined as a genuine mutation. The use of different sequencing depths introduces uncertainty for between-study comparisons. For example, studies that perform next-generation sequencing to an extended depth [e.g. x265 (38)] may achieve more accurate sequencing (lower error rates) than studies that sequence to a relatively minimal depth [e.g. x100 (27)]. The use of different frequency cut-off thresholds for the inclusion of mutations introduces uncertainty for between-study comparisons. For example, studies that apply a relatively high frequency threshold when analyzing exonic mutations (e.g. excluding mutations with frequencies >2% in the observed population) (37) will include a larger pool of mutations than studies that apply a more restrictive frequency cutoff (e.g. excluding mutations with a population allele frequency ≥0.5%) (50).

There is a risk of sampling bias with somatic mutations, given that PC is a very heterogeneous disease (51). This heterogeneity means that within a patient tumor there are multiple sub-tumors and normal tissues with different genotypes (different mutational profiles) or clones (52,53). For example, PC can have areas of moderately differentiated tumor and undifferentiated tumor, and each clone will have a different prognosis. Tumor heterogeneity impacts biomarker studies, since the sample taken for analysis may not be the same as the sample given to the pathologist, and false associations between biomarker and histological stage can arise. Any method other than micro-dissected tissue confirmed by a pathologist for tumor grade is at risk of sampling error.

In the present study, no prevalence data were available for CRPC populations with >50 participants. There was insufficient evidence to judge whether patterns of prevalence were influenced by the country of recruitment. While there was some evidence for all the DDR genes on which the study focused, evidence was particularly limited for *ATR*, *FANCA*, *MLH1* and *MRE11A*, as mutations in these genes were reported in five or fewer studies in total.

Future research should focus on other subgroups (including African-Americans, and young-onset, ductal and lethal prostate cancer) that may have DDR mutation prevalences that are different from that of the wider PC population. In addition, future work should consider the contribution of founder mutations in unselected populations and a consideration of mutations that are prevalent in other countries. A more focused review would be required to examine in detail whether mutations were pathogenic or were variants of uncertain significance.

In future research, authors should better clarify patient baseline characteristics, the diagnostic methods employed, and whether the somatic samples used for analysis were diagnosed directly or inferred from other pathology samples. Assessment of data according to cancer stage and grade rather than broad terms such as 'PC' may also be more useful. Definitions of what types of genetic changes constitute 'mutations' (e.g. single-copy deletion compared with homozygous deletion) need to be standardized, and pathogenic classification should be routinely incorporated into the reporting of mutations. Finally, reviews of biomarker studies need to consider the aforementioned scientific limitations of these studies, as well as study design limitations. Future guidelines/consensus are required for greater standardization of sequencing methods used for genetic association studies.

Given the generally poor quality and poor reporting of studies showing prevalence data, there is a need for future epidemiological studies that use recognized methodologies and reporting tools. Authors should be encouraged to adhere to the following reporting guidelines for prevalence studies: The Simon *et al* (54) guidelines for the use of archived specimens in the evaluation of prognostic and predictive biomarkers; Biospecimen Reporting for Improved Study Quality (55); Strengthening the Reporting of Genetic Association Studies, an extension of the STROBE statement (56); and the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data (to reduce the risk of bias) (10).

A number of recent updates (5-7) in clinical practice guidelines have followed the arrival of new types of genetic tests and ongoing clinical trials with drugs that specifically target germline and/or somatic DDR mutations in mCRPC. In the unselected PC population, the median prevalence of germline and/or somatic DDR mutations was 27%. In the mPC populations, the median rate of DDR mutations was 11.6% for germline mutations and 13.2% for somatic mutations. In mCRPC populations, the prevalence rate was 22.67% for germline and/or somatic mutations. In patients with a familial history of PC, the median rate of germline DDR mutations was 12.1% and the median rate of germline *BRCA2* mutations was 3.7%.

The present review highlighted variations in definitions and methodology among studies investigating biomarkers, including differences in tumor sampling, tumor heterogeneity, sequencing depth and mutational frequency thresholds, and comparability of mutational definitions (genetic terminology). Further large, well-reported prevalence studies in PC are needed to provide international prevalence data on the burden of DDR dysfunction in patients with PC.

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Availability of data and materials

All data analyzed during this study are included in this published article.

Authors' contributions

SHL, SLS, JK, RGWQ contributed to the conception and design, acquisition of data, analysis and interpretation of data. HW contributed to the acquisition of data, analysis and interpretation of data. KM designed and performed the search

strategies. All authors contributed to the writing of the manuscript and its final approval.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

SHL, SLS, HW, KM and JK are employees of Kleijnen Systematic Reviews Ltd., who were paid consultants to Pfizer, Inc. in connection with the development of this manuscript; they have no other competing interests. RGWQ is an employee of Pfizer, Inc..

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