Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer


BACKGROUND
Inherited mutations in DNA-repair genes such as BRCA2 are associated with increased risks of lethal prostate cancer. Although the prevalence of germline mutations in DNA-repair genes among men with localized prostate cancer who are unselected for family predisposition is insufficient to warrant routine testing, the frequency of such mutations in patients with metastatic prostate cancer has not been established.

METHODS
We recruited 692 men with documented metastatic prostate cancer who were unselected for family history of cancer or age at diagnosis. We isolated germline DNA and used multiplex sequencing assays to assess mutations in 20 DNA-repair genes associated with autosomal dominant cancer-predisposition syndromes.

RESULTS
A total of 84 germline DNA-repair gene mutations that were presumed to be deleterious were identified in 82 men (11.8%); mutations were found in 16 genes, including BRCA2 (37 men [5.3%]), ATM (11 [1.6%]), CHEK2 (10 [1.9% of 534 men with data]), BRCA1 (6 [0.9%]), RAD51D (3 [0.4%]), and PALB2 (3 [0.4%]). Mutation frequencies did not differ according to whether a family history of prostate cancer was present or according to age at diagnosis. Overall, the frequency of germline mutations in DNA-repair genes among men with metastatic prostate cancer significantly exceeded the prevalence of 4.6% among 499 men with localized prostate cancer (P<0.001), including men with high-risk disease, and the prevalence of 2.7% in the Exome Aggregation Consortium, which includes 53,105 persons without a known cancer diagnosis (P<0.001).

CONCLUSIONS
In our multicenter study, the incidence of germline mutations in genes mediating DNA-repair processes among men with metastatic prostate cancer was 11.8%, which was significantly higher than the incidence among men with localized prostate cancer. The frequencies of germline mutations in DNA-repair genes among men with metastatic disease did not differ significantly according to age at diagnosis or family history of prostate cancer. (Funded by Stand Up To Cancer and others.)
CARCINOMA OF THE PROSTATE IS A COMMON cancer with a wide spectrum of clinical behavior that ranges from decades of indolence to rapid metastatic progression and lethality.1,2 Prostate cancer is also among the most heritable of human cancers, with 57% (95% confidence interval [CI], 51 to 63) of the interindividual variation in risk attributed to genetic factors.3 Thus far, genomewide association studies have identified more than 100 common variants that account for approximately 33% of the excess familial prostate cancer risk.4-7

Mutations in other genes, including BRCA1, BRCA2, MSH2,8-10 and HOXB13,11 account for a small proportion of familial cases, with BRCA2 mutations associated with 1.2 to 1.8% of prostate cancer overall.3,12

Thus far, only mutations that disrupt the function of genes involved in repairing DNA damage through homologous recombination have been shown to be associated with the aggressive clinical behavior of localized prostate cancer and with cancer-specific mortality.5,12-14 The need for genetic prognostic markers is critical, because the clinicopathological diversity of prostate cancer has confounded efforts to develop effective screening strategies that avoid overdiagnosis and overtreatment yet capture cancers that are destined to affect survival.15 Persons who are shown to have cancer-predisposition mutations in the germline may serve as sentinels for the identification of families at high risk. It should be noted that men with metastatic prostate cancer and DNA-repair gene mutations have been reported to have sustained responses to poly-ADP ribose polymerase (PARP) inhibitors and platinum-based chemotherapy.16,17

Although the prevalence of germline DNA-repair gene mutations is low among men with localized prostate cancer who are unscreened for family predisposition, the frequency of such mutations among men with metastatic prostate cancer has not been established. We recently reported an analysis of the spectrum of somatic aberrations that occur in metastatic prostate cancer, using whole-exome sequencing of metastatic tumors.18 For comparison purposes, we also sequenced germline DNA exomes from these men and unexpectedly found that 8% carried pathogenic germline mutations in DNA-repair genes. This finding suggested that men with metastatic prostate cancer represent a population that is enriched for heritable defects in DNA repair. To confirm this finding and to further ascertain the spectrum and prevalence of germline DNA-repair gene mutations in metastatic prostate cancer, we recruited 542 additional men with a confirmed prostate cancer metastasis and used next-generation sequencing to analyze DNA-repair genes associated with autosomal dominant cancer-predisposition syndromes.

METHODS

STUDY POPULATIONS

Seven case series of men with metastatic prostate cancer across multiple institutions in the United States and United Kingdom, including a total of 602 patients, were analyzed. All the patients had a diagnosis of metastatic prostate cancer and were not selected on the basis of family history, age, or any knowledge of genetic background. The demographic characteristics of the men in each series are summarized in Table 1. Detailed information on the specific germline mutations and on clinical features of mutation carriers in each series is provided in Tables S1, S2, and S3 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Case Series 1, the Stand Up to Cancer–Prostate Cancer Foundation (SU2C-PCF) International Prostate Cancer Dream Team discovery series, was made up of 150 patients for whom data were previously reported in the SU2C-PCF study of molecular stratification of metastatic prostate cancer.18 Case Series 2, the SU2C-PCF validation series, was made up of 84 patients who were newly enrolled in the SU2C-PCF study and for whom data had not been reported previously. Case Series 3, Royal Marsden Prostate Cancer Genomics series, included 131 patients who were considered for enrollment in clinical trials at the Royal Marsden Hospital from January 2013 through July 2015. Case Series 4 consisted of 91 consecutive patients included in the University of Washington rapid autopsy program from 1997 through 2013. Case Series 5 included 69 consecutive patients who were enrolled in the Weil Cornell Medical College precision medicine program. Case Series 6 was made up of 43 consecutive patients from the University of Michigan rapid autopsy program. Case Series 7, from the Memorial Sloan Kettering Cancer Center,
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The New England Journal of Medicine
August 4, 2016

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Table 1. Demographic Characteristics of the Patients with Prostate Cancer.

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</table>

† L-I Risk: High Risk
Inherited DNA-Repair Gene Mutations in Prostate Cancer

Low-penetrance variants, such as CHEK2 p.I157T, were excluded.

**Statistical Analysis**

Associations between DNA-repair gene mutation status and age, race, or Gleason score strata were evaluated with the use of two-sided Fisher’s exact tests. The frequencies of DNA-repair gene mutations among the 692 patients with metastatic prostate cancer were evaluated relative to the expected frequencies from the Exome Aggregation Consortium (53,105 persons) or the Cancer Genome Atlas cohort (499 persons) with the use of two-sided exact binomial tests. We also performed analyses in which the 150 men from the previously reported Case Series 1 were excluded. No adjustments were made for multiple comparisons; P values of less than 0.05 were considered to indicate statistical significance.

**Results**

**Patient Characteristics**

All 692 men in our analysis had documented metastatic prostate cancer, as determined by histologic evaluation of a tumor-biopsy specimen or surgical-resection specimen. The demographic characteristics of the men from each case series are shown in Table 1.

**Germline DNA-Repair Gene Mutations**

We assessed 20 genes that maintain DNA integrity and have been associated with autosomal dominant cancer-predisposition syndromes (Table 2), using whole-exome sequencing or targeted next-generation sequencing assays designed to interrogate the status of DNA-repair genes. Of the 692 men evaluated, 82 (11.8%) had at least one presumed pathogenic germline mutation in a gene involved in DNA-repair processes (Table 2). Mutation frequencies were similar across independent case series (Table 3). The 84 germline mutations that were presumed to be pathogenic (2 men had mutations in 2 genes) included 79 truncating mutations and 5 known deleterious missense mutations (Fig. 1, and Table S1 in the Supplementary Appendix). Mutations were identified in 16 different genes, including BRCA2 (37 mutations [44% of total mutations]), ATM (11 [13%]), CHEK2 (10 [12%]), BRCA1 (6 [7%]), RAD51D...
Four genes had no clearly detrimental aberrations. One man had mutations in ATM and CHEK2, and one man had mutations in BRCA2 and CHEK2. The majority of men with DNA-repair gene mutations for whom the Gleason score was available (73 men) had primary tumors with high scores (Gleason scores range from 2 to 10, with higher scores associated with worse clinical outcomes): 56 men (77%) had a Gleason score of 8 through 10, 15 men (21%) had a score of 7, and 2 men (3%) had a score of 6. We found no association between the presence of a germline DNA-repair gene mutation and an age at diagnosis of younger than 60 years versus 60 years or older (P=0.90) or non-Hispanic white versus other race (P=0.84). There was marginal evidence that the presence of a germline DNA-repair gene mutation was associated with a Gleason score of 8 through 10 versus 7 or lower (odds ratio, 1.8; 95% confidence interval [CI], 1.0 to 3.5; P=0.04).

### FAMILY CANCER HISTORY

Information regarding family history was available for 72 of 82 men (88%) with presumed pathogenic mutations in DNA-repair genes and for 537 of 610 men (88%) without DNA-repair gene mutations. In both groups, 22% of the men (16 of 72 men with DNA-repair gene mutations and 117 of 537 men without such mutations) had

a first-degree relative with prostate cancer ($P=1.0$). However, 51 of the 72 patients with DNA-repair gene mutations (71%) had a first-degree relative with cancer other than prostate cancer, whereas 270 of the 537 patients without DNA-repair gene mutations (50%) had a first-degree relative with cancer other than prostate cancer (odds ratio, 2.4; 95% CI, 1.4 to 4.3; $P=0.001$). Inspection of extended pedigree information of probands with DNA-repair gene mutations revealed affected relatives with breast cancer (24 probands), ovarian cancer (10), leukemia and lymphoma (6), pancreatic cancer (7), or other gastrointestinal cancers (18).

**SOMATIC MUTATIONS IN DNA-REPAIR GENES**

Tumor sequencing data were available for 61 of the men with germline DNA-repair gene mutations. For 36 (59%) of these men, the second allele was clearly aberrant, in that either a second loss-of-function mutation or a gene-copy loss was present (Table S1 in the Supplementary Appendix). A study of cancer-predisposition genes in children with cancer showed that 66% of children with a presumed pathogenic gene mutation had a second “hit” somatic aberration within the tumor genome, and a study involving patients with advanced cancer showed that 21.4% of patients with a presumed pathogenic gene mutation had a somatic second-allele aberration. Although a subset of germline loss-of-function mutations may not represent the causal event in the genesis of a given tumor, inactivation of the remaining allele may occur through epigenetic mechanisms or other processes.

**GERMLINE MUTATIONS IN DNA-REPAIR GENES IN LOCALIZED PROSTATE CARCINOMAS**

We compared the frequency of germline DNA-repair gene mutations among men with metastatic prostate cancer with the frequency of such mutations among men with localized prostate cancer. In the Cancer Genome Atlas prostate cancer study, which included 499 men for whom germline whole-exome sequencing data were available, 23 men (4.6%) had germline mutations in DNA-repair genes ($P<0.001$ for the comparison with metastatic disease). In addition, 6 men harbored the BRCA2 K3326* polymorphism, a C-terminal truncating variant that is unlikely to be associated with a predisposition to prostate cancer. It should be noted that to accommodate Cancer Genome Atlas requirements, the majority of tumors had high-risk characteristics: 90% were clinical stage T2c or greater, and 91% of the carcinomas had a Gleason score higher than 6, which far exceeds the approximately 30% of cancers with a Gleason score higher than 6 that was reported among men whose cancer was diagnosed by screening. Presumed pathogenic mutations in DNA-repair genes were identified in 2 of 45 men (4%) who had cancer with a Gleason score of 6, in 9 of 249 men (4%) who had cancer with a Gleason score of 7, and in 12 of 205 men (6%) who had cancer with a Gleason score of 8, 9, or 10 ($P=0.37$ for trend). Four of 162 men (2%) with localized low-to-intermediate–risk tumors and 19 of 337 men (6%) with localized high-risk tumors, as categorized according to National Comprehensive Cancer Network risk criteria, had germline DNA-repair gene mutations (Table 1). The odds of DNA-repair gene mutations being present among men with metastatic prostate cancer differed significantly from the odds among men with localized low-to-intermediate–risk tumors (odds ratio, 5.3; 95% CI, 1.9 to 20.2; $P<0.001$) or among those with high-risk tumors (odds ratio, 2.2; 95% CI, 1.3 to 4.0; $P=0.002$) (Table S6 in the Supplementary Appendix). As observed in men with metastatic prostate cancer, there was no association between the presence of a germline mutation in a DNA-repair gene and an age at diagnosis of younger than 80 years.

**Table 3. Germline DNA-Repair Gene Mutations in Seven Metastatic Prostate Cancer Case Series.**

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<thead>
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<th>Case Series</th>
<th>Description</th>
<th>Patients</th>
<th>Patients with Mutations</th>
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<td>150</td>
<td>15 (10.0)</td>
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<tr>
<td>2</td>
<td>Stand Up To Cancer–Prostate Cancer Foundation validation series</td>
<td>84</td>
<td>9 (10.7)</td>
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<tr>
<td>3</td>
<td>Royal Marsden Hospital</td>
<td>131</td>
<td>16 (12.2)</td>
</tr>
<tr>
<td>4</td>
<td>University of Washington</td>
<td>91</td>
<td>8 (8.8)</td>
</tr>
<tr>
<td>5</td>
<td>Weil Cornell Medical College</td>
<td>69</td>
<td>7 (10.1)</td>
</tr>
<tr>
<td>6</td>
<td>University of Michigan</td>
<td>43</td>
<td>4 (9.3)</td>
</tr>
<tr>
<td>7</td>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>124</td>
<td>23 (18.5)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>692</strong></td>
<td><strong>82 (11.8)</strong></td>
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60 versus 60 years of age or older (P=0.28) or non-Hispanic white versus other race (P=0.39).

**Germline Mutations in DNA-Repair Genes in the Population**

To estimate the population frequencies of germline mutations in DNA-repair genes, we analyzed exome data compiled from 53,105 persons included in the Exome Aggregation Consortium. We excluded data from persons with cancer who had been included in the Cancer Genome Atlas studies, the inclusion of which could have biased the comparisons with men with prostate cancer. The odds of any deleterious DNA-repair gene mutation being present in men with metastatic prostate cancer differed significantly from the odds in the Exome Aggregation Consortium population (odds ratio, 5.0; 95% CI, 3.9 to 6.3; P<0.001); a similar result was obtained when men from the previously reported Case Series 1 were excluded (odds ratio, 5.2; 95% CI, 4.0 to 6.8; P<0.001) (Table S5 in the Supplementary Appendix). The relative risk of mutations in individual DNA-repair genes among men with metastatic prostate cancer, as compared with men in the Exome Aggregation Consortium population, was substantial, ranging from 18.6 (95% CI, 13.2 to 25.3; P<0.001) for BRCA2 to 3.1 (95% CI, 1.5 to 5.6; P=0.002) for CHEK2 (Table 2).

**Discussion**

Inherited and acquired defects in DNA damage repair are key mechanisms in the genesis of malignant tumors. The detection of mutations in DNA-repair genes identifies persons and families who have a predisposition to cancer and defines cancer subtypes that have distinct vulnerabilities to specific therapeutics. The ascertainment of germline mutations in DNA-repair genes in men with prostate cancer has several important clinical implications. First, the recent finding that pharmacologic inhibitors of PARP1 induce substantial objective responses in patients with metastatic prostate cancer expressing homologous recombination DNA-repair defects provides a clear treatment pathway in accordance with precision medicine strategies. These tumors also appear to be responsive to platinum-based chemotherapy, as has been documented for cancers of the ovary and breast in carriers of BRCA1 and BRCA2 mutations. Second, the identification of a germline mutation in a DNA-repair gene provides information that is key to relatives, both male and female, and that can prompt “cascade” counseling to identify cancer predisposition and deploy risk-reduction strategies. Prospective studies assessing the prognostic and predictive significance of mutations in DNA-repair genes with regard to clinical outcomes are now needed to inform personalized care.

The significant family history of nonprostate cancers among men with mutations in DNA-repair genes was largely accounted for by breast, ovarian, and pancreatic cancers, in which mutations in DNA-repair pathways are known. The possible association between mutations in DNA-repair genes and familial hematologic and gas-
trointestinal cancers requires further analysis of cosegregation in affected kindreds. As observed for BRCA1 and BRCA2 in breast cancer, mutations may be found in persons who do not have a known syndromic history.10,19 Thus, broader testing of patients with metastatic prostate cancer without regard to family history will increase the yield of actionable mutations identified, in a manner parallel to the recent inclusion of all patients with epithelial ovarian cancers for germline testing regardless of family history.20

This study has several limitations. First, although efforts were made to standardize DNA-sequencing analyses, direct comparability across institutions and with public data is not guaranteed. Second, we focused on clearly deleterious mutations in a selected set of DNA-repair genes; consequently, our findings may underestimate the true frequency of pathogenic events that influence the development of metastatic prostate cancer. Third, although patients across institutions and in the control populations were unselected for family history, possible bias cannot be ruled out. Finally, our case series and the Cancer Genome Atlas study include few persons who were older than 70 years of age at diagnosis, and the incidence of germline DNA-repair gene mutations may differ in this older age group.

In conclusion, the 11.8% overall frequency of germline aberrations in genes responsible for maintaining DNA integrity in men with metastatic prostate cancer is substantially higher than the 1.2 to 1.8% incidence of BRCA2 mutations alone in localized prostate cancer6,12 or the 7.3% incidence of mutations in 22 tumor-suppressor genes in familial prostate cancer.14 Because the high frequency of DNA-repair gene mutations is not exclusive to an early-onset phenotype and is associated with clinically and histologically aggressive disease, with compelling evidence for therapeutic relevance, it may be of interest to routinely examine all men with metastatic prostate cancer for the presence of germline mutations in DNA-repair genes.

Supported by a Stand Up To Cancer–Prostate Cancer Foundation (SU2C-PCF) International Prostate Cancer Dream Team Translational Cancer Research Grant. Stand Up To Cancer is a program of the Entertainment Industry Foundation administered by the American Association for Cancer Research (SU2C-AACR-DT0712). The project was also supported by the following National Institutes of Health and Department of Defense awards: Prostate SPORE (grants P50CA097186 and P50CA092829, F90CA088748, PC131820, PC140799, R01CA116337, and 1K08CA188615) and the Prostate Cancer Foundation (Movember Challenge Awards). Drs. Beltran and Van Allen are supported by Damon Runyon Clinical Investigator Awards. Drs. Pritchard, Abida, Cheng, Schultz, and Van Allen are supported by Prostate Cancer Foundation Young Investigator Awards. Drs. Chinnaiyan and Sawyers are supported by the Howard Hughes Medical Research Institute. We also acknowledge funding from the Richard M. Lucas Foundation, the Institute for Prostate Cancer Research, Prostate Cancer UK and Movember to the London Prostate Cancer Centre of Excellence, the Starr Cancer Consortium (support to Drs. Beltran and Rubin), a Medical Research Council-Prostate Cancer UK Fellowship (to Dr. Mateo), an Experimental Cancer Medical Centre grant, a Biomedical Research Centre grant to the Institute of Cancer Research–Royal Marsden, the Andrew Sabin Family Foundation, the Marie-Josée and Henry R. Kravis Center for Molecular Oncology, and the Robert and Kate Niehaus Center for Inherited Cancer Genomics at Memorial Sloan Kettering Cancer Center. Disclosure forms provided by the authors are available with the full text of this article at NEJM.org. We thank the men who participated in this study for helping us to gain a better understanding of the role of genetic predisposition in advanced prostate cancer, the investigators and staff participating in the Stand Up To Cancer–Prostate Cancer Foundation International Prostate Cancer Dream Team, and the following persons at our respective institutions who helped with this study: Hiep Nguyen, Mary-Claire King, Barbara Norquist, Celestia Higano, Lawrence True, and Robert Vessella (University of Washington); Claudia Berton, Susana Miranda, Penny Flohr, Roberta Ferraldeschi, Zsofia Kote-Jarai, Bindu Raobaidaky, Ajit Sarvadiker, Dione Alleluy, Lucy Hamilton, Sheena Vadgama, and Ada Balasubramanian (Institute for Cancer Research); Jacob Musinsky, Jossy Armenja, Diana Mandelker, Maria Arella, and David Hyman (Memorial Sloan Kettering Cancer Center); Xuhong Cao, Yi-Mi Wu, and Felix Feng (University of Michigan); Elizabeth Heath (Wayne State University); and Tuo Zhang (Weill Cornell Medical College). We also thank the Exome Aggregation Consortium and the groups that provided exome variant data for comparison; a full list of groups contributing to the Exome Aggregation Consortium can be found at http://exac.broadinstitute.org/about.

APPENDIX
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